Journal of Hepatocellular Carcinoma

Dovepress
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REVIEW

The Synergistic Mechanisms and Prospects of Transarterial Chemoembolization Combined with Immunotherapy for Hepatocellular Carcinoma

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Abstract: Hepatocellular carcinoma (HCC) represents a highly aggressive form of liver neoplasm that presents various therapeutic obstacles. Recently, the synergistic use of transarterial chemoembolization (TACE) in conjunction with immunotherapy has attracted considerable interest within the medical community. This review aims to explore the synergistic mechanisms between TACE and immunotherapy, analyze the current research evidence, and discuss their potential applications in the treatment of HCC. By examining how TACE can enhance the efficacy of immunotherapy, we seek to provide direction for future research and emphasize the importance of personalized treatment strategies in managing HCC.

Keywords: Hepatocellular carcinoma, HCC, TACE, transarterial chemoembolization, immunotherapy, synergistic mechanisms, epigenetics

Introduction

Hepatocellular carcinoma (HCC) represents a significant portion of the worldwide cancer burden, as it is the most common type of liver cancer. The frequency of HCC cases has been increasing, especially in areas with elevated incidences of hepatitis B and C infections, in addition to populations afflicted by metabolic disorders like obesity and type II diabetes.[1] The clinical presentation of HCC is often insidious, with many patients being diagnosed at advanced stages, which complicates treatment options and outcomes.[2]

Current locoregional treatment modalities for HCC include surgical resection, ablation, and transarterial interventional therapies such as transarterial chemoembolization (TACE).[3] However, the effectiveness of these treatments is often limited by the stage of the disease at diagnosis and the underlying liver function. The overall prognosis for HCC remains poor, with a high recurrence rate following locoregional treatments.[4] This necessitates a multifaceted approach to management, including early detection and innovative therapeutic strategies.

TACE has been emerged as a preferred therapeutic option, particularly for patients with intermediate-stage HCC who are not candidates for curative therapy. It involves the selective delivery of chemotherapeutic agents directly to the tumor via the hepatic artery, combined with embolic agents to obstruct blood flow and induce ischemic necrosis.[5] Despite its utility, TACE is not without limitations, including potential damage to surrounding normal liver tissue, the risk of post-embolization syndrome, and of course, the post-operation high recurrence rate.[6]

In recent years, the integration of immunotherapy into the treatment landscape for HCC has garnered attention, particularly with the advent of immune checkpoint inhibitors (ICIs).[7] As the results of IMbrave150 were reported in 2020, atezolizumab combined with bevacizumab had recommended as the preferred first-line treatment option for HCC,[8]

Received: 30 December 2024
Accepted: 23 April 2025
Published: 30 April 2025

demonstrating the superior of immunotherapy for HCC. Other ICI-based clinical trials, such as HIMALAYA[9] and ORIENT-32,[10] also yielded promising results, solidifying the role of immunotherapy in the evolving narrative of HCC treatment. These agents work by boosting the immune system's response to tumor cells and have demonstrated potential in enhancing the prognosis for individuals diagnosed with advanced HCC. However, a considerable proportion of HCC patients have a 'cold' tumor immune microenvironment (TME), which is characterized by low immune cell infiltration and immunosuppressive conditions, making immunotherapy essentially ineffective. In contrast, a 'hot' TME exhibits high immune cell infiltration and active immune responses, which are more responsive to immunotherapy.[11] Hence, it has been demonstrated that immunotherapy can play a synergistic anti-tumor role with a wide range of modalities, including targeted therapy, radiotherapy, chemotherapy or immunomodulator,[12–14] the main reason of which is that these methods can convert 'cold' TME to 'hot' TME. Up to now, the optimal sequencing and combination of TACE and immunotherapy remain areas of active investigation.[15]

In summary, while significant strides have been made in the understanding and treatment of HCC, challenges remain in optimizing therapeutic approaches and improving patient outcomes. Continued research into the mechanisms of disease progression and treatment response is essential to develop effective strategies for this complex malignancy, especially for the combination therapy. Herein, we focus on the synergistic anti-tumor effect and mechanism of TACE and immunotherapy (Figure 1), with the purpose of providing comprehensive understanding and future exploratory direction.

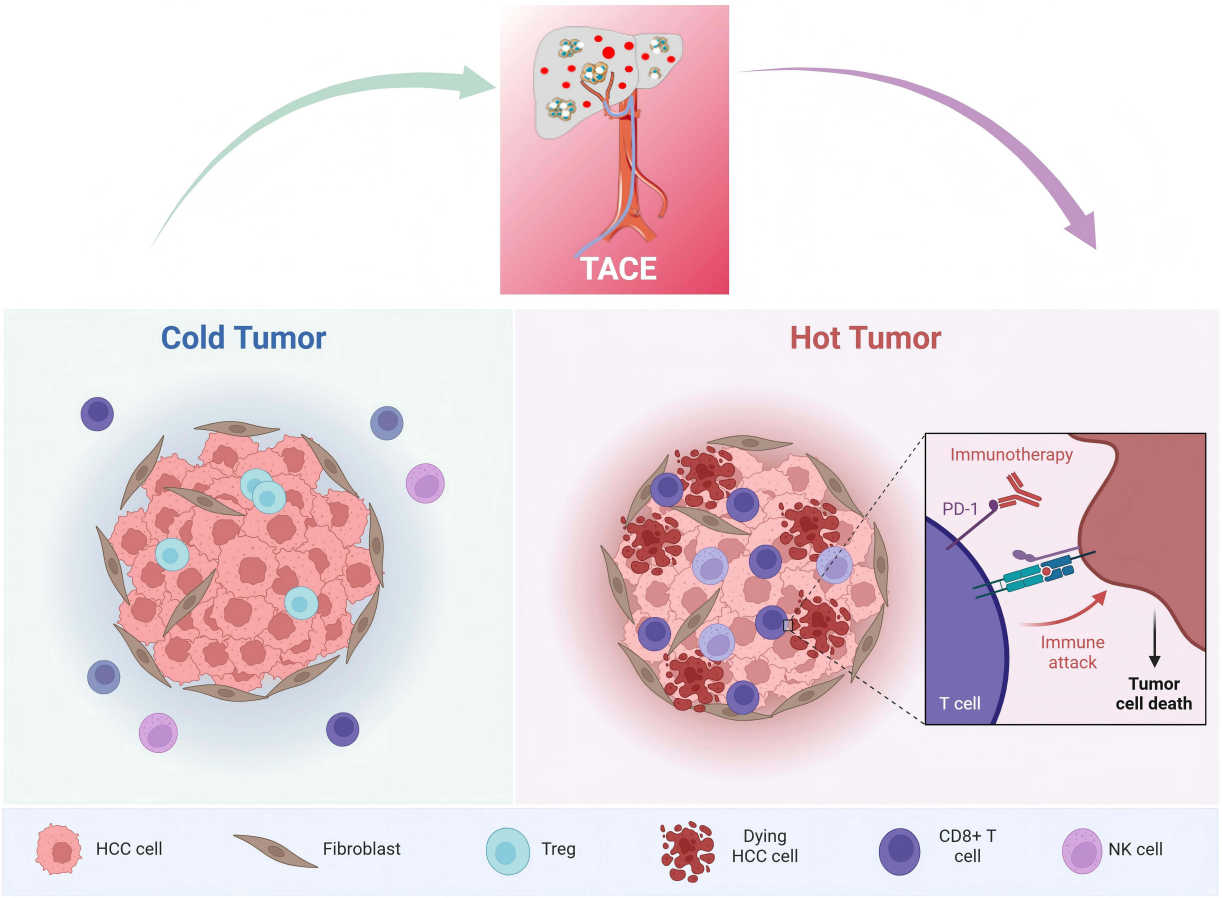

Figure 1 The synergistic anti-tumor effect and mechanism of TACE and immunotherapy. The combination of TACE and immunotherapy seeks to transform a "cold" tumor microenvironment (TME) into a "hot" TME, marked by enhanced immune cell activity and a better response to immunotherapy. After receiving TACE treatment, the tumor undergoes immunogenic cell death (ICD), leading to an increased release of tumor antigens and the recruitment of more effector $CD8^+$ T cells and NK cells for intratumoral infiltration. Meanwhile, the quantity and proportion of Tregs and other immunosuppressive cells are significantly reduced. Additionally, the expression of immune checkpoints on the surface of $CD8^+$ T cells is markedly upregulated, thereby further enhancing the efficacy of immunotherapy.

Synergistic Mechanisms of TACE and Immunotherapy

Upregulation of the Antigen Release

TACE has received acknowledgment not only for its direct cytotoxic impact on tumors but also for its capacity to bolster the immune response against HCC. One of the key mechanisms underlying this phenomenon is the release of tumor antigens (Figure 2).[16] TACE induces localized tumor necrosis, leading to the release of tumor-associated antigens. This antigen release is critical as it primes the immune system for an adaptive response. Studies have shown that TACE can increase the levels of circulating tumor antigens, which may activate dendritic cells and promote T-cell activation and proliferation.[17] For instance, expression levels of major histocompatibility complex (MHC) molecules on the surface of tumor cells may be increased, which in turn enhances the antigen presentation capabilities to T cells.[18] Additionally, the release of damage-associated molecular patterns (DAMPs) during cell death can further invigorate the immune response, creating a more robust anti-tumor immunity. This antigen release mechanism is crucial for the sequential application of immunotherapies, such as ICIs, which can leverage the pre-existing immune activation initiated by TACE.

Modulation of the Tumor Microenvironment (TME)

TME is crucial in influencing both the advancement of tumors and their responses to therapies. TACE not only exerts a direct cytotoxic effect on neoplastic cells but also modifies the TME in a manner that could potentially improve the efficacy of later immunotherapeutic interventions (Figure 2).[19] Following TACE, there is often a significant change in the immune cell composition within TME. For example, studies have reported an increase in the infiltration of effector T cells and a decrease in immunosuppressive cells such as regulatory T cells (Tregs) and myeloid-derived suppressor cells (MDSCs) after receiving TACE; research has demonstrated that tumor-associated macrophages (TAMs) can adopt different phenotypes depending on the TME, which can either promote or inhibit anti-tumor immunity.[20,21]

TAMs, Tregs, and MDSCs are pivotal in shaping the immunosuppressive TME following TACE, thereby influencing tumor progression and therapeutic resistance. TACE-induced hypoxia promotes the polarization of TAMs toward the M2-like

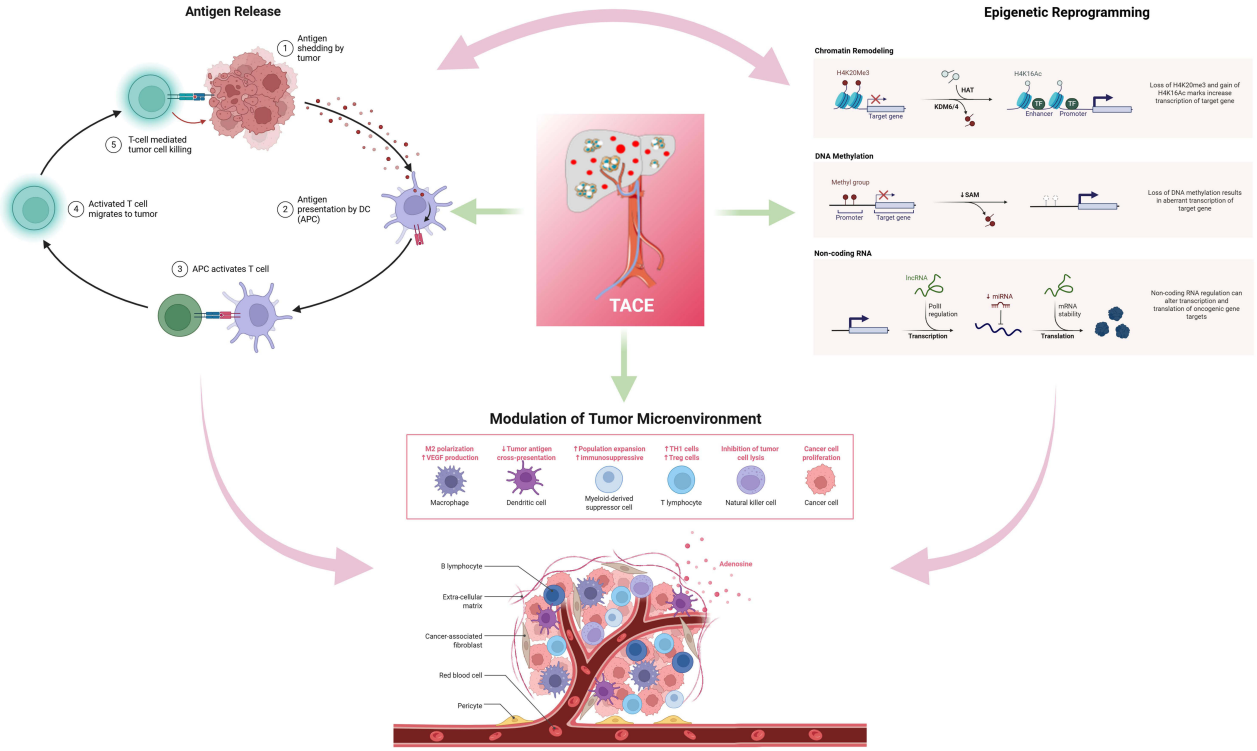

Figure 2 The synergistic mechanisms of TACE and immunotherapy. The synergistic mechanisms of TACE combined with immunotherapy mainly include upregulation of the antigen release, modulation of the TME, and the impact of epigenetic reprogramming.

https://doi.org/10.2147/JHC.S514881

phenotype, which secretes immunosuppressive cytokines such as IL-10 and TGF-β, driving angiogenesis and facilitating tumor regrowth and metastasis.[22] Similarly, hypoxia and tissue injury recruit Tregs that suppress cytotoxic T cells and NK cells while releasing TGF-β and IL-10, further dampening anti-tumor immunity.[23] Additionally, MDSCs expand post-TACE, secreting immunosuppressive factors and supporting angiogenesis and tumor survival under hypoxic conditions.[24] These immunosuppressive cells hinder the efficacy of ICIs and contribute to resistance mechanisms. Combining TACE with strategies that target TAMs (eg, CSF-1R inhibitors), deplete Tregs (eg, anti-CD25 antibodies), or reduce MDSCs (eg, CXCR2 inhibitors) holds promise for overcoming immunosuppression. This approach can synergize with immunotherapy to reprogram the TME, enhance immune activation, and improve therapeutic outcomes in HCC. As for the involved pathways, immunogenic cell death (ICD) triggered by TACE leads to the release of damage-associated molecular patterns (DAMPs), activating antigen-presenting cells (APCs) via pathways such as STING and TLR signaling.[25] Besides, increased antigen presentation stimulates T cell activation via the MHC-I pathway, leading to the recruitment and expansion of effector immune cells while reducing immunosuppressive components like Tregs and M2 macrophages.[26] Further research is essential to optimize these combination strategies for clinical application.

The relationship between tumors and the immune system is a complex and evolving interaction influenced by multiple factors.[27] Tumor cells possess the ability to alter the immune response by secreting cytokines and expressing immune checkpoint proteins, thereby establishing an immunosuppressive microenvironment that facilitates tumor advancement. Additionally, the recruitment of various immune cell types, such as Tregs and MDSCs, can further tilt the immune response in favor of tumor tolerance. This complex interplay underscores the importance of understanding the changes that govern immune cell behavior within the TME, as these alterations can profoundly affect the effectiveness of immunotherapies and the overall prognosis for patients.[28]

The combination of TACE with immunotherapy, therefore, aims to convert "cold" TME into "hot" TME, characterized by increased immune cell activity and improved response to immunotherapy.[29] This synergistic interaction between TACE and immunotherapy underscores the importance of understanding the dynamic changes within the TME to optimize treatment strategies for HCC.

Impact of Epigenetic Reprogramming

Epigenetic modifications are increasingly recognized as important factors in HCC biology, influencing both tumor progression and response to therapy. It has been reported that TACE can induce epigenetic changes of HCC, which may enhance their susceptibility to immunotherapy (Figure 2). For instance, cellular demise induced by TACE may result in the release of cytokines that modify the epigenetic landscape of residual surviving tumor cells, potentially increasing the immunogenicity.[18] This epigenetic reprogramming may involve changes in DNA methylation patterns, histone modifications, and the expression of non-coding RNAs, all of which can affect gene expression profiles related to immune evasion and tumor progression. Research has shown that TACE can downregulate immune checkpoint molecules, thereby enhancing T-cell responses against tumor antigens.[30] Furthermore, the interplay between metabolic reprogramming and epigenetic changes following TACE can create a more favorable environment for the action of ICIs, leading to improved outcomes.[31] Hypermethylation of the PD-L1 promoter can suppress its expression, reducing immune recognition and response to PD-1/PD-L1 inhibitors. Conversely, hypomethylation can upregulate PD-L1, making tumors more responsive to checkpoint blockade therapy.[32] EZH2, a histone methyltransferase, catalyzes H3K27me3, leading to transcriptional repression of tumor suppressor genes and immune-related genes. Inhibition of EZH2 can promote antigen presentation and T cell infiltration, thereby increasing sensitivity to immunotherapy.[33] Downregulation of miR-200 promotes epithelial-mesenchymal transition (EMT), leading to reduced antigen presentation and immune escape. Restoring miR-200 expression enhances MHC-I presentation, improving response to immunotherapy.[34] Understanding these epigenetic mechanisms may provide new avenues for enhancing the efficacy of combination therapies involving TACE and immunotherapy in HCC patients.

Current Evidence

China's TACE Studies - CHANCE Series

The combination of ICIs with anti-VEGF antibodies has become the standard first-line treatment for advanced HCC.[35] Over the past decade, there has been ongoing exploration of treatment options for advanced HCC, with significant attention focused on combining TACE with systemic therapies, primarily targeted treatments. The success of combining TACE with targeted therapies in treating HCC has sparked enthusiasm for integrating interventional treatments with immunotherapy.[36] Both preclinical and clinical evidence increasingly suggests that interventional oncology (IO) combined with immunotherapy (IO+IO) holds promise for improving the efficacy of inoperable HCC.[37] The CHANCE alliance is committed to establishing a clinical research platform for the Chinese HCC experts. This alliance focuses on multidisciplinary treatment as its core concept, pooling expertise from various disciplines to actively promote and transform the current state of HCC interventional therapies, thus contributing to the high-quality development of HCC treatment in China (Table 1).

CHANCE001 Study

The CHANCE001 study is a multi-center, retrospective study in China assessing the efficacy of combining TACE with immunotherapeutic and targeted treatment modalities for HCC.[38] This study was launched on April 16, 2021, based on the CHANCE research platform, with clinical registration number NCT04975932. The study includes HCC patients from 59 top-tier hospitals across 22 provinces in China. It enrolled patients from January 2018 to May 2021, including those receiving TACE combined with PD-(L)1 inhibitors and targeted therapies, as well as a control group receiving TACE alone. A total of 1142 patients were initially screened, and after matching and selection according to the study protocol, 228 patients were included in both groups for analysis. The study population primarily consisted of patients with HBV infection (71.5%), advanced-stage disease (65.8%), and high tumor burden (75.9%), including some with Child-Pugh B liver function (14.0%) and extrahepatic metastasis (33.3%). The findings indicated that the group receiving combination therapy achieved a progression-free survival (PFS) of 9.5 months, which was significantly superior to the 8.0 months observed in the TACE-only group (HR = 0.70, 95% CI: 0.56–0.88, P = 0.002). Furthermore, the median overall survival (OS) for the combination therapy cohort was 19.2 months, in contrast to 15.7 months for the TACE-alone cohort (HR = 0.63, 95% CI: 0.47–0.83, P = 0.001). The objective response rate (ORR) was recorded at 60.1% for the combination therapy group, compared to 32.0% for the TACE-only group (P < 0.001). This investigation illustrates that the integration of TACE with PD-(L)1 inhibitors and targeted therapies markedly enhances PFS, OS, and ORR in patients suffering from advanced HCC, while maintaining an acceptable safety profile.

CHANCE2211 Study

The CHANCE2211 study, a national multi-center retrospective cohort study, investigated the combination of Camrelizumab, Apatinib, and TACE in treating HCC.[39] This investigation, utilizing the CHANCE research platform, included a total of 586 patients diagnosed with HCC. Following propensity score matching at a ratio of 1:2, the study comprised 84 individuals receiving the combined treatment and 147 individuals undergoing TACE exclusively. The findings indicated that the cohort receiving the combination treatment exhibited markedly superior median OS, PFS, and ORR in comparison to the TACE-only group (median OS: 24.1 months versus 15.7 months; median PFS: 13.5 months versus 7.7 months; ORR: 59.5% versus 37.4%). This research represents the most extensive real-world dataset to date that evaluates the efficacy of Camrelizumab in conjunction with Apatinib against TACE alone for the management of HCC.

CHANCE2201 Study

The CHANCE2201 study is a nationwide multi-center real-world clinical trial that aims to evaluate whether combining TACE with systemic therapies benefits advanced HCC patients.[40] The study included 1244 patients from 65 top-tier hospitals across 30 provinces. The findings indicated that the integration of TACE with targeted and immunotherapy yielded a median OS of 22.6 months, which is markedly superior to the median OS of 15.9 months reported with systemic therapy alone. Furthermore, the median PFS for the combination therapy was recorded at 9.9 months, in

Table 1 China's TACE Series Studies

Study	Study Type	Treatment Groups	Number of Patients	Key Findings	PFS	OS	ORR	HR (P-value)
CHANCE001[38]	Multi-center, retrospective	TACE + PD-(L)1 inhibitors + Targeted therapies (Experimental group)	456 (228 in each group)	TACE combined with PD-(L)1 inhibitors and targeted therapies significantly improved PFS, OS, and ORR in advanced HCC	9.5 months (Experimental)	19.2 months (Experimental)	60.1% (Experimental)	PFS: HR = 0.70 (P = 0.002)
		TACE alone (Control group)			8.0 months (Control)	15.7 months (Control)	32.0% (Control)	OS: HR = 0.63 (P = 0.001)
CHANCE2211[39]	Multi-center, retrospective	Camrelizumab + Apatinib + TACE (Experimental group)	586 (84 in experimental, 147 in control)	The combination of Camrelizumab, Apatinib, and TACE resulted in significantly higher OS, PFS, and ORR compared to TACE alone	13.5 months (Experimental)	24.1 months (Experimental)	59.5% (Experimental)	PFS: 13.5 vs 7.7 months (P < 0.001)
		TACE alone (Control group)			7.7 months (Control)	15.7 months (Control)	37.4% (Control)	OS: 24.1 vs 15.7 months (P < 0.001)
CHANCE2201[40]	Multi-center, real-world	TACE + Targeted + Immunotherapy (Experimental group)	1244 (802 in experimental, 442 in control)	Combining TACE with targeted and immunotherapy significantly improved OS, PFS, and ORR in advanced HCC compared to systemic therapy alone	9.9 months (Experimental)	22.6 months (Experimental)	41.2% (Experimental)	PFS: 9.9 vs 7.4 months
		Systemic therapy alone (Control group)			7.4 months (Control)	15.9 months (Control)	22.9% (Control)	OS: 22.6 vs 15.9 months

Abbreviations: PFS, progression-free survival; OS, overall survival; ORR, objective response rate; HR, hazard ratio.

https://doi.org/10.2147/JHC.S514881

contrast to the 7.4 months noted in the monotherapy cohort. The ORR for the combination treatment reached 41.2%, whereas the monotherapy group exhibited an ORR of 22.9%. Although the incidence of adverse events was higher within the combination therapy cohort, these events were found to be manageable. The observed survival advantages were consistent across various sensitivity analyses and clinical subgroups. The study CHANCE2201 extends previous research and offers significant real-world evidence supporting the amalgamation of TACE with systemic therapies in the management of advanced HCC.

Future Outlook

With the publication of subsequent prospective multi-center randomized controlled trial data, it is expected that the treatment landscape for intermediate and advanced HCC will be significantly revolutionized.

International TACE Trials

Clinical investigations evaluating the effectiveness of TACE in conjunction with immunotherapy have reported encouraging outcomes.[41] The EMERALD-1 trial (NCT03778957), a Phase III study encompassing 724 participants, assessed the effectiveness of a triple therapy regimen comprising TACE, Durvalumab, and Bevacizumab, in comparison to TACE alone for patients diagnosed with HCC.[42] Preliminary findings presented at the 2024 ASCO-GI indicated that the combination therapy significantly enhanced PFS, yielding a median PFS of 15.0 months for the combination group, as opposed to 8.2 months for the TACE-only cohort (HR = 0.77, P = 0.032). Additionally, the LEAP-012 trial (NCT04246177), another Phase III investigation involving 450 participants, examined the efficacy of combining TACE with Pembrolizumab and Lenvatinib relative to TACE alone for HCC treatment.[43] Mid-term results presented at the 2024 ESMO demonstrated a substantial improvement in PFS for the combination therapy, with a median of 14.6 months (95% CI: 12.6–16.7) in the treatment group compared to 10.0 months (95% CI: 8.1–12.2) for the placebo group (HR = 0.66, P = 0.0002). Although interim OS data did not achieve statistical significance (HR = 0.80, P = 0.0867), a noticeable trend toward improved OS was evident. The one-year survival rates were 89.0% for the combination group and 83.1% for the placebo group, while the two-year survival rates were recorded at 74.6% and 68.6%, respectively. These results suggest that the amalgamation of locoregional and systemic treatment modalities may yield a more efficacious strategy for managing advanced HCC. Nevertheless, concerns have arisen regarding the safety profiles of these combined therapies, highlighting the need for continuous surveillance of treatment-related adverse events (TRAEs). Overall, the outcomes from these clinical trials emphasize the potential of TACE in conjunction with immunotherapy to improve patient outcomes in HCC cases.

In the intermediate stage of HCC, ongoing researches are evaluating the combination of TACE and immunotherapy. Notably, influential ongoing international randomized clinical trials exploring these combinations are summarized in Table 2. Collectively, these findings imply that the integration of immunotherapy with TACE not only amplifies therapeutic efficacy but also provides a feasible treatment alternative for patients with advanced HCC. Nonetheless, further investigation is crucial to refine treatment protocols and to thoroughly comprehend the long-term advantages and potential hazards associated with this combined therapeutic approach.

Epigenetic Influences

TACE Induced Epigenetic Modifications

TACE is a common interventional treatment for HCC that not only aims to reduce tumor size but also induces significant epigenetic changes in the TME.[44] Recent research has shown that TACE has the capacity to modify the expression of genes associated with apoptosis, cellular proliferation, and immune responses via epigenetic mechanisms, including DNA methylation and histone modifications.[31] For instance, TACE has been shown to promote the expression of pro-apoptotic genes while silencing anti-apoptotic genes via hypermethylation, thereby enhancing tumor cell death.[45] Additionally, TACE can influence the TME by inducing immune checkpoint molecules that modulate T cell responses.[46] The interplay between TACE-induced epigenetic modifications and the subsequent immune response highlights the complex relationship between therapy and tumor biology, suggesting that understanding these modifications can result in enhanced therapeutic approaches and better clinical outcomes for individuals diagnosed with HCC.[47]

https://doi.org/10.2147/JHC.S514881

Table 2 Ongoing International Randomized Clinical Trials Testing Combinations of TACE and Immunotherapy

Trial	Phase	Enrollment	Treatment	Comparator	Primary Endpoint	NCT Number	Preliminary Results
EMERALD-1	III	724	TACE + Durvalumab + Bevacizumab	TACE	Progression-free survival (PFS)	NCT03778957	Compared to TACE alone, the triple combination of Durvalumab, TACE, and Bevacizumab significantly improved PFS. The median PFS was 15.0 months for the combination group and 8.2 months for the TACE-alone group (HR = 0.77, P = 0.032).
EMERALD-3	III	725	TACE + Durvalumab + Tremelimumab + Lenvatinib	TACE	PFS	NCT05301842	Not reported
LEAP-012	III	450	TACE + Pembrolizumab + Lenvatinib	TACE	PFS, overall survival (OS)	NCT04246177	A mid-term study demonstrated that the PFS of the Lenvatinib + Pembrolizumab + TACE group was significantly superior to that of the placebo + TACE group (HR = 0.66, 95% CI: 0.51–0.84, P = 0.0002). The median PFS was 14.6 months (95% CI: 12.6–16.7) and 10.0 months (95% CI: 8.1–12.2), respectively. The interim OS data remain immature and have not yet reached statistical significance (HR = 0.80, 95% CI: 0.57–1.11, P = 0.0867). However, a trend toward OS improvement was observed with the combination therapy. Median OS has not been reached in either group, with 1-year survival rates of 89.0% and 83.1% and 2-year survival rates of 74.6% and 68.6%, respectively.
ML-42612	III	342	TACE + Atezolizumab + Bevacizumab	TACE	Time to failure of treatment strategy (TTFTS)	NCT04712643	Not reported
ABC-HCC	III	434	Atezolizumab + Bevacizumab	TACE	PFS by mRECIST	NCT04803994	Not reported
RENOTACE	III	496	Nivolumab + Regorafenib	TACE	PFS by mRECIST	NCT04777851	Not reported

Clinical Significance and Potential Biomarkers

The clinical significance of epigenetic modifications in HCC is substantial, especially regarding the identification of prospective biomarkers for diagnosis, prognosis, and therapeutic response.[48–52] Alterations in the epigenome, including modifications in DNA methylation patterns and histone changes, have been linked to numerous cancers and may function as biomarkers for the early detection and surveillance of disease advancement. Notably, specific microRNAs and long non-coding RNAs have surfaced as encouraging candidates, attributed to their involvement in the modulation of gene expression and their stability in body fluids.[53] Moreover, the identification of epigenetic signatures in tumors can help stratify patients based on their likely response to specific therapies, including targeted therapy and immunotherapy. As research continues to uncover the intricate relationship between epigenetic changes and tumor biology, the development of epigenetic-based biomarkers holds great promise for promoting precision medicine in HCC.[54]

Challenges and Limitations

Impact of Tumor Heterogeneity

Tumor heterogeneity is a significant challenge for HCC treatment, as it can manifest both intertumoral and intratumor variations.[55] Intertumoral heterogeneity refers to the difference observed among different patients, while intratumor heterogeneity pertains to the variations within one lesion. This heterogeneity can arise from genetic, epigenetic, and environmental factors, contributing to difference as to tumor behavior, treatment response, and outcomes. For example, research indicates that the existence of various cancer cell subpopulations within a tumor may result in differing responses to identical therapeutic interventions, complicating treatment strategies and potentially leading to treatment resistance.[56] Furthermore, the dynamic nature of tumor evolution can result in the emergence of resistant clones during treatment, making it essential to develop personalized therapeutic approaches that consider the unique tumor heterogeneity. Therefore, understanding and addressing tumor heterogeneity is crucial for improving therapeutic efficacy and outcomes in HCC.[57]

Effects of Hypoxic Environment on Treatment Outcomes

Hypoxia, or low oxygen levels within the tumor microenvironment, is a well-recognized factor that adversely affects the outcomes of patients with HCC.[58] The most important characteristic of TACE for HCC is that it induces hypoxia in tumor tissues and cells. First, TACE blocks tumor-feeding arteries, leading to oxygen depletion. Second, after embolization, surviving tumor cells exhibit elevated glycolysis, consuming remaining oxygen. Finally, as tumors expand, they outgrow their oxygen supply, exacerbating hypoxia. The main indicators for measuring hypoxia levels include hypoxia-inducible factor-1α (HIF-1α), vascular endothelial growth factor (VEGF) and glucose transporters (GLUT1). Malignancy often suffers from hypoxic condition due to inadequate blood supply and rapid growth, leading to an environment that promotes resistance to therapies, such as chemotherapy and radiotherapy. Hypoxia can induce a range of biological responses that contribute to tumor aggressiveness, including enhanced angiogenesis, altered metabolism, immune evasion, and so on.[59,60] Additionally, hypoxic tumor regions are often less sensitive to treatment, as the low oxygen levels can diminish the effectiveness of radiation therapy, which relies on oxygen to generate reactive oxygen species that damage lesions.[61,62] As a result, strategies to target hypoxia within tumor, such as the use of hypoxia-activated prodrugs (HAPs) or oxygen delivery systems, are currently under investigation to enhance the effectiveness of treatments and improve patient outcomes. The classification of HAPs mainly includes Quinone-Based HAPs, Nitroaromatic HAPs, Aliphatic N-Oxide HAPs, and Cobalt Complex HAPs.[63] Addressing the challenges posed by hypoxic environments is essential for optimizing HCC therapies.

Toxicity Reactions and Tolerability Issues

The treatment of HCC typically encompasses a range of therapeutic modalities, such as chemotherapy, targeted therapies, and immunotherapeutic approaches. Nevertheless, the administration of these treatments is frequently associated with the potential for adverse effects, which can considerably affect both the quality of life of patients and their adherence to treatment protocols.[64] The spectrum of toxic reactions may vary from mild symptoms, including nausea and fatigue, to more serious complications that may lead to organ dysfunction and life-threatening situations. The variability in tumor response to this

treatment can be attributed to factors such as genetic predisposition, pre-existing comorbidities, and the specific characteristics of the administration agents.[65] Additionally, the development of tolerance to certain drugs can lead to dose escalation, further increasing the risk of adverse effects. Therefore, it is crucial for healthcare providers to monitor patients closely, implement strategies to manage side effects, and come up with personalized approaches to minimize toxicity while maximizing the therapeutic benefits. Besides, in patients receiving transarterial chemoembolization (TACE) combined with immune checkpoint inhibitors (ICIs), common irAEs include diarrhea (26.5%), pruritus (22.9%), rash (22.4%), decreased appetite (17.0%), fatigue (17.0%), pyrexia (12.9%), nausea (12.1%), increased AST levels (12.4%), and hypothyroidism (10.3%).[66] Severe adverse events (grade 3 or higher) attributed to immunotherapy have been observed in approximately 10% of patients undergoing multimodal treatment.[67] Elderly patients (≥65 years) are more prone to cardiotoxicity, fatigue, and endocrinopathies, such as hypothyroidism, while those with pre-existing liver diseases (eg, cirrhosis, HBV, or HCV) face an increased risk of acute liver decompensation, with HBV reactivation occurring in 5–10% of cases without antiviral prophylaxis.[68] Liver function impairments post-TACE and immunotherapy are common, with ALT/AST levels rising beyond three times the upper limit of normal (20–40% of cases) and bilirubin elevation leading to jaundice in 5–10% of severe cases. Additionally, patients with Child-Pugh Class B/C liver function often experience higher rates of hepatic encephalopathy and exacerbated ascites.[69]

Future Perspectives

Exploration of Novel Combination Therapies

The landscape of HCC treatment is rapidly evolving, with novel combination therapies emerging as a promising frontier in oncology. Traditional monotherapy has often fallen short due to the complex nature of tumor, particularly in aggressive malignancies. Recent research has underscored the promising advantages of integrating ICIs, particularly anti-PD-1/PD-L1 agents, with various other treatment strategies to augment therapeutic effectiveness and address the resistance mechanisms that are naturally present in tumors. For example, a comprehensive review discussed the synergistic potential of combining anti-PD-1/PD-L1 therapy with chemotherapy and targeted therapies, indicating that such combinations may enhance the immunosuppressive TME and lead to improved clinical outcomes.[70] Besides, most patients exhibited resistant to TACE, which is called as "TACE refractory" or "TACE unsuitable".[71] For these patients, TACE may not be able to improve TME to play synergistic anti-tumor effect. For example, it was reported that intratumor $Trem2^{+}$ macrophage significantly elevated after receiving TACE, affecting the curative effect.[20] Hence, Targeting Trem2 or other similar targets may further improve the clinical efficacy of TACE combined with immunotherapy. Additionally, ongoing clinical trials are investigating the optimal sequencing and combination of these therapies to maximize therapeutic effects while minimizing adverse effects (Table 2). As research continues to elucidate the mechanisms behind these combination strategies, the future of HCC treatment may increasingly rely on tailored regimens that address the unique characteristics of individual patient.

Development and Application of Biomarkers

The advancement of biomarkers in HCC has become a pivotal aspect of personalized medicine, offering insights into prognosis, response and stratification.[72] Recent literature underscores the importance of developing and validating biomarkers that can guide therapeutic decisions, particularly in the context of immunotherapy. For example, the identification of biomarkers such as serum amyloid A (SAA) expression has been crucial for predicting responses to ICIs in HCC.[73] However, the search for more robust and comprehensive biomarkers needs to continue to explore, as existing markers often lack reliability across diverse patient populations. Emerging technologies, including genomic and proteomic analyses, are utilized to identify new biomarkers that can enhance the prediction of treatment results and track the advancement of diseases.[74] Additionally, the integration of artificial intelligence in biomarker discovery holds promise for improving the accuracy and efficiency of identifying predictive and prognostic markers, enabling more personalized treatment approaches.[75] As the field progresses, the successful implementation of biomarkers into clinical practice will be essential for optimizing patient care and improving outcomes.

Prospects and Challenges of Personalized Treatment

The future of HCC treatment is increasingly leaning towards individualized treatment, which tailor therapeutic strategies based on individual characteristics and tumor biology.[76] This approach has shown great potential in improving treatment

efficacy and reducing side effects. However, several challenges remain in the implementation of personalized strategy. One significant hurdle is the identification of predictive biomarkers that can reliably indicate which patients will benefit from specific therapy. For instance, the heterogeneity of tumor often complicates the development of universal biomarkers, necessitating a more nuanced understanding of tumor genetics and patient profiles.[77] Moreover, the integration of advanced technologies such as next-generation sequencing and artificial intelligence into clinical workflows poses logistical and regulatory challenges that need to be addressed.[78] Additionally, the cost-effectiveness of personalized therapy remains a concern, as these treatments can be expensive and may not be accessible to all patients.[79–81] Despite these challenges, the ongoing research and technological advancements in the field of personalized medicine offer a hopeful outlook for the future of cancer treatment, with the potential for more effective, targeted, and patient-centric therapies.[82,83]

Conclusion

In conclusion, the integration of TACE with immunotherapy has emerged as a promising strategy for improving the prognosis of patients with HCC. Current evidence suggests that while TACE effectively reduces tumor burden, but combining it with immunotherapy may boost immunity, leading to improved overall survival and disease-free intervals. This dual approach appears to synergize the cytotoxic effects of TACE with the immune checkpoint blockade, potentially overcoming the limitations of each modality when applied independently.

However, the path forward is not without challenges. The variability in tumor response to combined therapies necessitates a nuanced understanding of the underlying biological mechanisms at play. Future research should focus on identifying biomarkers that can predict which patients are most likely to benefit from this combination therapy. Additionally, the timing and sequencing of TACE and immunotherapy administration remain critical areas for investigation. Tailoring these treatment modalities to the individual patient will be essential in maximizing therapeutic efficacy.

Moreover, as we look to the future of HCC treatment, the significance of multidisciplinary collaboration cannot be overstated. Oncologists, radiologists, immunologists, and other healthcare professionals must work together to develop integrated treatment protocols that leverage the strengths of each discipline. Such collaboration will not only facilitate the sharing of knowledge and expertise but also accelerate the translation of research findings into clinical practice.

In summary, the combination of TACE and immunotherapy holds significant potential for improving outcomes in HCC patients. Continued exploration of this therapeutic strategy, coupled with a commitment to collaborative practice, will be paramount in advancing HCC treatment paradigms and ultimately enhancing patient care. The advancement of HCC management depends on our capacity to integrate various research outcomes and clinical perspectives, thereby facilitating the development of novel strategies that tackle the intricate nature of this formidable condition.

Data Sharing Statement

All data are included in this article. Further enquiries can be directed to the corresponding author.

Statement of Ethics

Our institutional ethics committees approved the study design and waived the requirement for informed consent because no human subjects were involved.

Author Contributions

All authors made a significant contribution to the work reported, whether that is in the conception, study design, execution, acquisition of data, analysis and interpretation, or in all these areas; took part in drafting, revising or critically reviewing the article; gave final approval of the version to be published; have agreed on the journal to which the article has been submitted; and agree to be accountable for all aspects of the work.

Funding

Supported by the National Natural Science Foundation of China (No. 82402403 and 82072022) and Guangdong Basic and Applied Basic Research Foundation (2025A1515011330).

Disclosure

The authors have no conflicts of interest to declare in this work.

References

1. Singal AG, Kanwal F, Llovet JM. Global trends in hepatocellular carcinoma epidemiology: implications for screening, prevention and therapy. *Nat Rev Clin Oncol*. 2023;20(12):864–884. doi:10.1038/s41571-023-00825-3
2. Vogel A, Meyer T, Sapisochin G, Salem R, Saborowski A. Hepatocellular carcinoma. *Lancet*. 2022;400(10360):1345–1362. doi:10.1016/S0140-6736(22)01200-4
3. Crocetti L, Bargellini I, Cioni R. Loco-regional treatment of HCC: current status. *Clin Radiol*. 2017;72(8):626–635.
4. Torimura T, Iwamoto H. Treatment and the prognosis of hepatocellular carcinoma in Asia. *Liver Int*. 2022;42(9):2042–2054.
5. Liu M, Sun Y, Zhou Y, et al. A novel coacervate embolic agent for tumor chemoembolization. *Adv Healthc Mater*. 2024;13(19):e2304488. doi:10.1002/adhm.202304488
6. Ebeling Barbier C, Heindryckx F, Lennernas H. Limitations and possibilities of transarterial chemotherapeutic treatment of hepatocellular carcinoma. *Int J Mol Sci*. 2021;22(23):13051. doi:10.3390/ijms222313051
7. Gordan JD, Kennedy EB, Abou-Alfa GK, et al. Systemic therapy for advanced hepatocellular carcinoma: ASCO guideline update. *J Clin Oncol*. 2024;42(15):1830–1850. doi:10.1200/JCO.23.02745
8. Finn RS, Qin S, Ikeda M, et al. Atezolizumab plus bevacizumab in unresectable hepatocellular carcinoma. *N Engl J Med*. 2020;382(20):1894–1905. doi:10.1056/NEJMoa1915745
9. Sangro B, Galle PR, Kelley RK, et al. Patient-reported outcomes from the phase III Himalaya study of tremelimumab plus durvalumab in unresectable hepatocellular carcinoma. *J Clin Oncol*. 2024;42(23):2790–2799. doi:10.1200/JCO.23.01462
10. Ren Z, Xu J, Bai Y, et al. Sintilimab plus a bevacizumab biosimilar (IBI305) versus sorafenib in unresectable hepatocellular carcinoma (ORIENT-32): a randomised, open-label, Phase 2-3 study. *Lancet Oncol*. 2021;22(7):977–990. doi:10.1016/S1470-2045(21)00252-7
11. Montironi C, Castet F, Haber PK, et al. Inflamed and non-inflamed classes of HCC: a revised immunogenomic classification. *Gut*. 2023;72(1):129–140. doi:10.1136/gutjnl-2021-325918
12. Brown ZJ, Tsilimigras DI, Ruff SM, et al. Management of hepatocellular carcinoma: a review. *JAMA Surg*. 2023;158(4):410–420. doi:10.1001/jamasurg.2022.7989
13. Wang XH, Fu YL, Xu YN, et al. Ginsenoside Rh1 regulates the immune microenvironment of hepatocellular carcinoma via the glucocorticoid receptor. *J Integr Med*. 2024;22(6):709–718. doi:10.1016/j.joim.2024.09.004
14. Wu J, Liu W, Qiu X, et al. A noninvasive approach to evaluate tumor immune microenvironment and predict outcomes in hepatocellular carcinoma. *Phenomics*. 2023;3(6):549–564. doi:10.1007/s43657-023-00136-8
15. Tamai Y, Fujiwara N, Tanaka T, Mizuno S, Nakagawa H. Combination therapy of immune checkpoint inhibitors with locoregional therapy for hepatocellular carcinoma. *Cancers*. 2023;15(20):5072. doi:10.3390/cancers15205072
16. Chen Y, Zeng L, Zhu H, et al. Ferritin Nanocaged Doxorubicin Potentiates Chemo-Immunotherapy against Hepatocellular Carcinoma via Immunogenic Cell Death. *Small Methods*. 2023;7(5):e2201086. doi:10.1002/smtd.202201086
17. Karimi A, Yarmohammadi H, Erinjeri JP. Immune effects of intra-arterial liver-directed therapies. *JVIR*. 2024;35(2):178–184. doi:10.1016/j.jvir.2023.10.019
18. Xu X, Peng Q, Jiang X, et al. Metabolic reprogramming and epigenetic modifications in cancer: from the impacts and mechanisms to the treatment potential. *Exp Mol Med*. 2023;55(7):1357–1370. doi:10.1038/s12276-023-01020-1
19. Duan Y, Zhang H, Tan T, et al. The immune response of hepatocellular carcinoma after locoregional and systemic therapies: the available combination option for immunotherapy. *Biosci Trends*. 2024;17(6):427–444. doi:10.5582/bst.2023.01275
20. Tan J, Fan W, Liu T, et al. TREM2(+) macrophages suppress CD8(+) T-cell infiltration after transarterial chemoembolisation in hepatocellular carcinoma. *J Hepatol*. 2023;79(1):126–140. doi:10.1016/j.jhep.2023.02.032
21. Ngambenjawong C, Gustafson HH, Pun SH. Progress in tumor-associated macrophage (TAM)-targeted therapeutics. *Adv Drug Deliv Rev*. 2017;114:206–221. doi:10.1016/j.addr.2017.04.010
22. Ghebremedhin A, Athavale D, Zhang Y, Yao X, Balch C, Song S. Tumor-associated macrophages as major immunosuppressive cells in the tumor microenvironment. *Cancers*. 2024;16(19):3410. doi:10.3390/cancers16193410
23. Iglesias-Escudero M, Arias-Gonzalez N, Martinez-Caceres E. Regulatory cells and the effect of cancer immunotherapy. *Mol Cancer*. 2023;22(1):26. doi:10.1186/s12943-023-01714-0
24. Li K, Shi H, Zhang B, et al. Myeloid-derived suppressor cells as immunosuppressive regulators and therapeutic targets in cancer. *Signal Transduct Target Ther*. 2021;6(1):362.
25. Pinato DJ, Murray SM, Forner A, et al. Trans-arterial chemoembolization as a loco-regional inducer of immunogenic cell death in hepatocellular carcinoma: implications for immunotherapy. *J Immunother Cancer*. 2021;9(9).
26. 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(1):215–225.
27. Dai E, Zhu Z, Wahed S, Qu Z, Storkus WJ, Guo ZS. Epigenetic modulation of antitumor immunity for improved cancer immunotherapy. *Mol Cancer*. 2021;20(1):171.
28. Knoche SM, Larson AC, Sliker BH, Poelaert BJ, Solheim JC. The role of tumor heterogeneity in immune-tumor interactions. *Cancer Metastasis Rev*. 2021;40(2):377–389.
29. Llovet JM, De Baere T, Kulik L, et al. Locoregional therapies in the era of molecular and immune treatments for hepatocellular carcinoma. *Nat Rev Gastroenterol Hepatol*. 2021;18(5):293–313.
30. Tian Z, Hou X, Liu W, et al. Targeted blocking of CCR2 and CXCR2 improves the efficacy of transarterial chemoembolization of hepatocarcinoma. *Can Cell Inter*. 2022;22(1):362.
31. Tao S, Liang S, Zeng T, Yin D. Epigenetic modification-related mechanisms of hepatocellular carcinoma resistance to immune checkpoint inhibition. *Front Immunol*. 2022;13:1043667.

32. Gong J, Chehrazi-Raffle A, Reddi S, Salgia R. Development of PD-1 and PD-L1 inhibitors as a form of cancer immunotherapy: a comprehensive review of registration trials and future considerations. *J Immunother Cancer*. 2018;6(1):8.
33. Goswami S, Apostolou I, Zhang J, et al. Modulation of EZH2 expression in T cells improves efficacy of anti-CTLA-4 therapy. *J Clin Invest*. 2018;128(9):3813–3818.
34. Lacunza E, Montanaro MA, Salvati A, et al. Small non-coding RNA landscape is modified by GPAT2 silencing in MDA-MB-231 cells. *Oncotarget*. 2018;9(46):28141–28154.
35. Zeng H, Xu Q, Wang J, et al. The effect of anti-PD-1/PD-L1 antibodies combined with VEGF receptor tyrosine kinase inhibitors versus bevacizumab in unresectable hepatocellular carcinoma. *Front Immunol*. 2023;14:1073133.
36. Petrowsky H, Fritsch R, Guckenberger M, De Oliveira ML, Dutkowski P, Clavien PA. Modern therapeutic approaches for the treatment of malignant liver tumours. *Nat Rev Gastroenterol Hepatol*. 2020;17(12):755–772.
37. Geevarghese R, Bodard S, Razakamanantsoa L, et al. Interventional oncology: 2024 update. *Can Assoc Radiol J*. 2024;75(3):658–670.
38. Zhu HD, Li HL, Huang MS, et al. Transarterial chemoembolization with PD-(L)1 inhibitors plus molecular targeted therapies for hepatocellular carcinoma (CHANCE001). *Signal Transduct Target Ther*. 2023;8(1):58.
39. Jin ZC, Zhong BY, Chen JJ, et al. 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(12):8669–8681.
40. Jin ZC, Chen JJ, Zhu XL, et al. 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. *EClin Med*. 2024;72:102622.
41. Rimassa L, Finn RS, Sangro B. Combination immunotherapy for hepatocellular carcinoma. *J Hepatol*. 2023;79(2):506–515.
42. Kloeckner R, Galle PR, Bruix J. Local and regional therapies for hepatocellular carcinoma. *Hepatology*. 2021;73(Suppl 1):137–149.
43. Llovet JM, Vogel A, Madoff DC, et al. Randomized phase 3 LEAP-012 study: transarterial chemoembolization with or without lenvatinib plus pembrolizumab for intermediate-stage hepatocellular carcinoma not amenable to curative treatment. *Cardiovasc Intervent Radiol*. 2022;45 (4):405–412.
44. Brandi N, Renzulli M. The synergistic effect of interventional locoregional treatments and immunotherapy for the treatment of hepatocellular carcinoma. *Int J Mol Sci*. 2023;24(10).
45. Anestopoulos I, Voulgaridou GP, Georgakilas AG, Franco R, Pappa A, Panayiotidis MI. Epigenetic therapy as a novel approach in hepatocellular carcinoma. *Pharmacol Ther*. 2015;145:103–119.
46. Oura K, Morishita A, Tani J, Masaki T. Tumor immune microenvironment and immunosuppressive therapy in hepatocellular carcinoma: a review. *Int J Mol Sci*. 2021;22(11):5801. doi:10.3390/ijms22115801
47. Shen KY, Zhu Y, Xie SZ, Qin LX. Immunosuppressive tumor microenvironment and immunotherapy of hepatocellular carcinoma: current status and prospectives. *J Hematol Oncol*. 2024;17(1):25. doi:10.1186/s13045-024-01549-2
48. Verma M, Srivastava S. Epigenetics in cancer: implications for early detection and prevention. *Lancet Oncol*. 2002;3(12):755–763. doi:10.1016/S1470-2045(02)00932-4
49. Huang ZL, Li W, Chen QF, Wu PH, Shen LJ. Eight key long non-coding RNAs predict hepatitis virus positive hepatocellular carcinoma as prognostic targets. *World J Gastrointest Oncol*. 2019;11(11):983–997. doi:10.4251/wjgo.v11.i11.983
50. Li W, Chen QF, Huang T, Shen L, Huang ZL, Wu P. Profiles of m(6)A RNA methylation regulators for the prognosis of hepatocellular carcinoma. *Oncol Lett*. 2020;19(4):3296–3306. doi:10.3892/ol.2020.11435
51. Li W, Chen QF, Huang T, Wu P, Shen L, Huang ZL. Identification and validation of a prognostic lncRNA signature for hepatocellular carcinoma. *Front Oncol*. 2020;10:780. doi:10.3389/fonc.2020.00780
52. Li W, Kong X, Huang T, Shen L, Wu P, Chen QF. Bioinformatic analysis and in vitro validation of a five-microRNA signature as a prognostic biomarker of hepatocellular carcinoma. *Ann Translat Med*. 2020;8(21):1422. doi:10.21037/atm-20-2509
53. Ratti M, Lampis A, Ghidini M, et al. MicroRNAs (miRNAs) and long non-coding RNAs (lncRNAs) as new tools for cancer therapy: first steps from bench to bedside. *Targeted Oncol*. 2020;15(3):261–278. doi:10.1007/s11523-020-00717-x
54. Braghini MR, Lo Re O, Romito I, et al. Epigenetic remodelling in human hepatocellular carcinoma. *J Exp Clin Cancer Res*. 2022;41(1):107. doi:10.1186/s13046-022-02297-2
55. El-Sayes N, Vito A, Mossman K. Tumor heterogeneity: a great barrier in the age of cancer immunotherapy. *Cancers*. 2021;13(4):806. doi:10.3390/cancers13040806
56. Pe'er D, Ogawa S, Elhanani O, Keren L, Oliver TG, Wedge D. Tumor heterogeneity. *Cancer Cell*. 2021;39(8):1015–1017. doi:10.1016/j.ccell.2021.07.009
57. Chan LK, Tsui YM, Ho DW, Ng IO. Cellular heterogeneity and plasticity in liver cancer. *Semin Cancer Biol*. 2022;82:134–149. doi:10.1016/j.semcancer.2021.02.015
58. Liao C, Liu X, Zhang C, Zhang Q. Tumor hypoxia: from basic knowledge to therapeutic implications. *Semin Cancer Biol*. 2023;88:172–186. doi:10.1016/j.semcancer.2022.12.011
59. Bernauer C, Man YKS, Chisholm JC, Lepicard EY, Robinson SP, Shipley JM. Hypoxia and its therapeutic possibilities in paediatric cancers. *Br J Cancer*. 2021;124(3):539–551. doi:10.1038/s41416-020-01107-w
60. Li C, Wiseman L, Okoh E, et al. Exploring hypoxic biology to improve radiotherapy outcomes. *Expert Rev Mol Med*. 2022; 24:e21.
61. Liu J, Cabral H, Song B, et al. Nanoprobe-based magnetic resonance imaging of hypoxia predicts responses to radiotherapy, immunotherapy, and sensitizing treatments in pancreatic tumors. *ACS Nano*. 2021;15(8):13526–13538. doi:10.1021/acsnano.1c04263
62. Debnath SK, Debnath M, Ghosh A, Srivastava R, Omri A. Targeting tumor hypoxia with nanoparticle-based therapies: challenges, opportunities, and clinical implications. *Pharmaceuticals*. 2024;17(10):1389. doi:10.3390/ph17101389
63. Wang H, Li J, Wang Y, et al. Nanoparticles-mediated reoxygenation strategy relieves tumor hypoxia for enhanced cancer therapy. *J Contr Release*. 2020;319:25–45. doi:10.1016/j.jconrel.2019.12.028
64. Lustberg MB, Kuderer NM, Desai A, Bergerot C, Lyman GH. Mitigating long-term and delayed adverse events associated with cancer treatment: implications for survivorship. *Nat Rev Clin Oncol*. 2023;20(8):527–542. doi:10.1038/s41571-023-00776-9
65. Hung SI, Mockenhaupt M, Blumenthal KG, et al. Severe cutaneous adverse reactions. *Nat Rev Dis Primers*. 2024;10(1):30. doi:10.1038/s41572-024-00514-0

66. Song YG, Yoo JJ, Kim SG, Kim YS. Complications of immunotherapy in advanced hepatocellular carcinoma. *J Liver Cancer*. 2024;24(1):9–16. doi:10.17998/jlc.2023.11.21
67. Marinelli B, Kim E, D'Alessio A, et al. Integrated use of PD-1 inhibition and transarterial chemoembolization for hepatocellular carcinoma: evaluation of safety and efficacy in a retrospective, propensity score-matched study. *J Immunother Cancer*. 2022;10(6):e004205. doi:10.1136/jitc-2021-004205
68. Sumimoto H, Noda S, Koide H, et al. Pre-existing autoimmune disease as a risk factor for immune-related adverse events in cancer patients receiving immune checkpoint inhibitors. *PLoS One*. 2024;19(7):e0306995. doi:10.1371/journal.pone.0306995
69. Costa F, Wiedenmann B, Roderburg C, Mohr R, Abou-Alfa GK. Systemic treatment in patients with Child-Pugh B liver dysfunction and advanced hepatocellular carcinoma. *Cancer Med*. 2023;12(13):13978–13990. doi:10.1002/cam4.6033
70. Pena-Asensio J, Calvo H, Torralba M, Miquel J, Sanz-de-Villalobos E, Larrubia JR. Anti-PD-1/PD-L1 based combination immunotherapy to boost antigen-specific CD8(+) T cell response in hepatocellular carcinoma. *Cancers*. 2021;13(8). doi:10.3390/cancers13081922
71. Kudo M, Han KH, Ye SL, et al. A changing paradigm for the treatment of intermediate-stage hepatocellular carcinoma: Asia-Pacific primary liver cancer expert consensus statements. *Liver Cancer*. 2020;9(3):245–260. doi:10.1159/000507370
72. Cky N, Dazert E, Boldanova T, et al. Integrative proteogenomic characterization of hepatocellular carcinoma across etiologies and stages. *Nat Commun*. 2022;13(1):2436. doi:10.1038/s41467-022-29960-8
73. He M, Liu Y, Chen S, et al. Serum amyloid A promotes glycolysis of neutrophils during PD-1 blockade resistance in hepatocellular carcinoma. *Nat Commun*. 2024;15(1):1754. doi:10.1038/s41467-024-46118-w
74. Yu B, Ma W. Biomarker discovery in hepatocellular carcinoma (HCC) for personalized treatment and enhanced prognosis. *Cytokine Growth Factor Rev*. 2024;79:29–38. doi:10.1016/j.cytogfr.2024.08.006
75. Chen B, Garmire L, Calvisi DF, Chua MS, Kelley RK, Chen X. Harnessing big 'omics' data and AI for drug discovery in hepatocellular carcinoma. *Nat Rev Gastroenterol Hepatol*. 2020;17(4):238–251. doi:10.1038/s41575-019-0240-9
76. Vitale A, Cabibbo G, Iavarone M, et al. Personalised management of patients with hepatocellular carcinoma: a multiparametric therapeutic hierarchy concept. *Lancet Oncol*. 2023;24(7):e312–e322. doi:10.1016/S1470-2045(23)00186-9
77. 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(5):468–480. doi:10.1200/JCO.21.01963
78. Zhou Y, Lauschke VM. Next-generation sequencing in pharmacogenomics - fit for clinical decision support? *Expert Rev Clin Pharmacol*. 2024;17(3):213–223. doi:10.1080/17512433.2024.2307418
79. Chen QF, Lyu N, Wang X, et al. Cost-effectiveness and prognostic model of hepatic arterial infusion chemotherapy for hepatocellular carcinoma with high tumor burden and/or Vp4 tumor thrombus compared with sorafenib: a post-hoc analysis of the FOHAIC-1 trial. *Inter J Surg*. 2023;109(12):3929–3939. doi:10.1097/JS9.0000000000000683
80. Chen QF, Chen S, Yi JZ, et al. Recommended 10-year follow-up strategy for small hepatocellular carcinoma after radiofrequency ablation: a cost-effectiveness evaluation. *Am J Gastroenterol*. 2024;119(10):2052–2060. doi:10.14309/ajg.0000000000002774
81. Chen QF, Jiang XY, Hu Y, et al. Additional hepatic arterial infusion chemotherapy to sorafenib was cost-effective for hepatocellular carcinoma with major portal vein tumor thrombosis. *J Hepatocell Carcinoma*. 2024;11:1473–1479. doi:10.2147/JHC.S470470
82. Chen Q-F, Chen S, Chen M, Lyu N, Zhao M. Improving the conversion success rate of hepatocellular carcinoma: focus on the use of combination therapy with a high objective response rate. *J Clin Transl Hepatol*. 2024;12(3):298–304. doi:10.14218/JCTH.2023.00403
83. Bitar R, Salem R, Finn R, Greten TF, Goldberg SN, Chapiro J. Interventional oncology meets immuno-oncology: combination therapies for hepatocellular carcinoma. *Radiology*. 2024;313(2):e232875. doi:10.1148/radiol.232875