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Combining locoregional and systemic therapies in liver cancer: from strategy to survival

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Hepatocellular carcinoma (HCC) remains a major global health challenge and accounts for the majority of primary liver cancers. Despite remarkable advances in surveillance, surgical techniques, locoregional interventions, and systemic therapies, the prognosis of many patients with HCC remains unsatisfactory because of frequent recurrence, treatment resistance, and the complex interplay between tumor progression and underlying liver disease. These challenges have driven a fundamental transformation in the therapeutic paradigm of HCC, moving beyond single-modality treatment toward multidisciplinary and integrated therapeutic strategies[1].

Historically, locoregional therapies and systemic therapies have developed as relatively independent treatment approaches. Locoregional modalities, including transarterial chemoembolization (TACE), thermal ablation, and selective internal radiation therapy (SIRT) with yttrium-90 (Y-90) microspheres, have primarily focused on achieving local tumor control. In contrast, systemic therapies, particularly immune checkpoint inhibitors (ICIs) and targeted therapies, have aimed to control tumor progression at a systemic level. However, advances in tumor biology have increasingly revealed that these two therapeutic domains are not mutually exclusive. Instead, they may complement each other through modulation of tumor immunity, angiogenesis, and the tumor microenvironment[2].

The concept of combining locoregional and systemic therapies has therefore evolved from empirical clinical practice toward biologically rational treatment strategies. Locoregional therapies can induce tumor necrosis, promote the release of tumor-associated antigens, and reshape the immune microenvironment. Meanwhile, treatment-induced hypoxia, angiogenic activation, and immunosuppressive changes may contribute to tumor recurrence and resistance. Systemic therapies, including immune checkpoint blockade and anti-angiogenic agents, may counteract these adaptive mechanisms and enhance the durability of local treatment effects. The emerging clinical evidence supporting TACE combined with systemic therapies illustrates this transition, while also highlighting unresolved questions regarding patient selection, treatment sequencing, and clinically meaningful endpoints.

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Against this rapidly evolving background, we organized this Special Topic entitled "Combining Locoregional and Systemic Therapies in Liver Cancer: From Strategy to Survival" in *Hepatoma Research*. The purpose of this collection is to provide a comprehensive perspective on how different therapeutic modalities can be integrated to achieve more effective and individualized management of liver cancer. Rather than simply combining available treatments, the ultimate goal of integrated therapy is to determine the optimal therapeutic strategy for each patient based on disease characteristics, biological mechanisms, treatment response, and safety considerations.

A central theme of this Special Topic is the transformation of TACE from a conventional locoregional treatment into an important component of multimodal therapy. TACE remains a cornerstone treatment for intermediate-stage HCC; however, repeated TACE procedures may be associated with reduced therapeutic efficacy and cumulative impairment of liver function. With the emergence of immunotherapy and targeted therapy, treatment strategies are shifting from repeated local tumor control toward early integration of systemic therapy to achieve more durable disease management. The article focusing on the relationship between TACE treatment frequency and prognosis highlights the importance of optimizing TACE intensity, avoiding unnecessary procedures, and adapting treatment strategies in the era of combination therapy.

Beyond TACE, this Special Topic also explores the expanding role of other locoregional modalities in combination strategies. Thermal ablation remains a potentially curative treatment for early-stage HCC, but tumor recurrence after ablation continues to represent an important clinical challenge. The review included in this collection summarizes the biological mechanisms underlying post-ablation recurrence, including autophagy activation, epithelial–mesenchymal transition, hypoxic microenvironment formation, and immune suppression[3]. These findings emphasize that improving local treatment precision and addressing residual or recurrent disease through complementary therapies are essential components of future treatment strategies.

Similarly, Y-90 radioembolization, also known as SIRT, represents an important platform for integrating local radiation delivery with systemic treatment approaches. By selectively delivering high-dose radiation to tumor tissue, SIRT provides effective local control while potentially inducing biological changes that may enhance the efficacy of systemic therapies. Current evidence suggests that combining Y-90 with targeted therapies or immune-based treatments represents a promising direction; however, further investigation is needed to define optimal patient selection, treatment sequencing, dosimetry strategies, and clinical endpoints[4].

An important consideration in the era of combination therapy is that increased therapeutic intensity must be accompanied by improved precision and safety management. As more patients receive locoregional therapy combined with immune-based treatments, identifying individuals at higher risk of treatment-related toxicity becomes increasingly important. In this Special Topic, an original study developed a baseline lymphocyte-subset-based nomogram to predict severe immune-related adverse events in patients receiving TACE plus immunotherapy, highlighting the potential value of biomarkers in guiding individualized treatment decisions[5].

A global perspective is essential when considering the future development of integrated treatment strategies for liver cancer. China carries a substantial proportion of the global burden of HCC, and many patients require multidisciplinary approaches because of advanced disease presentation and complex clinical conditions. In this context, locoregional therapies, particularly TACE, have accumulated extensive clinical

experience and remain central components of HCC management in China. The rapid development of immunotherapy and targeted therapy has further stimulated innovative combination strategies, and clinical studies from China have contributed important evidence regarding treatment optimization, patient selection, and real-world implementation[6,7]. Continued international collaboration will be essential to translate these advances into globally applicable treatment strategies.

The future of liver cancer treatment will likely depend on moving beyond the question of whether locoregional and systemic therapies should be combined, toward determining how they should be integrated. Key priorities include identifying predictive biomarkers, optimizing treatment sequencing and intensity, developing adaptive treatment strategies, and establishing standardized approaches across different healthcare settings. Artificial intelligence, radiomics, molecular profiling, and translational research may further facilitate precision-based combination therapy.

The integration of locoregional and systemic therapies represents a conceptual transformation in HCC management. Local and systemic treatments should no longer be viewed as separate therapeutic categories, but rather as complementary components within an individualized treatment ecosystem. Through multidisciplinary collaboration and continued innovation, integrated treatment strategies may ultimately improve long-term survival and quality of life for patients with liver cancer.

We sincerely thank all authors and reviewers who contributed their expertise to this Special Topic and appreciate the support of the editorial team of *Hepatoma Research*. We hope this collection will stimulate further research and international collaboration toward more effective and personalized therapeutic strategies for patients with liver cancer.

DECLARATIONS

Authors' contributions

The author contributed solely to the article.

Availability of data and materials

Not applicable.

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Not applicable.

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