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Combining local regional therapy and systemic therapy: Expected changes in the treatment landscape of recurrent hepatocellular carcinoma

Liang J *et al.* Local regional therapy and systemic therapy

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Abstract

Improvements in early screening, new diagnostic techniques, and surgical treatment have led to continuous downward trends in hepatocellular carcinoma (HCC) morbidity and mortality rates. However, high recurrence and refractory cancer after hepatectomy remain important factors affecting the long-term prognosis of HCC. The clinical characteristics and prognosis of recurrent HCC are heterogeneous, and guidelines on treatment strategies for recurrent HCC are lacking. Therapies such as surgical resection, radiofrequency ablation, and transhepatic arterial chemoembolization are effective for tumors confined to the liver, and targeted therapy is a very important treatment for unresectable recurrent HCC with systemic metastasis. With the deepening of the understanding of the immune microenvironment of HCC, blocking immune checkpoints to enhance the antitumor immune response has become a new direction for the treatment of HCC. In addition, improvements in the tumor immune microenvironment caused by local treatment may provide an opportunity to improve the therapeutic effect of HCC treatment. Ongoing and future clinical trial data of combined therapy may develop the new treatment scheme for recurrent HCC. This paper reviews the pattern of recurrent HCC and the characteristics of the immune microenvironment, demonstrates the basis for combining local treatment and systemic treatment, and reports current evidence to better understand current progress and future approaches in the treatment of recurrent HCC.

Key Words: Recurrent hepatocellular carcinoma; Local regional therapy; Systemic therapy; Tumor microenvironment; Recurrence type; Immune checkpoint inhibitors

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Core Tip: Hepatocellular carcinoma (HCC) ⁶¹ is a highly recurrent malignancy; at present, there is a lack of definite treatment strategies for recurrent HCC. Recurrent HCC has particularities in recurrence mode and tumor microenvironment, so its treatment strategy should be different from that of primary HCC. Systemic therapy based on the immune microenvironment ⁶¹ has emerged as a potential alternative treatment option for advanced HCC. Combining local therapy and systemic therapy for recurrent HCC may achieve better effects and is worthy of further exploration.

INTRODUCTION

Primary liver cancer is a common digestive system tumor with a high degree of malignancy. According to global epidemiological statistics in 2020, ³⁶ the number of new cases of liver cancer ranks 7th among malignant tumors, and liver cancer-related death ranks 2nd among tumor-related mortality^[1]. ²⁰ Hepatocellular carcinoma (HCC) is the most common primary hepatic malignancy. Surgical resection ⁶³ is the most effective radical treatment method, but the 5-year recurrence rate after surgery ⁵⁴ is as high as 40%-70%^[2-4]. An appropriate treatment plan for patients with recurrent HCC is key to increasing the survival of patients after surgery. Although different regions and societies have developed many guidelines for the treatment of HCC, guidance on treatment strategies for recurrent HCC is lacking due to the heterogeneity of recurrent cancer and the presence of impaired liver function, portal hypertension, and vascular invasion^[5-7]. Developing a suitable treatment plan for recurrent HCC and prolonging the survival time of patients are issues that remain to be studied.

Local regional therapies for intrahepatic tumors, including traditional surgical resection, liver transplantation, ablation therapy, and transhepatic arterial

chemoembolization (TACE), remain the main approaches by which patients can obtain long-term benefits. Systemic therapy refers to antitumor therapies such as molecular targeted drugs, immunotherapy, and chemotherapy and has become an important component of antitumor therapies. Many retrospective studies advocate repeat resection (RR) as the preferred method for the treatment of recurrent HCC. Researchers believe that in the case of limited liver lesions and sufficient reserve function, the safety and effectiveness of RR are similar to those of initial hepatectomy. The 5-year overall survival (OS) rate is 25%-87%^[8-10]. However, due to limited liver reserves after liver resection and the heterogeneity of recurrence patterns, the number of patients who meet the criteria RR in actual clinical practice is limited. Salvage liver transplantation (SLT) is also an effective radical treatment option. Compared with RR, SLT can simultaneously eliminate tumors and radically treat primary liver disease and has a longer survival time^[11,12]. However, due to the shortage of donor organs in some areas and the limited capacity for liver transplantation, SLT implementation is low. Currently, nonsurgical local regional therapies, such as radiofrequency ablation (RFA) and TACE, are common treatments for unresectable recurrent HCC^[13,14]. Due to the success of immune-targeted drugs such as atezolizumab and bevacizumab, combination therapies have been used in the systemic treatment of HCC. These treatments are likely to be a new paradigm for improving the long-term prognosis of recurrent HCC.

This paper aims to review the recurrence pattern of HCC and the changes in the tumor microenvironment; provide updated data on liver-targeted therapy for recurrent HCC, including the application value and status of systemic therapy and combined local therapy in recurrent HCC; and explore treatment strategies for improving the prognosis of recurrent HCC patients.

DIFFERENT RECURRENCE PATTERNS AND CHARACTERISTICS OF RECURRENT HCC

Recurrence of HCC after radical treatment is very common, and the recurrence rate after hepatectomy is approximately 70%. Many scholars have studied the risk factors

for and recurrence patterns of HCC. Male sex, a high degree of fibrosis, HBV load, tumor diameter, and vascular invasion are positively correlated with HCC recurrence^[15-18]. The recurrence pattern of HCC is often divided into early recurrence and late recurrence^[19,20]. Early recurrence is considered to be caused by occult ¹⁸ intrahepatic metastasis of the primary tumor and has a worse prognosis^[21], as it is more likely to be accompanied by extrahepatic metastasis^[22]. In contrast, late recurrence is considered to be HCC of polyclonal origin unrelated to the primary tumor or neoplastic foci, mostly with intrahepatic metastasis. Early recurrence is usually associated with the invasive pathological characteristics of the tumor, such as large tumor size, multiple tumors, poor differentiation and vascular infiltration^[23-26]. The main manifestation of late recurrence is intrahepatic recurrence, and the cause of recurrence is usually related to underlying liver diseases, such as uncontrolled hepatitis, the extent of cirrhosis and HBV replication^[27,28]. Differentiating recurrence patterns is important for monitoring and preventing recurrent HCC and selecting different treatment strategies^[29,30].

Regarding the time limits for early relapse and late recurrence, most studies have considered the time limit for early recurrence to be 2 years after surgery^[2,16,19]. A recent multicenter study used the survival period as the evaluation standard; early recurrence was limited to 8 mo or 6 mo after surgery, which allowed the survival period after recurrence to be better distinguished^[22,31]. However, determining recurrence patterns based on the time of recurrence alone may lead to inaccurate results. Recently, molecular genetic techniques such as microsatellite instability, loss of heterozygosity, and short tandem repeat and next-generation sequencing have been used to analyze the origin of tumor clones to more accurately identify foci origins, recurrence patterns and mechanisms^[30,32]. Intrahepatic metastatic hepatocellular carcinoma (IM-HCC) refers to recurrent tumors derived ⁹ from the same monoclonal cells as the primary tumor. Multicenter ⁹ origin hepatocellular carcinoma (MO-HCC) is caused by polyclonal cancer^[33]. Early and late recurrence suggests IM-HCC and MO-HCC, respectively. In addition, early recurrence is usually diffuse and spreads through the portal venous system, while the prognosis of late recurrence is better. Distinguishing the source of

tumor heterogeneity by cloning techniques explains the low survival associated with early recurrence. Recurrence patterns suggest that the time of HCC recurrence and invasiveness should be considered when choosing a treatment. Although clarifying the clonal origin of recurrent HCC has certain application prospects, its application in clinical practice requires more standardized diagnostic procedures and further technical capabilities^[34].

Liquid biopsy based on biomarkers is being explored as a new approach for monitoring HCC recurrence. The detection of circulating tumor DNA (ctDNA) by gene sequencing is used to detect minimal residual disease and predict the recurrence of HCC earlier and more accurately^[35]. Moreover, comparing the mutations of the driver gene in ctDNA in the blood and in the primary tumor tissue in patients with recurrent HCC may help reveal the heterogeneity of recurrent HCC^[36].

TUMOR MICROENVIRONMENT WITH THE PROGRESSION TO RECURRENCE OF HCC

The liver is rich in a variety of immunocompetent cells, including liver sinusoidal endothelial cells, Kupffer cells, hepatic stellate cells, NK cells, lymphocytes, and dendritic cells^[37]. These immune cells interact with surrounding stromal cells to form a complex immune dynamic network and play important roles in the proliferation, migration, invasion and angiogenesis of HCC^[38]. Immune cell infiltration, fibroblast proliferation, and the induction of angiogenesis in the tumor microenvironment (TME) are closely related to the progression and metastasis of HCC^[39].

The inhibitory environment of immune cells and tumor blood vessels with abnormal structures and functions together constitute the HCC microenvironment, which plays a key role in determining the outcome of HCC, including the risk of recurrence after HCC resection or ablation^[40]. Tumor-infiltrating lymphocytes (TILs) are a representative component of the host antitumor immune response^[41]. CD3⁺, CD4⁺, CD8⁺, and Foxp3⁺ positive T lymphocytes are the most common subpopulations of TILs^[42]. An increase in the number of TILs, especially activated cytotoxic T lymphocytes, is associated with the

prognosis and survival of patients with HCC^[43,44]. Meta-analysis of multiple studies has shown that tumor-infiltrating CD8⁺ positive T cells are a strong prognostic factor for recurrence-free survival in HCC patients after hepatectomy^[45,46]. Nakagawa *et al*^[47] reported that TILs were significantly associated with a high recurrence rate and poor OS in all study patients, including HBV-associated and non-B non-C HCC patients. Most studies have shown that CD3⁺ and CD4⁺ TILs play a protective role in HCC^[46,48,49]. Another study of HCC patients after surgical resection found that high CD3⁺ TIL density in the center and margin of a tumor predicted low recurrence and long-term disease-free survival (DFS)^[50]. Fu *et al*^[51] found that CD4⁺ T-cell dysfunction caused by FoxP3⁺ regulatory T cells was associated with a high recurrence rate in HCC patients.

Additionally, the proportion of TILs in multiple subpopulations is related to tumor activity and has predictive value for HCC recurrence. Mathai *et al*^[52] found that a high postoperative Foxp3⁺/CD8⁺ TIL ratio was associated with poor tumor differentiation, high recurrence, and low OS and DFS in HCC patients.

The infiltration of immunosuppressive cell types [such as myeloid-derived suppressor cells (MDSCs) and regulatory T cells (Tregs)] is also associated with the high recurrence rate of HCC. Tregs facilitate the immune escape of tumor cells by inhibiting the function of antigen-presenting cells and hindering the proliferation or activation of NK cells and effector T cells^[53]. High Treg expression is associated with poor DFS in HCC patients^[54,55]. The proportion of Tregs and cytotoxic T cells is an independent predictor of postoperative recurrence and survival^[56]. MDSCs mediate tumor angiogenesis and exert immunosuppressive effects by inhibiting dendritic cells and NK cells^[57]. A systematic retrospective study showed that the proportion of MDSCs was associated with poor clinical outcomes after HCC resection or local ablation^[58] and was associated with early postoperative recurrence of HCC^[59]. Additionally, some studies have suggested that the inhibitory effect of MDSCs and highly programmed death ligand 1 (PD-L1) inhibitors have a synergistic effect^[60]. The high expression of PD-L1 in

tumor cells or immune cells is associated with highly invasive tumors and is a predictor of recurrence^[61,62].

³⁹ Vascular endothelial growth factor (VEGF) is an important cytokine involved in angiogenesis during tumor proliferation and plays a key role in HCC invasion and recurrence^[63-65]. VEGF accelerates the early recurrence of HCC after radiofrequency by promoting the proliferation of CD133⁺ cancer stem cells^[66]. Additionally, VEGF regulates immunosuppressive cells such as MDSCs and Tregs to promote tumor immune escape^[67,68]. Therefore, we speculate that VEGF-induced immunosuppression ²⁴ plays a key role in the TME of HCC and is also an important driving factor in HCC recurrence.

⁶ The complex interaction between immune cells and effector molecules in the TME of HCC alters immune status and promotes or inhibits the growth of HCC. The recurrence of HCC has been shown to be related to immune characteristics. An in-depth understanding of the TME provides a basis for the exploration of targeted multimodal immunity and targeted therapy.

LIVER-TARGETED LOCAL THERAPY STILL DOMINATES

Traditionally, local regional therapies for HCC are divided into curative and palliative treatments. The former group includes surgery, liver transplantation, RFA, microwave ablation (MWA), and percutaneous ethanol injection, while the latter group includes ⁵⁸ conventional TACE, drug-eluting bead TACE (DEB-TACE), chemotherapy, and radiotherapy. Intrahepatic recurrence is the main type of HCC recurrence; therefore, local treatment for intrahepatic tumors clearly dominates recurrent HCC treatment. RR of recurrent HCC ²⁹ is considered the best treatment option for patients with resectable tumors^[8,69], and high survival rates have been extensively reported in the literature^[70,71]. A recent meta-analysis of RR for recurrent HCC showed that the 5-year OS was 42%-55%, the 5-year DFS was 19%-39%, and ⁵⁹ the 2-year and 5-year OS and DFS were superior to those of RFA^[72]. A randomized controlled study of early recurrent HCC showed that ⁷ there was no significant difference in 5-year OS for patients who received RR or RFA

(43.6% vs 38.5%). However, for tumors with a diameter larger than 3 cm, RR may be associated with a better local disease control rate and longer survival^[73]. For patients with isolated recurrent lesions and adequate liver function, resection remains one of the preferred treatment decisions, and the occurrence of serious complications does not differ from RFA treatment^[74]. When the number of lesions is large or there is vascular invasion, the use of RR is restricted^[75]; additionally, declines in liver function and portal hypertension progression may be related to poor postoperative outcomes, complications, and a high decompensation rate^[76,77]. In clinical practice, only approximately 15%-30% of HCC patients who relapse after initial resection are eligible for RR^[75,78]. The implementation of laparoscopic hepatectomy has reduced the incidence of postoperative complications and the length of the hospital stay^[79], but the survival time remains similar to that of open hepatectomy, with no significant improvement in the overall prognosis of recurrent HCC patients^[80,81].

SLT is considered an effective and curative treatment approach that can simultaneously resolve liver tumors, potential liver dysfunction and the original underlying diseases. For recurrent HCC, as long as patients meet the criteria, the prognosis is relatively high^[11,82,83]; the 5-year survival rate is 42%-73%^[84]. A systematic retrospective analysis of the prognosis of SLT and RR in the treatment of recurrent HCC showed that patients in the SLT group generally had larger liver lesions but better relapse-free survival (RFS) than those in the RR group and that the OS of the two groups was similar^[85]. The main limitation of this treatment technique is the shortage of liver donors and the high level of technical requirements^[86].

Compared with RR and SLT, ablation therapy (including RFA and MWA) is minimally invasive, has a good local control rate and low rate of postoperative liver dysfunction and is a reproducible treatment for recurrent HCC^[70,78]. For early recurrent HCC with small lesions, the 5-year survival rate is 26.7%-64.5%^[8,14,70,87,88]. The 5-year long-term survival of patients with BCLC stage 0/A receiving RFA is comparable to that of patients receiving RR, but the length of the hospital stay is shorter, and there are fewer complications^[88,89]. There is no significant difference in long-term survival

between RFA and TACE treatments in patients with early recurrent HCC (BCLC stage 0/A, diameter < 3 cm)^[90,91]. However, a meta-analysis that included patients with early and mid-stage recurrent HCC showed that the 1-, 3-, and 5-year survival rates were higher for the RFA treatment group than for the TACE treatment group^[92]. The indications for local ablation are limited in terms of the size and number of lesions, and there are also certain requirements for HCC location. If HCC recurs after local ablation, TACE is the most commonly used rescue treatment.

Due to the heterogeneity of recurrent HCC, the options for radical treatment are limited for patients with larger lesions and multicentric lesions. TACE is the most widely used treatment for recurrent HCC, accounting for approximately 60% of patients with recurrent HCC^[93-95]. The indications for TACE include impaired liver function, a large number of tumors, complex location, combined portal vein invasion and contraindications for RR. TACE has always been the main strategy for treating unresectable intrahepatic multiple recurrence with the goal of preserving liver function^[95]. TACE can be used for patients with early recurrent HCC and later-stage HCC. Consequently, the prognosis after treatment varies greatly, but overall, TACE can improve the OS of multifocal tumor patients. A number of studies have shown that the 5-year survival rate after TACE treatment for recurrent HCC is 12-56%^[70,83,84,87,96]. A prospective study showed that for patients with early HCC recurrence, the 5-year survival rate after TACE treatment was 27.7%, which is lower than those for RR and RFA. However, TACE treatment is more suitable for multifocal tumors and early-stage (≤ 1 year) recurrent HCC^[87]. Because TACE embolizes the blood supply artery, it may be more effective for patients with early recurrence due to microvascular invasion (MVI) and tumor remnants^[78,97]. For early recurrent HCC with MVI, TACE combined with RFA treatment results in better survival than surgical resection or RFA alone^[98]. In recent years, DEB-TACE and transarterial radioembolization with yttrium-90-labeled microspheres have been applied to unresectable HCC and have shown a better objective remission rate, disease control rate and survival^[99-102].

As a palliative treatment, TACE can be combined with other treatments and has advantages. A long-term follow-up observation of recurrent HCC with a diameter less than 5 cm showed that the 1-, 3-, and 5-year DFS rates after TACE combined with RFA treatment were 55.1%, 22.5%, and 9.7%, respectively, significantly higher than those after TACE treatment alone (41.1%, 9.9%, and 4.9%)^[103]. A study of DEB-TACE combined with RFA for the treatment of recurrent HCC showed that the 1-, 2-, and 3-year OS rates were 90%, 82.3%, and 66.4%, respectively, percentages that were superior to those after surgical resection and RFA alone^[104]. Compared with using RFA or TACE alone, combining the two methods has demonstrated advantages in the control of early and mid-stage recurrent HCC. In the case of insufficient residual liver reserves after surgical resection, the combination of the two local treatments is effective in the treatment of recurrent HCC^[105,106].

For unresectable HCC, other local liver-directed therapies, including yttrium-90, stereotactic body radiation therapy (SBRT), proton beam therapy (PBT), and hepatic artery infusion chemotherapy (HAIC), have been applied in clinical practice, but there is still a lack of strong evidence to replace traditional treatment methods. Studies have reported on the efficacy of yttrium-90 radiotherapy, SBRT, PBT, and HAIC in recurrent HCC and confirmed that these treatments inhibit the progression of recurrent HCC with few side effects. These methods can be used as new adjuvant treatments^[107-110]. However, more data on the treatment of recurrent intrahepatic HCC are needed.

SYSTEMIC TREATMENT OF RECURRENT HCC SHOULD BE ADVANCED

Before the advent of sorafenib, systemic treatment for HCC was lacking. Sorafenib is the standard first-line drug for the systemic treatment of HCC. Although sorafenib prolongs the survival time of patients with advanced HCC, its objective response rate is low, and side effects lead to poor patient tolerance. In 2017, lenvatinib was approved by the Food and Drug Administration as a first-line treatment for advanced HCC, and regorafenib, cabotinib, and ramucirumab were successively approved as second-line treatments for advanced HCC. With the deepening of the understanding of the immune

microenvironment of HCC, immunotherapy that modulates the immune function of the body to enhance the tumor immune response and block tumor immunosuppression has become a new direction for the treatment of HCC. Among immunotherapy drugs, immune checkpoint inhibitors (ICIs) are the most widely used. However, the efficacy rates of single-agent ICIs in the treatment of HCC are still very low, indicating that it is necessary to use ICIs in combination with other drugs to improve efficacy^[111]. As a tumor with abundant blood vessels, HCC is driven by growth factors such as VEGF. Abnormal angiogenesis contributes to tumor growth and metastasis. Therefore, combining antiangiogenic drugs and ICI therapy may be an ideal strategy to further overcome tumor immunosuppression and to optimize the efficacy of ICI therapy by inducing tumor vascular normalization. High efficacy rates of dual immunotherapy with ICIs plus tyrosine kinase inhibitors (TKIs), ICIs plus VEGF inhibitors, and ICIs combined with anti-cytotoxic T lymphocyte-associated protein 4 have been reported in recent studies of unresectable HCC^[112-114]. The latest NCCN guidelines have been updated^[115], and the IMbrave150 trial has established atezolizumab combined with bevacizumab as a new first-line treatment standard for patients with advanced HCC. This combination has also become the preferred first-line treatment for HCC^[116,117]. Systemic treatment has been shown to be beneficial for the survival of patients with advanced HCC^[114].

The high recurrence rate of early-stage HCC after radical treatment has spurred studies of adjuvant therapy for patients with a high risk of postoperative recurrence^[5,118,119]. Phase III clinical trials of sorafenib as an adjuvant therapy after hepatectomy or ablation have not shown a positive effect on RFS and OS^[120]. Although there is no definitive evidence to confirm the effectiveness of this treatment and it is not recommended in current mainstream treatment guidelines, given the highly invasive characteristics of recurrent HCC, systemic treatment should have value in the early prevention of recurrence^[121,122]. Therefore, many clinical studies are exploring this topic^[26,123].

Early studies found that compared with primary HCC, cell lines derived from recurrent HCC have stem cell-like characteristics and are more susceptible to TIL-mediated recognition and cytotoxicity; therefore, it is beneficial for immunotherapy to target recurrent HCCs with stem cell-like characteristics^[124]. Studies have found that high PD-L1 expression in tumor cells or immune cells is associated with more aggressive tumors and is a predictor of HCC recurrence^[61,62]. Given these immune characteristics, immunotherapy for recurrent HCC can improve the tumor immune environment and shrink tumors by reversing the immunosuppression induced by HCC. Because most clinical studies of systemic treatment exclude HCC patients with a history of treatment, there are few clinical studies on systemic treatment for recurrent HCC, and some of the available clinical evidence is for recurrent HCC after liver transplantation^[125-135]. In these studies, TKIs were mainly used (Table 1); the 1-year survival rate of patients with recurrence after transplantation treated with sorafenib was 63%, and the average time to progression was 5.6 mo. However, increased adverse events should be a concern for the combination of sorafenib with immunosuppressants^[136]. For patients with a history of liver transplantation, ICI treatment should be considered very carefully due to the possibility of transplant rejection^[137]. However, patients with HCC recurrence after hepatectomy are not subject to this limitation.

A retrospective study by Li *et al*^[138] examined 58 patients with early recurrence after hepatectomy and found that the average survival time of patients receiving TKIs combined with programmed cell death protein 1 (PD-1) treatment was 35.8 mo, a significant increase of 17.8 mo compared with the average survival time of patients receiving TKIs alone. He *et al*^[139] reported a patient with residual liver recurrence, multiple pulmonary metastases, and suspected splenic metastasis. After the successive application of sorafenib and regorafenib followed by lenvatinib combined with pembrolizumab treatment, partial remission (PR) was achieved, along with 24 mo of progression-free survival (PFS) and 60 mo of postoperative OS.

29 Systemic therapy has become the standard treatment regimen for advanced HCC. The risk of tumor recurrence is higher for recurrent HCC than for the original tumor^[95]. Therefore, there is a more urgent need for safe and effective drugs to reduce the effect of tumor recurrence on patient survival. The role of systemic therapy can be expanded from an adjuvant therapy to an active treatment strategy.

LOCAL TREATMENT COMBINED WITH SYSTEMIC TREATMENT HAS APPLICATION PROSPECTS IN RECURRENT HCC

Continuous progress in immunizations and targeted drugs have brought breakthroughs in treatment patterns in recent years, including new treatment methods and guidelines and expansion from single choices to multiple choices. The published data for combination therapy show that the combination of local therapy and systemic therapy has a theoretical basis and is technically feasible^[106,140]. Although ICIs show good therapeutic effects, dysfunctional T cells that infiltrate the tumour microenvironment (TME) are one of the reasons for ICI failure^[141], and the ratio of T-cell activity to tumor burden is a key predictor of the clinical efficacy of ICIs^[142,143]. Therefore, reducing the tumor burden by local regional therapy in combination with ICI therapy will better improve patient prognosis, and improvements in the HCC microenvironment due to combination therapy may also improve patient outcomes (Figure 1).

After multiple percutaneous ablation or TACE treatments, many patients experience disease progression and liver function deterioration^[144,145]. Regardless of the treatment strategy, physical performance and the maintenance of residual liver function are prerequisites for cancer treatment^[146]. 6 Combining local regional therapy with systemic therapy at an appropriate time may prolong the survival of patients with recurrent HCC and improve their prognosis. Combined systemic therapy can reduce tumor progression, thereby reducing recurrence and prolonging the interval between local regional therapies to ensure residual liver function. Patients with recurrent HCC who may benefit from combination therapy include: (1) 13 Patients with a high risk of

recurrence after the remission of RR and ablation; (2) patients with progression under TACE; and (3) patients with distant metastasis.

The effect of local treatment on the body may create conditions for improving the efficacy of systemic treatment. TACE causes local hypoxia in tumors, and the expression of hypoxia-responsive genes regulated by hypoxia-inducible factor-1 α triggers the expression of VEGF, leading to angiogenesis, which can promote tumor recurrence and metastasis^[147-149]. Thus, combining VEGF inhibitors with TACE may improve local tumor control by inhibiting hypoxia-induced angiogenesis after TACE. Ablation combined with immunotherapy is also considered a potentially beneficial method. Ablation therapy itself may help activate antigen-specific CD4⁺ and CD8⁺ T cells in HCC patients^[150,151]. Heat-induced tissue necrosis releases tumor antigens and induces the accumulation of inflammatory cytokines [interleukin (IL)-1 β , IL-6, IL-8, and tumour necrosis factor alpha (TNF)] around the necrotic area. Therefore, RFA can increase the sensitivity of HCC cells to immunotherapy^[152-154]. Compared with RFA, cryoablation induces a stronger immune response, including increasing the levels of IL-1, IL-6, NF- κ B, and TNF- α and upregulating the expression of PD-L1/PD-1 in the circulation^[155].

Different local therapies can be combined with systemic therapy successively or simultaneously to obtain strong immune stimulation, slow tumor vascular reconstitution, and increase antitumor efficacy^[156]. In primary HCC, objective response rates (ORRs) and disease control rates (DCRs) of 50.0% and 78.6% were observed in microwave ablation combined with apatinib and carrelizumab in the treatment of advanced hepatocellular carcinoma, respectively^[157]. In a randomized, multicenter prospective study, TACE plus sorafenib in patients with unresectable HCC resulted in longer PFS (25.2 mo *vs* 13.5 mo) than TACE alone^[158]. Real-world evidence showed a higher tumor response with the combination of HAIC, anti-PD-1 antibodies and TKIs in patients with advanced HCC^[159]. These encouraging data contributed to the application of combination therapy in recurrent HCC.

Due to the relatively recent clinical application of immunotherapy, current follow-up studies on combination therapy for recurrent HCC mainly focus on ablation therapy or

interventional therapy combined with TKI drugs, with preliminary results for the effect of combination therapy on relapse and OS^[160-170] (Table 2). A multicenter retrospective study by Wei *et al*^[168] included 211 patients with early postoperative recurrence of HCC with MVI, and the survival rate after RFA combined with sorafenib treatment was significantly better than that after RFA treatment alone. Feng *et al*^[169] evaluated the efficacy of sorafenib combined with RFA in 128 patients with BCLC stage 0-B1 HCC. Among them, 75% of patients had recurrent HCC; the 1-, 2-, and 3-year OS rates after combined treatment were 64.0%, 58.7%, and 50.3%, respectively, which were significantly higher than those after RFA treatment. Mahn *et al*^[170] provided a case report of a 36-year-old patient with HCC recurrence after transplantation. The patient underwent surgery, radiofrequency ablation, and second-line treatment with sorafenib and cabozantinib and achieved a survival time longer than 10 years after tumor recurrence. Although current data on recurrent HCC are limited, many clinical studies of the combination of systemic treatment and local treatment are ongoing (Table 3).

In animal model studies, radiotherapy (including conventional radiotherapy and SBRT) has been shown to enhance the immune response to ICIs and treatment efficacy by upregulating the expression of major histocompatibility complex class I, mediating the release of tumor antigens, and increasing the number of TILs^[171,172]. Oxaliplatin enhanced the efficacy of ICIs in a mouse model of lung cancer by inducing immunogenic cell death and depleting macrophages^[173]. Although these mechanisms have been validated in animal models and HCC models, clinical research data are lacking. However, the combination of the two treatments holds promise for HCC^[174].

CONCLUSION

In summary, there is a lack of guidance for the treatment of recurrent HCC based on the recurrence patterns of recurrent HCC and the characteristics of the TME. The treatment mode and prognosis of recurrent HCC differ from those for the initial diagnosis of HCC. In the era of targeted immunotherapy, surgery and local regional therapy continue to be irreplaceable. However, due to the bimodal distribution of recurrence,

early combined systemic therapy may be the most ideal choice for patients with early recurrence to eliminate or control residual tumor cells. For patients with late recurrence, local regional therapy can be performed first, followed by observation and follow-up. Timely combined systemic treatment should be performed considering the staging and progression risk of HCC. Additionally, an inherent advantage of recurrent HCC is that the tumor pathology obtained in the previous stage can be used to evaluate the accuracy of treatment and predict the effectiveness of systemic treatment. However, many problems with the systemic treatment of recurrent HCC must still be resolved, and not all patients can benefit from it. Systemic treatment has limitations, such as a low response rate and a lack of effective clinical biomarkers. The identification of populations that will benefit from these treatments and development of reliable predictive markers and models are areas that need to be explored. Although combination therapy with local regional therapy and systemic therapy may have good application prospects, further improvements in the safety and effectiveness of combined therapy are needed. The correct timing, dose, and reasonable combinations to maintain residual liver function and achieve better survival need to be established. The above clinical problems need to be further explored through a large number of clinical trials.

Figure Legends

Figure 1 Complementary effects of local therapy combined with systemic therapy in recurrent hepatocellular carcinoma. Local therapies, including surgery, transhepatic arterial chemoembolization (TACE), ablation, hepatic artery infusion chemotherapy (HAIC), stereotactic body radiotherapy (SBRT), are targeted-hepatocellular carcinoma (HCC) to reduce tumor load. Systematic therapy represented by tyrosine kinase inhibitor, vascular endothelial growth factor (VEGF) inhibitor, anti-cytotoxic T lymphocyte-associated protein 4 inhibitor; programmed cell death protein-1/programmed cell death ligand-1 inhibitor is mainly aimed at improving tumor microenvironment. VEGF inhibitor can reduce hypoxia induced angiogenesis after

TACE. Local ablation, HAIC and SBRT can promote or regulate the release of tumor antigens and enhance the response of immunotherapy. The combination of local therapy and systematic therapy is expected to improve the outcome of recurrent HCC. rHCC: Recurrent hepatocellular carcinoma; TACE: Transhepatic arterial chemoembolization; SBRT: Stereotactic body radiotherapy; HAIC: Hepatic artery infusion chemotherapy; TKI: Tyrosine kinase inhibitor; VEGF: Vascular endothelial growth factor; CTLA4: Anti-cytotoxic T lymphocyte-associated protein 4; PD-1: Programmed cell death protein-1; PDL-1: Programmed cell death ligand-1; TME: Tumor microenvironment.

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Table 1 Clinical studies of systemic therapy in recurrent hepatocellular carcinoma after liver transplantation

Ref.	Medication regimen	Study type	Number of patients	OS (mo)	PFS (mo)	1-year OS
Iavarone <i>et al</i> ^[125]	Regorafenib	Retrospective	28	12.9		
Li <i>et al</i> ^[126]	Sorafenib lenvatinib chemotherapy chemotherapy plus bevacizumab pembrolizumab	79%; Retrospective 2.3%; 4.7%; plus 7.0%; 2.3%	41	17.0		
Li <i>et al</i> ^[127]	Sorafenib	Retrospective	10	10.0		
de'Angelis <i>et al</i> ^[128]	Sorafenib	Retrospective	15			60%
Gomez-Martin <i>et al</i> ^[129]	Sorafenib	Retrospective	31	19.3	6.77	
Zavaglia <i>et al</i> ^[130]	Sorafenib	Retrospective	11	5.0		
Stauffer <i>et al</i> ^[131]	Sorafenib	Retrospective	13	7.0		
López Ortega <i>et al</i> ^[132]	Sorafenib	Retrospective	17			62%
Weinmann <i>et al</i> ^[133]	Sorafenib	Retrospective	11	20.1		
Piñero <i>et al</i> ^[134]	Lenvatinib	Case	1	84.0		
Sotiropoulos <i>et al</i> ^[135]	Sorafenib	Retrospective	14	25.0		

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 OS: Overall survival; PFS: Progression-free survival.

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Table 2 Clinical studies of systemic therapy combined with local regional therapy in recurrent hepatocellular carcinoma

Ref.	Interventions	Study type	Disease	Outcome
²⁶ Wang <i>et al</i> [160]	Anti-PD-1 + RFA (<i>n</i> = 40) <i>vs</i> RFA (<i>n</i> = 40)	Retrospective	Recurrent HCC after resection	RFS 39.1 wk <i>vs</i> 19.3 wk, <i>P</i> = 0.002
Gu <i>et al</i> [161]	Apatinib + TACE (<i>n</i> = 40) <i>vs</i> TACE (<i>n</i> = 40)	Prospective	Intrahepatic recurrence after resection	RFS 17.2 m <i>vs</i> 12.5 m, <i>P</i> = 0.041
Peng <i>et al</i> [162]	Sorafenib + TACE (<i>n</i> = 128) <i>vs</i> TACE (132)	Retrospective	³⁷ Intermediate-stage recurrent HCC	²⁷ 5-year OS: 38.9% <i>vs</i> 20.5%, <i>P</i> = 0.01; 5-year PFS, ³⁷ 37.5% <i>vs</i> 18.7%, <i>P</i> = 0.003
Wan <i>et al</i> [163]	Sorafenib + TACE (<i>n</i> = 127) <i>vs</i> TACE (<i>n</i> = 127)	Retrospective	Unresectable recurrent HCC	OS 30.7 m <i>vs</i> 18.2 m, <i>P</i> = 0.003
³² Zhou <i>et al</i> [164]	Sorafenib + RFA (<i>n</i> = 174) <i>vs</i> RFA (<i>n</i> = 174)	Retrospective (multicenter)	³⁰ Recurrent HCC after curative resection	1-, 3-, 5-year OS: 97.7%, 83.7%, 54.7% <i>vs</i> 93.1%, 61.3%, 30.9%, <i>P</i> < 0.001
Guo <i>et al</i> [165]	Camrelizumab + TACE (<i>n</i> = 20) <i>vs</i> TACE (<i>n</i> = 59)	Retrospective	Recurrent HCC after curative resection	ORR 40.0% <i>vs</i> 56.9% NS; PFS 6 m <i>vs</i> 9 m NS
Iwata <i>et al</i> [166]	Sorafenib + HAIC	Case	Recurrent HCC after resection	OS 24 m
Chen <i>et al</i> [167]	Toripalimab + TKI + Radiation (<i>n</i> = 17)	Prospective	Advanced recurrent HCC	1-, 2-year OS: 60%, 24%
Wei <i>et al</i> [168]	Sorafenib + RFA (<i>n</i> = 103) <i>vs</i> RFA (<i>n</i> = 108)	Retrospective (multicenter)	Early-stage recurrent HCC with MVI	⁵² RFS: 17.7 m <i>vs</i> 13.1 m, <i>P</i> < 0.001; OS: 32.0 m <i>vs</i> 25.0 m, <i>P</i> = 0.002
Feng <i>et al</i> [169]	Sorafenib + RFA (<i>n</i> = 48) <i>vs</i> RFA (<i>n</i> = 40)	Retrospective (multicenter)	BCLC Stage 0-B1 recurrent HCC	1-, 2-, 3-, and 4-year OS: 85.6%, 64.0%, 58.7%, 50.3% <i>vs</i> 80.7%, 47.2%, 30.9%, 30.9%, <i>P</i> = 0.036
Mahn <i>et al</i> [170]	Resection, RFA; Sorafenib, Cabozantinib	Case	Recurrent HCC after LT	OS longer than 10 years

HAIC: Hepatic artery infusion chemotherapy; ²⁷HCC: Hepatocellular carcinoma; LT: Liver transplantation; MVI: Microvascular invasion; NS: Not significant; ²⁸ORR: Objective response rates; OS: Overall survival; PD-1: Programmed death-1; PFS: Progression-free survival; ²¹RFA: Radiofrequency ablation; RFS: Relapse-free survival; TACE: Transhepatic arterial chemoembolization; TKI: Tyrosine kinase inhibitor.

Table 3 Ongoing clinical trials investigating systemic therapy and/or local regional therapy against hepatocellular carcinoma

Clinical trials number	Study type	Agent(s)	Local regional therapy	Estimated enrollment	Primary endpoint
chiCTR2100044057	Phase II	Camrelizumab + Bevacizumab	Microwave Ablation	30	PFS
chiCTR2100046533	Prospective	Apatinib + Camrelizumab	TACE	37	PFS
NCT05162898	Prospective	Toripalimab + Lenvatinib	Radiofrequency Ablation	90	PFS
NCT05010434	Phase II	Sintilimab + Bevacizumab	Radiofrequency Ablation		ORR
NCT05444478	Prospective	Lenavatinib	Microwave Ablation	274	3-year PFS%
NCT05277675	Prospective	Tislelizumab/Sintilimab +Lenvatinib/Bevacizumab	Radiofrequency Ablation	160	1-year PFS%
NCT05162898	Prospective	Toripalimab + Lenvatinib	Radiofrequency	90	RFS

			Ablation		
NCT04663035	Phase II	Tislelizumab	Ablation	120	1-year PFS%
NCT05355155	Phase II	Bevacizumab + Biosimilar IBI305	-	15	ORR
NCT05103904	Phase II	Lenvatinib	-	19	ORR
NCT04615143	Prospective	Tislelizumab/Tislelizumab	+	80	PFS
		Levatinib			
NCT04564313	Phase I	Camrelizumab	-	20	ORR
NCT04237740	Phase III	Relenvatinib	-	40	3-year PFS%
NCT04204850	Phase II	Cabozantinib		20	DCR

21

DCR: Disease control rates; ORR: Objective response rates; PFS: Progression-free survival; RFA: Radiofrequency ablation; RFS: Relapse-free survival; TACE: Transhepatic arterial chemoembolization.

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