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## **Advances in postoperative adjuvant therapy for primary liver cancer**

Zeng ZM *et al.* Advances in postoperative adjuvant therapy for PLC

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### **Abstract**

Hepatocellular carcinoma (HCC) is a highly heterogeneous, invasive, and conventional chemotherapy-insensitive tumor with unique biological characteristics. The main methods for the radical treatment of HCC are surgical resection or liver transplantation. However, recurrence rates are as high as 50% and 70% at three and five years after liver resection, respectively, and even in Milan-eligible recipients, the recurrence rate is approximately 20% at five years after liver transplantation. Therefore, reducing the postoperative recurrence rate is the key to improving the overall outcome of liver cancer. This review discusses the risk factors for recurrence in patients with HCC radical surgical resection and adjuvant treatment options that may reduce the risk of recurrence and improve overall survival, including local adjuvant therapy (*e.g.*, transcatheter arterial chemoembolization), adjuvant systemic therapy (*e.g.*, molecular targeted agents and immunotherapy), and other adjuvant therapies (*e.g.*, antiviral and herbal therapy). Finally, potential research directions that may change the paradigm of adjuvant therapy for HCC are analyzed.

**Key Words:** Adjuvant therapy; Liver cancer; Immunotherapy; Chemotherapy; Targeted therapy

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**Core Tip:** This review discusses the risk factors for recurrence in patients with hepatocellular carcinoma (HCC) radical surgical resection and adjuvant treatment options that may reduce the risk of recurrence and improve overall survival, including local adjuvant therapy (e.g., transcatheter arterial chemoembolization), adjuvant systemic therapy (e.g., molecular targeted agents), and other adjuvant therapies (e.g., antiviral and herbal therapy). Finally, potential research directions that may change the paradigm of adjuvant therapy for HCC are analyzed.

## <sup>21</sup> INTRODUCTION

Primary liver cancer (PLC) is one of the most common malignancies worldwide. According to the Global Cancer Data (GLOBOCAN) 2020, <sup>16</sup> the annual number of new cases of liver cancer reached 905677 worldwide, ranking 7<sup>th</sup> in malignant tumors, whereas the annual number of deaths caused by PLC was 830180, ranking 2<sup>nd</sup> in malignant tumors<sup>[1]</sup>. Approximately 50% of the cases of global liver cancer occur in China, and data released by the National Cancer Center in 2021 showed that liver cancer has become the 4<sup>th</sup> most common malignant tumor in China, and its mortality rate ranks 2<sup>nd</sup>, with a ratio of incidence to mortality rates reaching 1:0.8<sup>[2]</sup>, which seriously threatens the life and health of the population. The predominant histological type of PLC is the hepatocellular carcinoma (HCC), which accounts for approximately <sup>1</sup> 85% to 90% of the cases. HCC often occurs in the setting of chronic liver disease with or without cirrhosis, and the most common etiologies are chronic hepatitis B virus (HBV) and hepatitis C virus (HCV) infection, alcohol intake, and aflatoxin exposure. Growing

evidence suggests that nonalcoholic fatty liver disease especially nonalcoholic steatohepatitis-related cirrhosis is associated with the development of HCC and represents an increasingly common risk factor for HCC in Western countries<sup>[3-6]</sup>. Cirrhosis is a crucial risk factor for HCC, and long-term follow-up studies have found that approximately 1% to 8% of patients with cirrhosis develop HCC each year<sup>[7]</sup>. As a result, HCC treatment faces two simultaneous challenges: the malignancy itself and the underlying liver disease, which not only increases the difficulty of the treatment but also increases the risk of tumor recurrence or new cancer. The main curative methods for the long-term survival of patients with HCC include surgical resection, liver transplantation, and radiofrequency ablation. However, the lack of liver transplant donors, the high cost of the procedure, and the small scope of radiofrequency ablation have limited their clinical application. Therefore, the current radical treatment for HCC is mainly hepatectomy. However, the 5-year recurrence rate after hepatectomy in patients with HCC eligible for surgical resection is as high as 70%<sup>[8,9]</sup>, and even if they receive liver transplantation, the 5-year recurrence rate in recipients who meet the Milan criteria can reach approximately 20%<sup>[10]</sup>. HCC recurrence seriously affects the long-term outcome and quality of life of patients after surgery. Therefore, reducing the postoperative recurrence rate is the key to improving the overall outcome of HCC<sup>[11]</sup>.

### **RISK FACTORS AFFECTING RECURRENCE OF LIVER CANCER AFTER SURGERY**

It is currently accepted that HCC recurrence may originate from intrahepatic metastases or from *de novo* development of tumors. The clinical pattern of postoperative recurrence is usually divided into early and distant recurrences. Early recurrence refers to the one that occurs within two years after the initial treatment and is of monocentric origin (also called monoclonal origin), *i.e.*, tumors arising from occult micrometastases of the primary tumor or residual microscopic cancer foci *in situ* at the site of postoperative resection<sup>[12]</sup>. These recurrences, which are usually associated with invasive tumor characteristics, are considered true recurrences accounting for approximately 70% or



more of the total. In contrast, the distant recurrence is defined as the one that appears two years after the initial treatment and is multicentric in occurrence (also known as polyclonal in origin), *i.e.*, *de novo* tumors induced by the oncogenic microenvironment of the diseased liver associated with hepatic inflammation or cirrhosis<sup>[13]</sup>. Studies have shown that independent risk factors associated with early recurrence are mainly related to the initial characteristics of the tumor and surgical variables, including large tumor size (> 5 cm in diameter), multiple nodes (two or more tumor nodes), macrovascular/microvascular invasion, non-anatomic liver resection, satellite nodes, cut margins < 1 cm, high preoperative HBV-DNA load and serum alpha fetoprotein (AFP) > 400 µg/L<sup>[14-16]</sup>. Studies have shown that in addition to high viral load and progression of cirrhosis, factors such as the tumor size, microvascular invasion, and no/irregular postoperative antiviral therapy are also associated with distant recurrence<sup>[14-17]</sup>. Factors affecting the recurrence of liver cancer after liver transplantation mainly include preoperative factors, such as the selection criteria for the recipients of liver transplants (Milan criteria, UCSF criteria that exceeds Milan criteria, Hangzhou criteria that exceeds Milan criteria and introduces biological characteristics); preoperative descending therapy and biomarkers; and intraoperative factors, such as surgical operation, bleeding volume, time of ischemia of the donor liver, postoperative immunosuppressive regimen, and systemic treatment regimen in three areas<sup>[18]</sup>.

It is not difficult to find a recurrence of HCC after surgery in relation to the tumor biology, medical history, and viral infection. Therefore, individualized adjuvant treatment strategies based on risk factors for recurrence should be the most effective ones. At this stage, there is no accepted postoperative adjuvant treatment option for HCC, but recent clinical studies have provided new approaches to improve the prognosis of the disease. This article reviews the current research on postoperative adjuvant therapy for HCC and discusses possible directions for future adjuvant therapy research.

## **ADJUNCTIVE LOCAL TREATMENT**

## POSTOPERATIVE ADJUVANT TRANSCATHETER ARTERIAL CHEMOEMBOLIZATION

The blood supply to normal liver tissue is 20% to 25% from the hepatic artery and 70% to 75% from the portal vein, whereas 95% to 99% of the blood supply to HCC tissue originates from the hepatic artery. Transcatheter arterial chemoembolization (TACE) is a mixture of an embolic agent and chemotherapeutic drugs injected precisely into the lesion through the branch of tumor blood supply artery to achieve embolization of the tumor neovascularization, induce ischemia, hypoxia, and necrosis of the tumor tissue, and achieve the purpose of killing the tumor through the cytotoxic effect of chemotherapeutic drugs. TACE is widely used for locally progressive HCC that is not suitable for surgical resection or liver transplantation. However, the results available are inconsistent in their conclusions regarding the benefits of adjuvant TACE therapy after hepatectomy. The conclusions of several successive Asian randomized controlled trials (RCTs) starting in 1994, support postoperative adjuvant TACE therapy to reduce recurrence rates and/or improve overall survival (OS) in patients at moderate to high risk of recurrence; in addition, the therapy is well tolerated by patients<sup>[19-23]</sup>. These results were confirmed by two recently published RCTs. Wang *et al*<sup>[24]</sup> reported a randomized, open-label, single-center phase III RCT that included 280 patients with HBV-related HCC at moderate to high risk of recurrence (single tumor diameter > 5 cm without large vessel invasion, single tumor with large vessel invasion, or 2-3 tumors), in which patients were randomly assigned to either the TACE or the observation groups after radical hepatectomy. Patients in the TACE group have a significantly lower recurrence rate and significantly longer recurrence-free survival (RFS) and OS compared to those of the observation group<sup>[24]</sup>. In another randomized, open-label, single-center phase III study including 250 cases Wei *et al*<sup>[25]</sup> randomly assigned 1:1 patients with HCC and tumor diameter > 5 cm with microvascular invasion (MVI) to either the adjuvant TACE or the non-adjuvant treatment groups. The results show a median disease-free survival (DFS) of 17.45 mo in the TACE group compared with 9.27 mo in the control group (HR = 0.70, *P* = 0.020)<sup>[25]</sup>. Qi *et al*<sup>[26]</sup> reported a prospective

clinical study in which 200 patients with postoperative pathologically MVI-positive HCC were divided into adjuvant TACE and control groups and results show that TACE improves the prognosis of the disease, especially in patients with tumors > 5 cm in diameter or multinodular tumors. Several large single-center retrospective studies<sup>[27-31]</sup> found that postoperative adjuvant TACE therapy prolongs OS and DFS/RFS in patients with high-risk recurrence factors, such as MVI positivity, tumor diameter > 5 cm, poorly differentiated pairs, and multiple tumors. Concerning safety, the adjuvant TACE treatment is generally well tolerated, although it increases the incidence of adverse events.

In patients at low risk of recurrence, a retrospective study<sup>[32]</sup> including 180 patients with hepatectomized HCC reported that the median progression-free survival of patients treated with TACE after surgery is 52.0 mo compared to 11.1 mo in the surgery-only group, and the median OS of 90.7 mo in the TACE group is significantly longer than that of 54.4 mo in the surgery-only group, suggesting that prophylactic interventions are equally effective in reducing recurrence in patients at low risk of recurrence, and that the results of this study may be related to the rigorous screening of TACE-treated patients. In addition, a meta-analysis and systematic review of randomized studies of the adjuvant TACE therapy suggest that patients with low-risk recurrent HCC do not seem to benefit from the adjuvant therapy<sup>[33]</sup>. However, patients with high-risk recurrence of HCC (including tumor diameter > 5 cm, combined vascular invasion, multiple tumors or satellite lesions, and the presence of residual lesions) undergo hepatic resection followed by hepatic artery intervention as adjuvant therapy based on standardized antiviral and hepatoprotective therapy, which may reduce the postoperative recurrence rate and improve DFS/RFS and OS<sup>[34,35]</sup>. Huang *et al*<sup>[36]</sup> developed a scoring system based on data from 1150 patients with HCC who underwent hepatectomy between 2002 and 2008 to test the efficacy of the TACE adjuvant therapy. This system uses multivariate analysis to identify tumor diameter, multiple tumors, presence of MVI, incomplete tumor envelope, and surgical margins as independent risk factors for OS. The weighted sum method was used to develop the

scoring system to predict OS: MVI (present = 3, absent = 0) + envelope (incomplete = 2, complete = 0) + tumor diameter (< 5 cm = 4, 3-5 cm = 2, ≤ 3 cm = 0) + number of tumors (multiple = 1, single = 0) + surgical margin (≤ 1 cm = 1, > 1 cm = 0). Patients were divided into three prognostic subgroups based on scores of 0-5, 6-9, and 10, with better, intermediate, and worse survival outcomes, respectively. Moreover, through validation with data from 379 surgical patients between 2008 and 2010, the results showed that the adjuvant TACE treatment improves OS in patients with a score ≥ 10 and observation groups with 1-, 3-, and 5-years OS rates of 63.9%, 22.6%, and 9.0% *vs* 33.8%, 5.6%, and 2.8%, respectively ( $P = 0.001$ ), suggesting that this scoring system has good discriminatory validity for screening the population for adjuvant TACE therapy<sup>[36]</sup>. In summary, adjuvant TACE is safe and effective in Asian patients with HCC at high risk of recurrence and may be an effective treatment to prevent tumor recurrence and metastasis after surgical resection of early to mid-stage hepatocellular carcinoma. However, there are different reports on the population, treatment protocol, timing, and course of adjuvant TACE that deserve in-depth clinical exploration.

#### **POSTOPERATIVE ADJUVANT HEPATIC ARTERY OR PORTAL VEIN INFUSION CHEMOTHERAPY**

Hepatic arterial infusion chemotherapy (HAIC) and portal vein infusion chemotherapy (PVC) are considered to have higher drug concentration and lower systemic toxicity than those of the standard systemic chemotherapy. HAIC and PVC have been reported less frequently in the postoperative adjuvant treatment of HCC. The results of a retrospective study including 85 patients in China showed that the 5-year RFS is significantly better in the postoperative adjuvant HAIC group (5-fluorouracil, oxaliplatin, and mitomycin combination regimen) than in the non-chemotherapy group<sup>[37]</sup>. In addition, for patients with HCC with combined portal vein tumor thrombosis (PVTT), a retrospective study showed that the median time to recurrence (TTR) and OS are significantly longer in the postoperative adjuvant PVC group ( $n = 67$ ) than in the control group, and the cumulative recurrence rate is significantly lower in

the PVC group compared to that of the control group<sup>[38]</sup>. Hamada *et al*<sup>[39]</sup> reported that DFS and OS are higher in patients with HCC with combined portal infiltration treated with adjuvant HAIC than those in patients without HAIC. For patients with multiple tumors combined with MVI, Hsiao *et al*<sup>[40]</sup> reported higher OS in the HAIC group than that in the surgery alone group. A meta-analysis based on 11 retrospective cohort studies showed that adjuvant HAIC after surgical resection improves OS and DFS compared to surgical treatment alone<sup>[41]</sup>. Li *et al*<sup>[42]</sup> reported a prospective, open-label, phase III, randomized controlled trial that included 127 patients and results showed that the postoperative transarterial infusion chemotherapy (FOLFOX regimen) as adjuvant therapy in patients with HCC with MVI prolong OS and DFS compared to those of the postoperative observation group. However, more patients need to be included in prospective randomized controlled clinical trials and long-term follow-up to confirm this result.

## **POSTOPERATIVE ADJUVANT RADIATION THERAPY**

### ***Postoperative adjuvant external radiation therapy***

Radiation therapy (RT) is an important tool in oncology treatment, and there is limited information about postoperative radiotherapy as an adjuvant treatment after surgical resection of HCC. Studies have shown that three-dimensional conformal RT may have some application in the anti-recurrence of HCC after surgery. For central HCC, it is often difficult to obtain adequate resection margins. A prospective randomized study enrolling 119 patients with centrally located HCC who underwent narrow margin hepatectomy <sup>6</sup> found that adjuvant radiotherapy for centrally located HCC does not improve RFS and OS; the subgroup analysis <sup>6</sup> showed that RFS is significantly longer in the adjuvant radiotherapy group than that in the control group in the subgroup of patients with small HCC (< 5 cm)<sup>[43]</sup>. Another prospective randomized controlled study provides an update of 10-year real-world evidence exploring the feasibility and efficacy of adjuvant radiotherapy after narrow margin hepatectomy (< 1 cm) for central HCC. The results show no significant difference in RFS between the adjuvant radiotherapy



and the control groups, while RFS is significantly longer in patients with small HCC (5 cm) and OS is significantly improved in patients with small HCC compared to those of the control group 2-5 years after treatment<sup>[44]</sup>. In contrast, Wang *et al*<sup>[45]</sup> showed that in patients with HCC close to large vessels, the postoperative adjuvant radiotherapy has better OS and DFS in patients with narrow margins (< 1 cm) than those in the non-radiotherapy group. A single-arm prospective phase II trial enrolled 76 eligible patients who underwent narrow margin resection and received adjuvant radiotherapy, and showed a 3-year OS and DFS of 88.2% and 68.1%, respectively, and a 5-year OS and DFS of 72.2% and 51.6%, respectively. Intrahepatic recurrence is the predominant form, with no marginal recurrence observed<sup>[46]</sup>. In patients with positive MVI, the study showed that the postoperative adjuvant radiotherapy group has significantly better RFS and OS than those of the TACE and unadjuvanted groups in patients with HCC combined with MVI<sup>[47]</sup>. A study of patients with MVI combined with narrow margin HCC showed that postoperative radiotherapy is significantly superior to controls, regardless of the degree of MVI staging<sup>[48]</sup>. Sun *et al*<sup>[49]</sup> reported an RCT in which the postoperative radiotherapy significantly prolongs DFS and OS in patients with combined PVTT HCC, with 1-, 2-, and 3-year DFS rates (radiotherapy group: 86.2%, 70.5%, and 63.4%; control group: 46.4%, 36.1%, and 36.1%,  $P = 0.006$ ) and OS rates (radiotherapy group: 96.6%, 80.7%, and 80.7%; control group: 79.7%, 58.3%, and 50.0%,  $P = 0.004$ ), which are significantly higher than those in the observation group. Therefore, intensity-modulated radiotherapy after hepatectomy in patients with narrow margins, combined MVI, or PVTT may be a favorable treatment approach.

### ***Postoperative adjuvant internal radiation therapy***

Currently, the commonly used routes for internal radiation therapy include the hepatic artery infusion and local modality particle implantation. Lau *et al*<sup>[50]</sup> first proposed the use of intra-arterial iodine-131 (131I)-labeled iodine oil after hepatectomy as adjuvant therapy for HCC, and in this prospective randomized trial, DFS and OS are significantly better in patients with a postoperative intra-arterial infusion of 131I-iodine oil than in

patients with hepatectomy alone. An RCT included 43 patients with radical resection of HCC, 21 of whom received postoperative iodine-131 particulate hepatic artery infusion and 22 did not receive the treatment, and showed that intra-arterial adjuvant 131I-iodine oil significantly improves long-term DFS and OS for up to seven years<sup>[51]</sup>. Subsequently, several non-randomized studies also confirmed that adjuvant 131I-iodine oil after HCC resection improves DFS and OS after hepatectomy<sup>[52-54]</sup>. However, a multicenter RCT involving 103 patients showed that the adjuvant 131I-iodine oil treatment does not improve RFS and OS<sup>[55]</sup>. Another retrospective study with the largest sample to date showed no significant survival improvement with the 131I-iodine oil adjuvant therapy<sup>[56]</sup>. The results of the meta-analysis showed that intra-arterial instillation of 131I-iodine oil after hepatectomy significantly reduce the risk of HCC recurrence and improve DFS and OS<sup>[57,58]</sup>, but it still needs to be confirmed by multicenter large sample RCTs. A recent multicenter RCT included 156 patients with HCC with positive HAb18G/CD147 antigen expression in HCC tissues who underwent radical resection and showed that the hepatic artery infusion of iodine-131-labeled HAb18G/CD147 monoclonal antibody (methotrexate monoclonal antibody) significantly improves 5-year RFS in patients with CD147-expressing tumors after hepatectomy and is well tolerated by patients; a subgroup analysis showed that the main effective targets are high-risk recurrent patients with MVI-positive, tumor diameter > 5 cm, poorly differentiated tumors, and incomplete tumor envelope<sup>[59]</sup>. In addition, the intraoperative implantation of iodine-125 particles in the hepatectomy wound has been performed in some units in China, and the RCT showed that 125I brachytherapy significantly prolongs TTR and OS in patients with HCC who underwent radical resection<sup>[60]</sup>.

## **ADJUNCTIVE SYSTEM THERAPY**

### **POSTOPERATIVE ADJUVANT TARGETED THERAPY**

Sorafenib monotherapy is used as a standard treatment option for advanced HCC, while its effectiveness in postoperative adjuvant therapy has been unsatisfactory. The



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STORM trial, a randomized, double-blind, placebo-controlled phase III clinical study of sorafenib as adjuvant therapy for patients with HCC, enrolled 1114 patients treated with surgical resection or local ablation for limited HCC. Patients were randomly assigned to either the sorafenib treatment or the placebo groups<sup>[61]</sup>, which showed no statistical difference in RFS between the two groups (33.3 mo vs 33.7 mo,  $P = 0.26$ ).<sup>15</sup> Conversely, the sorafenib treatment increases adverse effects. The failure of the STORM study may be due to a deficiency in effectively selecting patients at high risk of recurrence. A meta-analysis of data from five studies with 296 participants<sup>[62]</sup> reported results consistent with the STORM trial. However, several retrospective studies have shown the efficacy of the adjuvant therapy with sorafenib after hepatectomy to prevent recurrence and metastasis in patients with HCC with high-risk recurrence factors. In a phase II clinical trial of 31 patients with HCC with high-risk recurrence factors after radical resection, 14 patients who received sorafenib adjuvant have a longer time to recurrence (21.45 mo  $\pm$  1.98 mo in the sorafenib group vs 13.44 mo  $\pm$  2.66 mo in the control group,  $P = 0.006$ ), and the recurrence rate is significantly lower in the sorafenib-treated than in the control group (29.4% vs 70.7%,  $P = 0.032$ )<sup>[63]</sup>. Li *et al*<sup>[64]</sup> showed that patients treated with sorafenib within 30 d after surgery have seven months longer tumor-free survival than those treated with surgery only, with safe and manageable side effects. A retrospective analysis found that the treatment with the adjuvant sorafenib is beneficial for patients with postoperative high-risk recurrence HCC. Wang *et al*<sup>[65]</sup> retrospectively collected data from 209 patients with intermediate to advanced HCC at high risk of recurrence after hepatectomy at 15 study centers in China and showed that the 1-year survival rate is significantly higher in the sorafenib group than in the control group.<sup>9</sup> Another retrospective study including 728 patients with HCC after R0 resection but with MVI-positive surgical specimens showed that for patients with HCC with combined MVI, patients in the adjuvant sorafenib group have significantly better OS and RFS than those of the surgery alone group<sup>[66]</sup>. Several novel targeted therapeutics have been successful in phase III studies in advanced HCC, including first-line treatment with lenvatinib, second-line treatment with regorafenib, ramucirumab

(for AFP > 400 ng/mL HCC), and cabozantinib. There has been some progress in the adjuvant treatment with novel targeted drugs. A single-center, open-label, single-arm, phase II study of apatinib for postoperative adjuvant treatment of HCC combined with PVTT showed that patients with HCC after radical hepatectomy have 1-year RFS 36.1%, 1-year OS 93.3%, median RFS, 7.6 mo; therefore, the results obtained are better than previous historical ones in terms of the median RFS<sup>[64]</sup>. Moreover, the apatinib is tolerated by most of the patients, which is significant for patients with HCC in combination with PVTT. The American Society for Clinical Oncology reported in 2020 the interim results from a multicenter, prospective cohort study of 90 patients with HCC at high risk of recurrence after surgery, treated with lenvatinib combined with TACE for the adjuvant treatment, and showed that the median DFS is significantly longer in the lenvatinib combined with TACE group than that in the TACE alone group (12.0 mo *vs* 8.0 mo; HR 0.5,  $P = 0.0359$ )<sup>[67]</sup>. These results show the effectiveness of new targeted drugs, such as apatinib and lenvatinib, in reducing the risk of recurrence after HCC surgery, and that a combination therapy may be a more optimal treatment modality.

Liver transplantation is an effective curative tool for HCC. For patients beyond Milan criteria, the risk of recurrence after transplantation is significantly increased, and the need to receive adjuvant therapy with targeted drugs has not been supported by high-level medical evidence. Teng *et al*<sup>[68]</sup> reported a case-control study dividing 17 patients with beyond Milan criteria for HCC after liver transplantation into three groups: the adjuvant group ( $n = 5$ ) was given adjuvant sorafenib starting within six weeks postoperatively, the palliative group ( $n = 6$ ) was given sorafenib after the development of recurrent metastases postoperatively, and the control group ( $n = 6$ ) was not given sorafenib. The results showed that RFS at 6, 12, and 18 mo is better in the adjuvant group than in the palliative care and control groups ( $P$  values for each group are 0.034, 0.026, and 0.011, respectively), and OS at 24 mo of follow-up show the same trend ( $P = 0.031$ ). Shetty *et al*<sup>[69]</sup> found a reduction in the overall recurrence rate of HCC in the adjuvant sorafenib treatment group (seven patients) compared to 12 historical control

patients (29% *vs* 75%,  $P = 0.07$ ). Huang *et al*<sup>[70]</sup> divided 30 patients with HCC after beyond Milan criteria liver transplantation into two groups of 15 patients each. The test group was given sorafenib orally and the control group was given capecitabine orally, and the drug was discontinued in both groups who did not show recurrence 18 mo after surgery. The results showed that the 1-year recurrence rate is significantly lower in the test group compared to the control group (53.3% *vs* 86.6%,  $P < 0.05$ ) and the OS is significantly longer [(28.3  $\pm$  2.5) mo *vs* (17.9  $\pm$  3.5) mo,  $P < 0.05$ ]. Han *et al*<sup>[71]</sup> retrospectively analyzed 23 patients at high risk of recurrence who underwent liver transplantation, including 14 in the adjuvant lenvatinib group and 9 in the control group, and showed that the median DFS in the adjuvant lenvatinib group is 291 (95%CI 204 to 516) days, which is significantly longer than that in the control group of 182 (95%CI 56 to 537) days ( $P = 0.04$ ); the drug safety and patient tolerability are acceptable.

The aforementioned studies were all single-center, small-sample clinical explorations, and although the credibility of the results is limited, the survival benefit of the adjuvant therapy with targeted agents was observed in patients who received liver transplantation either by radical surgery or by beyond Milan criteria. Further confirmation is urgently needed in prospective, multicenter, randomized controlled phase III studies.

## **POSTOPERATIVE ADJUVANT IMMUNOTHERAPY**

The liver is a natural immune-tolerant organ, shielded from autoimmune damage and thus creating a microenvironment of autoimmune tolerance<sup>[72]</sup>, but also favoring immune escape of HCC cells<sup>[73]</sup>. The current immunotherapy for HCC mainly includes tumor pericyte therapy as well as immune checkpoint inhibitor therapy.

### ***Tumor relay cellular immunotherapy***

Cytokine-induced killer cells have shown promising applications in the overt immunotherapy of HCC. An RCT<sup>[74]</sup> on the application of secondary immunotherapy after surgery for hepatocellular liver cancer showed that secondary immunotherapy

reduce the risk of recurrence by 41% compared with that of the control group, and RFS and disease-specific survival are significantly better in the immunotherapy group than in the control group, but the difference in OS between the two groups is not statistically significant. A large phase III RCT<sup>[75]</sup> randomized 230 patients with HCC treated with surgical resection and ablation into an autologous cytokine-induced killer (CIK) cells infusion group and an observation group. The results showed that adjuvant immunotherapy not only extends the median RFS time from 30 to 44 mo, but also reduces the overall risk of death, and has mild toxic effects. A median follow-up of 68.5 mo showed a significant 33% reduction in the risk of recurrence or death in the immunization group ( $P = 0.009$ )<sup>[76]</sup>. A single-center, phase III, open-label RCT that included 200 patients with BCLC stage A or B HCC treated with radical hepatectomy showed that adjuvant CIK therapy is safe and effective in prolonging the median TTR in patients with radical resected HCC, but does not improve patient DFS and OS<sup>[77]</sup>. A meta-analysis that included eight RCTs and two cohort studies containing 2120 patients showed that patients with HCC treated with adjuvant overt immunotherapy have significantly lower recurrence rates at 1, 3, and 5 years than those of the surgical treatment alone group<sup>[78]</sup>. However, another meta-analysis containing eight RCTs showed that CIK reduces the 1- and 3-year postoperative recurrence rates and increases OS from 1 to 5 years in patients with HCC but has no effect on the 5-year recurrence rate and 6-year OS<sup>[79]</sup>. Although several RCTs have demonstrated the efficacy of CIK cell immunotherapy in the adjuvant treatment of early-stage HCC, the results are not yet conclusive, and the value and the prospect of CIK therapy in the adjuvant treatment of HCC after radical treatment remains to be proven.

### *Immune checkpoint inhibitors*

There is an increasing understanding of the immune microenvironment of liver tumors, and researchers have identified PD-1 and PD-L1 upregulated tumor-infiltrating lymphocytes in HCC and HCC-associated Kupffer cells<sup>[80]</sup> as well as the emergence of PD-1 and PD-L1 inhibitors and their promising results in the treatment of advanced



liver cancer. These findings showed that there is an interest in adjuvant immunotherapy after resection of HCC. Several immune checkpoint inhibitors have been approved by the Food and Drug Administration (United States) for the systemic treatment of advanced HCC, and adjuvant therapy is often derived from the effective treatment of the advanced disease. As more immunotherapies are shown to be safe and effective for advanced disease, we speculate that these therapies could be successful in adjuvant therapy for the appropriate patients. Additional clinical studies have preliminarily validated the efficacy and safety of immune checkpoint inhibitors used in the perioperative period. Kudo *et al*<sup>[81]</sup> explored the efficacy and safety of the adjuvant nivolumab in the treatment of patients with HCC after radical resection or radiofrequency ablation in a multicenter, single-arm, phase II clinical study. A total of 55 patients with HCC at moderate-to-high risk of recurrence were included in the study. The results showed a 1-year RFS rate of 76.7%, a median RFS of 26 mo, and a safe and manageable grade 3-4 adverse event rate of 18.9%. Several clinical studies of the immune checkpoint inhibitor-related adjuvant therapy for postoperative HCC, such as CheckMate 9DX, KEYNOTE 937, and IMBrave050 (Table 1), are currently under evaluation, and their results are worthy of anticipation.

In addition, the local combination systemic therapy is currently the trend in adjuvant therapy, such as an ongoing clinical, open-label, multicenter, single-arm observational study designed to explore the efficacy and safety of sequential tislelizumab adjuvant therapy with TACE in patients with high-risk recurrent HCC after surgery (NCT04981665).

### **POSTOPERATIVE ADJUVANT CHEMOTHERAPY**

The basic principle of adjuvant chemotherapy is to remove tumor cells or microscopic tumor lesions circulating in the body. An RCT that included 160 patients with HCC treated with oral uracil-tegafur showed no difference in RFS and OS between the adjuvant chemotherapy and observation groups after hepatectomy. Conversely, the proportion of patients with late recurrence is significantly higher in the adjuvant

chemotherapy group than in the control group<sup>[82]</sup>. In a randomized controlled trial of 60 patients after hepatectomy for HCC conducted in China, patients who received oral capecitabine postoperative adjuvant therapy have a reduced risk of tumor recurrence, but no significant improvement in 5-year survival after surgery<sup>[83]</sup>. A recently published prospective RCT<sup>[84]</sup> showed that postoperative oral cotrimoxazole adjuvant chemotherapy does not prolong recurrence-free and OS in patients with HCC compared with those with surgery alone. The role of systemic chemotherapy in patients after liver transplantation is currently inconclusive. Zhang *et al*<sup>[85]</sup> randomized 58 patients with HCC who underwent liver transplantation beyond Milan criteria into adjuvant chemotherapy and observation groups (29 patients in each group), and the chemotherapy group was given six cycles of chemotherapy with the FOLFOX regimen after transplantation. The results showed a significant increase in 1-year survival with adjuvant FOLFOX regimen chemotherapy compared with that of the control group ( $P = 0.043$ ), a 24.1% increase in 6-mo tumor-free survival in the treatment group, and a significant decrease in the 6-mo recurrence rate ( $P = 0.036$ ), but no significant difference in the 3-year recurrence rate ( $P = 0.102$ ). Subsequently, Wang *et al*<sup>[86]</sup> divided 58 patients with HCC after beyond Milan criteria liver transplantation into two groups, in which 26 patients in the treatment group were given six cycles of OXA+5-Fu+CF adjuvant chemotherapy after surgery and 32 patients in the observation group were treated with graft surgery alone. The results showed that the 1-, 2-, and 3-year survival rates are 89.7%, 86.2%, and 78.8% in the adjuvant chemotherapy group, respectively, which are significantly higher than those in the observation group (64.5%, 61.1%, and 53.6% in the 1-, 2-, and 3-year survival rates, respectively). Another retrospective study that included 117 patients with beyond Milan criteria *in situ* liver transplantation for HCC show 1-year survival rates of 87.5%, 84.2%, 81.6%, and 67.5% in the adjuvant gemcitabine group, conventional chemotherapy (adriamycin + 5-fluorouracil + cisplatin), oxaliplatin plus capecitabine, and best supportive care (BSC) groups, respectively, and 3-year survival rates of 48.1%, 25.9%, 31.6%, and 33.7%, respectively. Stratified analysis showed that the gemcitabine regimen and conventional chemotherapy significantly

improve survival and DFS in patients with HCC who developed macrovascular invasion and/or microvascular invasion after liver transplantation compared to those of the BSC group<sup>[87]</sup>. Although earlier studies suggested that adjuvant systemic chemotherapy might be associated with reduced recurrence and prolonged RFS<sup>[88]</sup>, the results failed to be validated. The reasons may be related to the relative lack of efficacy of cytotoxic chemotherapeutic for HCC drugs and the poor tolerance of chemotherapeutic drugs because of the combined hepatitis, liver fibrosis, and cirrhosis in patients with HCC. The failure of the adjuvant chemotherapy for HCC to achieve the same effect as for other solid tumors may be largely determined by the biological characteristics of the HCC and the underlying liver disease of the patients.

## **OTHER ADJUVANT TREATMENTS**

### **POSTOPERATIVE ADJUVANT ANTIVIRAL THERAPY**

Viral hepatitis is the main cause of HCC in China. Nearly 90% of the patients with HCC are associated with chronic hepatitis B, and very few are associated with hepatitis C caused by the HCV. In patients with HBV-associated HCC, higher HBsAg levels<sup>[89]</sup> and viral load (serum HBV DNA > 10<sup>6</sup> copies/mL) before and after surgery<sup>[90,91]</sup> are associated with an increased risk of recurrence after resection. In patients with HBV infection, antiviral therapy with nucleoside analogues significantly inhibits progression to cirrhosis and reduces the risk of HCC<sup>[92]</sup>. Two randomized trials<sup>[93,94]</sup> supported significantly higher OS and RFS in patients with HCC treated with postoperative adjuvant antiviral therapy. One of these studies<sup>[94]</sup> showed that the antiviral therapy is an independent prognostic factor for distant recurrence after HCC surgery (HR 0.348) but not for recurrence within two years after resection (HR 0.949). A meta-analysis that included 13 cohort studies on HBV-associated HCC and the two randomized controlled trials mentioned above (8060 patients in total) came to the same conclusion, with a significantly lower recurrence rate in patients receiving antiviral therapy (1-year recurrence rate RR 0.50, 3-year recurrence rate RR 0.70)<sup>[95]</sup> and a significantly higher OS rate in the antiviral therapy group (5-year survival rate RR 1.40). HBV infection is a



major risk factor for the development of HCC, which may occur even after HBsAg serum clearance. The guidelines recommend prompt and effective antiviral therapy for HBV-associated HCC if HBV replication is found to be active (HBV-DNA  $\geq$  1000 copies/mL or 2000 IU/mL). Even in those cases with low HBV-DNA quantification, if HBsAg (+) and/or HBcAb (+), the combination of antiviral drugs is recommended before and throughout antitumor therapy to avoid HBV reactivation<sup>[96,97]</sup>. The results suggest that IFN-based HCV antiviral therapy reduces recurrence rates and improves survival, but this regimen is no longer recommended for current HCV antiviral therapy. A retrospective multicenter cohort study enrolled a total of 797 patients with HCV-associated HCC who achieved complete remission with initial therapy over four years<sup>[98]</sup>, of whom 383 patients were treated with direct antiviral agents (DAAs), and showed significantly lower mortality in the DAA-treated group compared with that of patients not treated with DAAs. This study provides evidence of the potential benefit of the DAA adjuvant therapy for HCV-associated HCC. Similar results were obtained in another small prospective analysis that included <sup>22</sup>163 consecutive patients with HCV-related cirrhosis and a diagnosis of early HCC treated with DAA after achieving complete remission on imaging by radical resection or ablation, compared with a historical cohort of 328 patients treated for early HCC but not with DAA<sup>[99]</sup>, showing that the DAA treatment does not reduce HCC recurrence rates, but significantly improves OS. Studies have shown that the use of DAA, either before or after hepatectomy, can improve the prognosis of the disease<sup>[100]</sup>, but the optimal timing for anti-HCV therapy in relation to HCC treatment has yet to be determined. For HCV-associated HCC, the antiviral therapy has a protective effect on the liver function, and current Chinese Society of Clinical Oncology guidelines state that the antiviral therapy for HCV has entered the pan-genotypic era of direct antivirals, with a preference for interferon-free pan-genotypic regimens.

#### **ADJUVANT TRADITIONAL HERBAL MEDICINE TREATMENT**

Traditional herbal medicine has been shown to exhibit antitumor activity by inhibiting tumor cell growth, inducing apoptosis, inhibiting angiogenesis, and enhancing immune function<sup>[101,102]</sup>. Traditional herbal medicine (THM) has its own unique advantages in controlling the progression of patients with liver cancers, reducing recurrence, reducing symptoms and signs, improving survival quality, and prolonging survival. A cohort study based on Taiwanese population showed that the treatment with THM in patients with chronic hepatitis B significantly reduces the risk of HCC<sup>[103]</sup>. A retrospective study with a large sample size showed that a comprehensive THM treatment can improve OS in patients with HCC<sup>[104]</sup>. THM may prevent disease recurrence and prolong survival by modulating immunity and altering the local microenvironment. To investigate the clinical efficacy of THM in preventing recurrence of small HCC after surgery, an open-label, prospective, multicenter RCT enrolling 364 patients was conducted in five centers in China. A total of 180 patients in the THM group were treated with intravenous cinobufagin and oral detoxification granules, and 184 patients in the TACE group were treated with a single course of TACE, and at a mean follow-up of 26.61 mo, THM was found to be superior than TACE in preventing recurrence of small HCC and prolonged OS<sup>[105]</sup>. Another randomized, controlled, national multicenter phase IV clinical study that included 1,044 patients with HCC showed that in patients with HCC in BCLC staging A and B, the administration of the modern herbal medicinal preparation Huaier granules after radical resection results in a significantly longer RFS and a significantly lower rate of extrahepatic recurrence<sup>[106]</sup>. Lei *et al*<sup>[107]</sup> retrospectively analyzed 53 patients with HCC who underwent liver transplantation and divided them into the Huaier-granule treatment and control groups, in which 28 patients received Huaier granules after surgery and 25 patients did not. The long-term predicted OS is similar between the two groups ( $P = 0.202$ ). However, the tumor-free survival rate is higher in the Huaier-granule treatment group than that in the control group ( $P = 0.029$ ). The predicted recurrence rates at 10 and 30 mo in the Huaier-granule treatment group are 17.9% and 35.7%, respectively, which are significantly lower than those in the control group (60% and 64%;  $P < 0.05$ ). THM has shown some efficacy in the postoperative

adjuvant treatment of HCC, but most of the regimens lack strong medical evidence, and their efficacy still needs to be confirmed through more prospective studies.

### **ADJUVANT INTERFERON**

Interferon is considered as a promising adjuvant therapy after hepatic resection for hepatitis virus-induced HCC due to its antiviral, antiproliferative, antiangiogenic and immunomodulatory effects. Several randomized controlled trials, the majority of which were undertaken in Asian patients with HCC, have looked into the efficacy of postoperative interferon-alpha<sup>[108-116]</sup> and interferon-beta<sup>[117]</sup>. Ikeda *et al*<sup>[117]</sup> suggested adjuvant interferon-beta administration lowered postoperative recurrence rate in patients with hepatocellular carcinoma after their hepatic resection or ablation. However, RCTs on curative effects of interferon-alpha showed conflicting results. Mazzaferro *et al*<sup>[110]</sup> reported that IFN- $\alpha$ 2b induced a decrease on late recurrence rate in HCV-infected patients but showed no influence on overall prevention of tumor recurrence after surgery. Chen *et al*<sup>[114]</sup> indicated it made no contribution to postoperative recurrence reduction, while Lo *et al*<sup>[115]</sup> found that patients with pTNM stage III and IVA tumors showed dramatically lower risk of recurrence compared to the untreated group. Numerous systematic reviews and meta analyses including these RCTs and plentiful comparative studies revealed that additional interferon suppressed tumor recurrence and increased overall survival within certain time periods<sup>[118-129]</sup>. Notwithstanding, interferon-alpha significantly reduced recurrence rate in patients with HCC caused by HCV but not by HBV, according to subgroup analysis<sup>[118,126,128]</sup>.

### **ADJUVANT VITAMIN K2 ANALOGS AND RETINOIDS**

As a crucial hydrophobic vitamin, VK2 has been demonstrated to show substantial anti-angiogenic effects, induce cell cycle arrest and inhibit the proliferation of hepatocellular carcinoma cells<sup>[130-132]</sup>. The effects of VK2 were explored in six RCTs<sup>[133-138]</sup> and a cohort trial<sup>[139]</sup> conducted in Japan, focusing on recurrence prevention and prolonging survival periods in patients with HCC following local ablative therapy or resection. The studies

from Mizuta *et al*<sup>[133]</sup>, Kakizaki *et al*<sup>[135]</sup> and Yoshiji *et al*<sup>[139]</sup> pointed out that VK2 or the combination utilization of VK2 and angiotensin-converting enzyme inhibitor was efficacious in reducing HCC recurrence. Other studies, on the other hand, reported no change in DFS between treated and untreated participants<sup>[134,136-138]</sup>. VK2 analogues showed no noticeable impact on OS after hepatic resection and ethanol ablation in all mentioned investigations, while it significantly reduced tumor recurrence rates at the 2<sup>nd</sup> and 3<sup>rd</sup> year, and improved 1-, 2-, and 3-year OS according to the findings of Zhong *et al*<sup>[140]</sup>. Current research results may be inconsistent regarding the curative effects of VK2 and its analogs for postoperative patients with HCC, so more investigations with larger sample size and longer observation period are in great need.

### **ADJUVANT PI-88**

In exploratory clinical studies of HCC therapy, phosphomannopentaose sulfate (PI-88), an efficient inhibitor of heparanase, exerted anti-recurrence and anti-metastasis effectiveness<sup>[141,142]</sup>. It was reported to inhibit the relapse in patients who have undergone hepatectomy through disrupting the rapid growth of heparanase level after liver resection<sup>[143]</sup>. Liu *et al*<sup>[144]</sup> assessed the efficacy, safety and optimal dosage of PI-88 with a phase II/stage 1 RCT, concluding that 160 mg/d is acceptable and shows the potential to prolong time to recurrence. Additionally, in the observational follow-up study conducted by the same research group, they reported that PI-88 at 160 mg/d increased the recurrence-free rate and postponed the time to recurrence, despite both RFS or OS was not significantly improved<sup>[145]</sup>.

### **CONCLUSION**

This review summarizes several adjuvant therapies that may have anti-HCC recurrence efficacy, including TACE, targeted therapy, immunotherapy, and THM therapy. Although many adjuvant therapies other than the antiviral drug therapy have been reported to improve survival and/or reduce the risk of postoperative recurrence in patients after HCC surgery or liver transplantation, there is a lack of strong evidence-



based support for other treatments, and there is no globally accepted adjuvant treatment option for postoperative HCC at this stage. Asian guidelines are usually more favorable than Western ones for postoperative adjuvant therapy for HCC. Differences in recommendations for adjuvant therapy between Asian and Western guidelines are not surprising, as differences in ethnicity, environment, and causative factors may influence the pathogenesis and survival of patients with liver cancer. In addition, larger tumors are usually removed through surgery in Asian countries, while surgical treatment is usually not considered in Western countries.

Due to the heterogeneity of tumors, the underlying liver disease, recurrence patterns in patients with HCC, and the presence of multiple risk factors in most patients with the disease, there is often a wide variation in the efficacy and tolerance of patients to the same treatment regimen. Therefore, it is important to identify the most effective postoperative adjuvant therapy for a specific subgroup of patients. The most frequently mutated genes of HCC patients were TP53, TERT, and CTNNB1, which mainly lead to the occurrence and development of HCC<sup>[146-148]</sup>. Many of these abnormalities may be pharmacologically tractable. However, biomarker-matched trials are still limited in this disease, and many of the genomic alterations in HCC remain challenging to target. Future research on adjuvant therapy after HCC surgery may focus on three points: first, the signaling pathways of HCC recurrent metastasis may be different from those of the primary tumor. More in-depth basic research is needed to elucidate the mechanisms of HCC at the level of signaling pathways or driver genes to find ways to contain tumor recurrence and metastasis. Second, patients with early and distant recurrences need to be identified and stratified for the risk of recurrence, and different treatment strategies need to be adopted for patients with liver cancer with different predicted timing of recurrence. Finally, appropriate postoperative adjuvant treatment modalities were explored based on specific preoperative subgroups of patients with HCC. Several studies have explored statistical models for predicting the risk of recurrence after HCC surgery<sup>[149,150]</sup>, aiming to guide clinicians to estimate the risk of recurrence in individual patients. These findings will also help to design clinical trials of

drugs aimed at reducing recurrence in subgroups with different recurrence risks. Combination therapies, such as targeted combined with immunotherapy and targeted combined with TACE therapies, have also been conducted in the field of advanced HCC in successive clinical studies and have initially shown good efficacy. Optimized postoperative adjuvant therapy should focus on improving the immune system and liver functions while removing residual tumor cells. For patients with a high risk of recurrence, optimizing a more individualized combination therapy model may be a breakthrough in the bottleneck of postoperative adjuvant therapy for HCC.

In conclusion, there is still a lack of perspective, phase III, multicenter, randomized controlled clinical studies with large samples to confirm the efficacy of particular adjuvant treatment after HCC surgery. Therefore, comprehensive treatments with multidisciplinary cooperation, more randomized controlled trials, and new therapies need to be promoted to explore treatment modalities to reduce the postoperative recurrence of HCC and improve patient survival.

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