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AIMS AND SCOPE

The primary aim of *World Journal of Gastrointestinal Surgery* (*WJGS*, *World J Gastrointest Surg*) is to provide scholars and readers from various fields of gastrointestinal surgery with a platform to publish high-quality basic and clinical research articles and communicate their research findings online.

WJGS mainly publishes articles reporting research results and findings obtained in the field of gastrointestinal surgery and covering a wide range of topics including biliary tract surgical procedures, biliopancreatic diversion, colectomy, esophagectomy, esophagostomy, pancreas transplantation, and pancreatectomy, *etc*.

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RESPONSIBLE EDITORS FOR THIS ISSUE

Postoperative adjuvant therapy for hepatocellular carcinoma with microvascular invasion

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Abstract

Hepatocellular carcinoma (HCC) is one of the most lethal tumors in the world. Liver resection (LR) and liver transplantation (LT) are widely considered as radical treatments for early HCC. However, the recurrence rates after curative treatment are still high and overall survival is unsatisfactory. Microvascular invasion (MVI) is considered to be one of the important prognostic factors affecting postoperative recurrence and long-term survival. Unfortunately, whether HCC patients with MVI should receive postoperative adjuvant therapy remains unknown. In this review, we summarize the therapeutic effects of transcatheter arterial chemoembolization, hepatic arterial infusion chemotherapy, tyrosine protein kinase inhibitor-based targeted therapy, and immune checkpoint inhibitors in patients with MVI after LR or LT, aiming to provide a reference for the best adjuvant treatment strategy for HCC patients with MVI after LT or LR.

Key Words: Microvascular invasion; Hepatocellular carcinoma; Liver resection; Liver transplantation; Postoperative; Adjuvant treatment

Core Tip: Microvascular invasion (MVI) is considered to be one of the important prognostic factors affecting postoperative recurrence and long-term survival. Unfortunately, whether hepatocellular carcinoma (HCC) patients with MVI should receive postoperative adjuvant therapy remains unknown. In this review, we summarize the therapeutic effects of transcatheter arterial chemoembolization, hepatic arterial infusion chemotherapy, tyrosine protein kinase inhibitor-based targeted therapy, and immune checkpoint inhibitors in patients with MVI after liver resection (LR) or liver transplantation (LT), aiming to provide a reference for the best adjuvant treatment strategy for HCC patients with MVI after LT or LR.

INTRODUCTION

Hepatocellular carcinoma (HCC) is the seventh most common cancer and the second leading cause of cancer-related deaths in the world, with unsatisfactory long-term outcomes[1]. Nowadays, hepatectomy liver resection (LR) and liver transplantation (LT) are still the most efficient strategies for HCC with relatively preserved liver function[2]. Unfortunately, the surgical resection rate of HCC is still low in clinical practice due to untimely diagnosis and delayed treatment in most HCC patients. Even with radical surgery, the 5-year recurrence rate is still 70%-80%[3]. Accordingly, decreasing the recurrence rate after surgical resection is of utmost importance to improve the clinical outcomes for early-stage HCC patients.

Various risk factors are associated with the recurrence of HCC. Malignant biological characteristics of the tumor and the condition of the underlying liver disease, such as hepatitis and liver cirrhosis, were found to be more significant prognostic factors than tumor size and warrant closer attention in clinical practice[4]. Among malignant biological characteristics of HCC, microvascular invasion (MVI) is considered a risk factor for intrahepatic microscopic metastatic disease and one of the crucial factors for early HCC recurrence after LR or LT. As a consequence, In the 8th edition of the American Joint Committee on Cancer staging system, it was further included as an important prognostic factor, where it is considered an independent risk factor for poor clinical outcomes[5]. Currently, MVI is usually defined as tumor cells invading into the portal vein, hepatic vein, or a large capsular vessel of the surrounding tumor tissues, partially or totally lined by endothelial cells visible only by microscopical examination of specimens obtained from surgical excision, which is acknowledged as a histological feature[6]. MVI plays a crucial role in the selection of surgical modalities and also a vital indicator of early tumor recurrence in HCC patients[7]. Due to differences of MVI status, the surgical outcomes are likely inconsistent among different treatment groups. The presence of MVI in HCC is strongly correlated with the recurrence rates after surgical resection and should be classified as locally advanced-stage biological behavior[7,8]. Moreover, time to recurrence after curative surgical resection is a critical prognostic factor for clinical outcomes, as early tumor recurrence is associated with worse overall survival (OS). Therefore, postoperative adjuvant treatments may be partly beneficial to decrease the tumor recurrence rates in HCC patients with MVI. Unfortunately, there is still no consensus on the optimal adjuvant treatment after LR or LT for HCC with MVI.

Advances in systemic therapy for advanced HCC, as well as promising strategies for perioperative management of LR, have led to a substantial improvement of surgical outcomes in recent years. Transcatheter arterial chemoembolization (TACE), hepatic arterial infusion chemotherapy (HAIC), as well as targeted therapies based on tyrosine kinase inhibitors (TKIs) or immune checkpoint inhibitors (ICIs), are the current state-of-the-art strategies, which have shown great promise in the treatment of advanced HCC[8-12]. However, whether TACE/HAIC, TKIs (such as sorafenib and lenvatinib), and ICIs [such as programmed cell death protein 1 (PD-1)/programmed death ligand 1 (PD-L1) inhibitors] are beneficial for decreasing tumor recurrence rates in HCC patients with MVI remains controversial. In view of this, results derived from all the studies were analyzed, aiming to outline the optimal treatment strategy for HCC with MVI after LR. For patients with early-stage HCC, LR, LT, and local ablation (LA) are considered as first-line treatments. However, MVI cannot be precisely evaluated in HCC patients who underwent LA. Therefore, we mainly discuss the effect of postoperative treatments on the surgical outcomes after LT and LR. This review article aims to provide updated information on the recent developments in postoperative adjuvant therapy in HCC patients with MVI.

LR

MVI has been widely identified as a crucial risk factor for intrahepatic recurrence after R0 surgical resection, which was evidenced by increased local recurrence rates and reduced recurrence-free survival (RFS) after LR compared to HCC patients without MVI. Whether postoperative adjuvant therapy could improve the surgical outcomes for HCC with MVI remains unclear. There is an urgent need to discuss several postoperative adjuvant treatments such as TACE/HAIC and TKI and ICI therapy, aiming to shed a new light on ways to improve the prognosis for such HCC patients.

TACE

The main purpose of TACE after LR is to eliminate the tumor cells released due to compression during operation and destroy the existing microscopic foci in the remnant liver that cannot be found by preoperative imaging examination. It delivers specific drugs, along with iodized oil, mainly to suspected tumor areas, followed by embolization to cause tumor cell necrosis and prevent residual lesions from growing into clinically visible tumors. Some studies demonstrated a superior effect of postoperative TACE in terms of OS and RFS[13,14], while other studies reported comparable results with or without postoperative TACE[15,16]. The benefits of adjuvant TACE in HCC patients with MVI remain controversial. A meta-analysis indicted that adjuvant TACE plus LR may improve the surgical outcomes of HCC patients with MVI compared to LR alone and should be recommended for HCC patients with MVI[17]. Another meta-analysis showed that postoperative adjuvant HAIC could improve the long-term prognosis of HCC patients, especially those with microvascular or macrovascular invasion[18]. A retrospective study showed that postoperative HAIC offers better OS than simple surgical resection in patients with MVI[19]. The beneficial effect of postoperative adjuvant TACE may be related to a number of factors. First, the poor efficacy of surgical resection in patients with liver cancer complicated with MVI is due to the micrometastasis of residual cancer cells before or during LR [20,21]. Postoperative adjuvant TACE can kill or ablate these cells and improve the prognosis. Second, patients with MVI are prone to micrometastasis before surgery[22,23]. Therefore, TACE is a suitable and effective treatment 3-4 wk after LR, when the patients recover from surgery and the residual tumor is still small. Third, the majority of HCC blood supply comes from the hepatic artery, and recurrent tumors often occur near the edge of LR[24,25]. The use of postoperative adjuvant TACE increases the concentration of these marginal local anticancer drugs, which may improve the prognosis of such patients. However, there is no uniform standard for drug combination, dose, frequency of TACE, and time interval of each treatment. Nevertheless, other studies showed conflicting results. A meta-analysis of randomized clinical trials (RCTs) found that TACE did not improve RFS and OS after radical resection of HCC unless the tumor size was 5 cm[26]. A retrospective study showed that adjuvant HAIC using 5-fluorouracil and cisplatin did not improve disease-free survival (DFS) and OS after LR[27]. It remains unclear if HCC patients with MVI can benefit from adjuvant TACE treatment after surgery. The effectiveness of TACE may be due to the fact that chemotherapy drugs enter the blood vessels, and thereby come in contact with the migrating tumor cells to destroy them. However, due to the different tumor microenvironment and tumor heterogeneity in different populations, some patients still cannot benefit from this treatment. The tumor microenvironment may play a key role in the initiation and maintenance of drug resistance through various mechanisms such as pH changes, hypoxia, vascular system abnormalities, changes in immune populations, and extracellular matrix[28].

The pro-tumor environment that induces immunosuppression, such as myeloid-derived suppressor cells, regulatory T cells, and tumor-associated macrophages in the liver immune cell population, may play a major role in the limited effectiveness of chemotherapy drugs. Moreover, chemotherapy drugs themselves may change the composition of the inflammatory cell population[29]. In addition to the interaction of immune cells, hepatocirrhosis microenvironment composes a physical barrier that stimulates tumor growth by altering biomechanical properties, cytokine secretion, and activation of multiple signaling pathways, preventing drugs from reaching targets in the tumor parenchyma and thus reducing drug availability.

Moreover, high-dose TACE can damage liver cells, leading to the deterioration of liver function, reduced immunity against tumor cells, and increased risk of hepatitis B virus reactivation. In TACE, the combined use of multiple drugs may increase the burden on the liver leading to drug-induced liver injury, and ultimately adversely affect the therapeutic effect. Therefore, factors such as liver function and operation time should be considered in postoperative combined TACE treatment[19]. In addition, tumor load, tumor invasion, and postoperative recovery may be factors affecting the efficacy. The relevant studies on the postoperative application of TACE or HAIC as adjuvant therapy are listed in Table 1. However, these results need to be further verified by high-quality RCTs.

Target therapy-TKIs

Intrahepatic tumor recurrence after LR can be divided into early recurrence and late recurrence. Early recurrence is related to intrahepatic metastasis of primary tumors that cannot be detected clinically, which may be related to the spread and metastasis of tumor cells in portal vein circulation caused by the shedding of cancer cells before surgery or the pressure exerted on tumors during LR. As liver cancer

Table 1 Transcatheter arterial chemoembolization approved as an adjuvant therapy for hepatocellular carcinoma patients with microvascular invasion

Ref.	Study type	Adjuvant therapy	Number	2-yr DFS (%)	*P* value	2-yr OS (%)	*P* value	PMID
Li *et al*[17]	RCT	HAIC	63	58.7	0.023	97.7	0.037	32418078
		NAT	64	38.6		78.5		
Sun *et al*[72]	Retrospective	TACE	137	55.5	0.012	78.8	0.006	26714945
		NAT	185	36.2		62.2		
Wei *et al*[73]	RCT	TACE	125	44.7	0.02	64.3	0.029	30305149
		NAT	125	30.6		49.8		
Ye *et al*[13]	Retrospective	TACE	86	58.3	0.002	86.5	0.019	29151695
		NAT	174	41.1		65.7		
Liu *et al*[74]	Retrospective	TACE	24	26.9	0.03	NA	NA	27038790
		NAT	26	4.2		NA		
Wang *et al*[75]	Retrospective	TACE	57	66	0.008	94	0.04	30249510
		NAT	57	50		83		
Cai *et al*[76]	Retrospective	TACE	25	39.1	0.06	NA	NA	34926296
		TACE + T cell self	23	58.2		NA		
Kim *et al*[27]	RCT	HAIC	31	9.1	0.324	87.1	0.561	22067673
		NAT	62	4.2		78.3		
Nitta *et al*[77]	Retrospective	HAIC	38	33.1		56.2	0.318	23435678

DFS: Disease-free survival; OS: Overall survival; TACE: Transcatheter arterial chemoembolization; HAIC: Hepatic arterial infusion chemotherapy; NAT: No adjuvant therapy; NA: Not available; RCT: Randomized clinical trial.

cells gradually infiltrate the tumor capsule surrounding matrix, and vascular wall, they further invade blood vessels to form MVI. The multi-kinase inhibitors that target tumor cells and tumor blood vessels act on a variety of kinases and pro-angiogenic receptors, blocking downstream signaling pathways, inhibiting the proliferation and promoting apoptosis of tumor cells, as well as inhibiting tumor cell angiogenesis, and migration, with a wide range of anti-tumor effects that promote the prevention and treatment of tumor recurrence[30].

Sorafenib is a multi-kinase inhibitor that blocks multiple molecular pathways through its anti-angiogenic and anti-proliferative effects. A RCT revealed that sorafenib could effectively improve the survival time with advanced HCC patients[31]. In addition, sorafenib has been reported to inhibit postoperative intrahepatic recurrence and abdominal metastasis, thereby extending postoperative survival time[32,33].

Sorafenib can improve the prognosis of MVI in HCC patients after R0 LR. A meta-analysis invest-igated the preventive effect of sorafenib against tumor recurrence in HCC with MVI, and the results showed that LR plus sorafenib significantly improves the prognosis of HCC with MVI compared to LR alone. However, this meta-analysis has some shortcomings. First, it only included retrospective studies, which may cause selection bias. Second, the patients in these four studies were all Chinese, which also weakens the universality of the conclusion[34].

Recent studies have demonstrated the efficacy of sorafenib in preventing recurrence of HCC after LR [35]. Li *et al*[36] as well as Xia *et al*[37] found that the OS and DFS of Barcelona Clinic Liver Cancer stage C HCC patients treated with oral sorafenib after LR was significantly longer than those of patients only treated by LR. Wang *et al*[38] proved that sorafenib as an adjuvant therapy for HCC can prevent early recurrence after LR. Huang *et al*[39] evaluated the impact of sorafenib as an adjuvant therapy on the clinical outcomes in HCC with MVI. The results indicated that adjuvant sorafenib significantly prolonged both OS and RFS of patients with HCC after radical resection.

However, a RCT revealed that sorafenib treatment after LR did not improve the DFS of HCC patients, but increased the incidence of side effects, such as hand-foot skin reaction, diarrhea, and fatigue[40]. Similarly, it was found that postoperative sorafenib adjuvant therapy cannot improve RFS in HCC patients with MVI[41]. The relevant studies on postoperative application of TKIs as adjuvant therapy are listed in Table 2. There are differences in the results from different centers. In addition to the sample size and research methods that may affect the results, these differences may also be caused by different

Table 2 Tyrosine kinase inhibitor approved as an adjuvant therapy for hepatocellular carcinoma patients with microvascular invasion

NCT number	Title	Interventions	Characteristics	*n*	Date	Current status
NCT02678806	Radiotherapy in Hepatocellular Carcinomas After Hepatectomy With Narrow Margin (< 1 cm) and/or Microvascular Invasion (RHCC:BCLC-A)	Radiation: Postoperative radiotherapy. Drug: Postoperative TACE	Phase: Not applicable. Allocation: Randomized. Intervention model: Parallel. Outcome measures: Overall survival	620	November 1, 2017 to November 1, 2022	Recruiting
NCT04053972	The Impact on Recurrence Risk of Adjuvant Lenvatinib for Patients With Hepatocellular Carcinoma And Microvascular Invasion (MVI) After Hepatectomy: A Random, Controlled, Stage III Clinical Trial	Drug: Lenvatinib	Phase: 3. Allocation: Randomized. Intervention model: Parallel. Outcome measures: RFS and OS recurrence rate	377	January 31, 2018 to December 31, 2022	Recruiting
NCT02867280	Sorafenib Treatment in Patients With Hepatocellular Carcinoma With Microvascular Invasion After Radical Resection	Drug: Sorafenib	Phase: 3. Allocation: Non_x005f randomized. Outcome measures: Recurrence free survival; time to recurrence; recurrence rate; overall survival; incidence of treatment related; adverse events; incidence of dose modification of sorafenib due to adverse events	154	June 1, 2016 to January 31, 2020	Terminated
NCT03192618	The Impact on Recurrence Risk of Adjuvant Transarterial Chemoinfusion (TAI) for Patients With Hepatocellular Carcinoma And Microvascular Invasion (MVI) After Hepatectomy: A Random, Controlled, Stage III Clinical Trial	Procedure: Adjuvant transarterial chemoin-fusion. Drug: mFOLFOX6 (oxaliplatin, calcium folinate, and 5-fluorouracil)	Phase: 3. Allocation: Randomized. Outcome measures: DFS; recurrence rate; OS	290	July 1, 2017 to December 31, 2024	Recruiting
NCT02436902	Adjuvant Therapies for Patients With HCC and MVI	Procedure: TACE. Drug: Sorafenib, TACE plus sorafenib and empty control	Phase: 3. Allocation: Non_x005f randomized. Outcome measures: Overall survivals; hospital mortality; recurrence rates	240	February 1, 2019 to August 30, 2022	Recruiting
NCT03732105	Radiotherapy/Apatinib for Adjuvant Treatment of HCC Patients receIved Curative resection With Microvascular Invasion	Radiotherapy. Drug: Apatinib and radiotherapy + apatinib	Phase: 2. Allocation: Randomized. Outcome measures: RFS; time to recurrence; overall survival; safety events; health related quality of life	160	November 1, 2018 to December 31, 2023	Not yet recruiting
NCT03575806	Combine TACE and Autologous Tcm Immunotherapy Versus TACE Alone for HCC With MVI After Radical Resection	Combination product: TACE plus autologous Tcm immunotherapy. Procedure: TACE	Phase: 2. Allocation: Non_x005f randomized. Outcome measures: RFS time; OS rate at 24 mo	52	January 9, 2017 to October 31, 2019	Completed
	Should we apply sorafenib in hepatocellular carcinoma patients with microvascular invasion after curative hepatectomy?	Drug: Sorafenib	Phase: Not applicable. Allocation: Retrospective study. Outcome measures: DFS; recurrence rate; OS	49	January, 2009 to December, 2016	Completed
	Microvascular Invasion as a Predictor of Response to Treatment with Sorafenib and Transarterial Chemoembolization for Recurrent Intermediate-Stage Hepatocellular Carcinoma	Procedure: TACE. Drug: Sorafenib, TACE plus sorafenib, and TACE	Phase: Not applicable. Allocation: Retrospective study. Outcome measures: DFS; recurrence rate; OS	127	January, 2010 to December, 2016	Completed
	Postoperative adjuvant sorafenib improves survival outcomes in hepatocellular carcinoma patients with microvascular invasion after R0 liver resection: a propensity score matching analysis	Drug: Sorafenib	Phase: Not applicable. Allocation: Retrospective study. Outcome measures: DFS; recurrence rate; OS	728	January, 2009 to December, 2016	Completed
NCT00692770	Adjuvant sorafenib for hepatocellular carcinoma after resection or ablation (STORM): a phase 3, randomised, double-blind, placebo-controlled trial	Drug: Sorafenib	Phase: 3. Allocation: Randomized. Outcome measures: DFS; recurrence rate; OS	1114	August 15, 2008 to November 17, 2010	Completed

TACE: Transcatheter arterial chemoembolization; DFS: Disease-free survival; OS: Overall survival; RFS: Recurrence-free survival; HCC: Hepatocellular carcinoma; MVI: Microvascular invasion.

definitions and classifications of MVI. It may be necessary to conduct systematic research under uniform definitions and standards to make the results more comparable.

Although targeted drugs have greatly improved the prognosis of patients with advanced liver cancer, the efficacy of single drugs is still limited, and drug resistance may occur during treatment due to tumor heterogeneity and changes in the immune microenvironment. In addition, the side effects of drugs and the tolerance of patients also affect the therapeutic effect. In the future, it may be necessary to standardize the population suitable for targeted therapy, and consider combined therapy to improve the efficacy when single drugs are insufficient. In view of the above results, the role of targeted drugs as adjuvant therapy may still be controversial, and a large number of prospective RCTs are needed to further verify their efficacy in the future.

PD-1/PD-L1 treatment

ICIs are a new class of anti-tumor drugs that target regulatory signals between T cells, target cells, and other immune cells. T cells can recognize specific antigens presented on target cells by major histocompatibility complex proteins through their T cell receptors, and can induce apoptosis of target cells. T-cell activity is precisely regulated by co-stimulatory and co-inhibitory molecules to maintain an appropriate immune response without harmful overactivation. Therefore, adjuvant application of ICI after LR, may activate T cells to destroy circulating tumor cells and prevent recurrence.

At present, the main immune checkpoint molecules targeted by immunotherapy are PD-1, PD-L1, and cytotoxic T lymphocyte-associated protein 4. Cancer immunotherapy may have a significant impact in adjuvant settings, as it can immediately induce tumor cell killing and potentially produce durable immune responses that eliminate residual micrometastases that are thought to lead to early recurrence. Anti-PD-1/PD-L1 antibody, either alone or in combination, has shown successful induction of pathological reactions in a variety of tumor types, while also inducing tumor-specific T cell amplification, which may produce a vaccine effect capable of systemic monitoring[42,43]. The response rate to PD-1 blockade is about 20%, and the response to combined therapy may be higher[44,45].

At present, no large-scale clinical datasets have confirmed the role of ICIs in preventing postoperative recurrence and improving long-term survival in HCC. CheckMate-9DX is an ongoing trial investigating whether nivolumab can improve RFS compared with placebo in HCC patients who have a high risk of recurrence after LR or ablation, which includes patients with MVI.

Prevention of postoperative recurrence is an important part of the treatment of HCC, which is still an unsolved clinical problem. For early operable HCC with MVI, optimal liver function reserve, good physical condition, and increased tolerance to immune-related toxicity may improve the curative opportunity of the patients. However, the response of such patients to immunotherapy or drug resistance is still a challenge that cannot be ignored.

Considering the potential adverse reactions to combined administration, it is particularly important to select specific patients that most likely benefit from such therapies. Therefore, it is necessary to establish an effective predictive model, and a large number of prospective clinical studies are still needed to provide reliable guidance. In addition, there are studies on targeted drugs combined with immunotherapy for postoperative assistance, as shown in Table 3. We expect these effective research results to provide a reference for clinical decision-making. Since MVI is one of the critically important risk factors for relapse and metastasis, surgical resection alone may not completely eliminate the adverse effects of MVI and improve the prognosis of patients. Although there is no uniform standard for adjuvant therapy after LR, it may be one of the most promising strategies to improve the efficacy HCC therapy in patients with MVI.

LT

LT is suitable for patients with early HCC[46], but unfortunately, many patients are diagnosed at an advanced stage. Although many centers have expanded the indications beyond the Milan criteria and achieved promising results, there is still a high risk of relapse after transplantation, with HCC recurrence peaking about 2-3 years after LT[47-50].

Theoretically, LT completely eliminates tumors and potential lesions in the liver. However, MVI or undetected extrahepatic lesions can lead to HCC recurrence after transplantation. MVI was reported to be a major risk factor for HCC recurrence after LT[51]. Milan and other similar criteria are based on tumor size according to imaging, which does not provide sufficient information about pathological features and tumor biology, such as MVI and differentiation/grade. Therefore, these criteria cannot fully predict the recurrence of HCC after LT. MVI in the liver can predict tumor recurrence and indicate a poor prognosis. However, although MVI is an important predictor of tumor recurrence, without pathological examination, it is almost impossible to detect MVI before LT. Therefore, MVI largely determines the long-term prognosis of patients after resection and transplantation[52]. Theoretically, adjuvant therapy after LT may eradicate residual tumor cells in the blood. Therefore, it is very important to explore adjuvant therapy to improve the survival rate after transplantation.

At present, there is no systematic adjuvant therapy for HCC patients with MVI after transplantation, and most of the related studies focused on the treatment of recurrence after transplantation. Only some studies investigated adjuvant treatments for patients with a high risk of recurrence after transplantation

Table 3 Immune checkpoint inhibitors as an adjuvant therapy for hepatocellular carcinoma patients with microvascular invasion

NCT number	Title	Interventions	Characteristics	n	Date	Current status
NCT04682210	Sintilimab Plus Bevacizumab as Adjuvant Therapy in HCC Patients at High Risk of Recurrence After Curative Resection	Drug: Sintilimab. Drug: Bevacizumab	Phase: 3. Allocation: Randomized. Intervention model: Parallel	246	December, 2020 to December, 2024	Not yet recruiting
NCT04981665	A Study to Evaluate TACE Sequential Tislelizumab as Adjuvant Therapy in Participants With HCC at High Risk of Recurrence After Curative Resection	Drug: Tislelizumab. Drug: TACE	Phase: 2. Allocation: N/A. Intervention model: Single group assignment	50	November 8, 2021 to December, 2024	Recruiting
NCT05407519	A Study to Evaluate Tislelizumab Combined With Sitravatinib as Adjuvant Therapy in Participants With HCC at High Risk of Recurrence After Curative Resection	Drug: Tislelizumab. Drug: Sitravatinib	Phase: 2. Allocation: N/A. Intervention model: Single group assignment	52	July 25, 2022 to June 30, 2026	Recruiting
NCT04639180	A Study to Evaluate Camrelizumab Plus Rivoceranib (Apatinib) as Adjuvant Therapy in Patients With Hepatocellular Carcinoma (HCC) at High Risk of Recurrence After Curative Resection or Ablation	Drug: Camrelizumab.Drug: Rivoceranib (apatinib)	Phase: 3. Allocation: Randomized. Intervention model: Crossover assignment	674	April 1, 2021 to July 31, 2024	Recruiting
NCT03839550	Combine Apatinib Mesylate With PD-1 Antibody SHR-1210 for HCC With High Risk of Recurrence After Radical Resection	Drug: Apatinib Mesylate. Drug: SHR-1210	Phase: 2. Allocation: Randomized. Intervention model: Parallel	200	February 15, 2019 to February 28, 2023	Not yet recruiting
NCT03847428	Assess Efficacy and Safety of Durvalumab Alone or Combined With Bevacizumab in High Risk of Recurrence HCC Patients After Curative Treatment (EMERALD-2)	Drug: Durvalumab. Drug: Bevacizumab. Other: Placebo	Phase: 3. Allocation: Randomized. Intervention model: Parallel	908	April 29, 2019 to May 31, 2024	Not yet recruiting
NCT04102098	A Study of Atezolizumab Plus Bevacizumab Versus Active Surveillance as Adjuvant Therapy in Patients With Hepatocellular Carcinoma at High Risk of Recurrence After Surgical Resection or Ablation (IMbrave050)	Drug: Atezolizumab. Drug: Bevacizumab	Phase: 3. Allocation: Randomized. Intervention model: Parallel	668	December 31, 2019 to July 16, 2027	Not yet recruiting

TACE: Transcatheter arterial chemoembolization; HCC: Hepatocellular carcinoma.

beyond the Milan criteria. Nevertheless, patients with MVI were included in these studies, as summarized below and listed in Table 4.

There is a high burden of early immunosuppression, especially in the case of calcineurin inhibitors such as cyclosporine and tacrolimus, which are usually the basic drugs against organ rejection after transplantation and may also increase the risk of HCC recurrence[53-55]. By contrast, immunosuppressive regimens based on mammalian target of rapamycin inhibitors, such as sirolimus and everolimus, have antitumor properties *in vitro* and *in vivo* and may reduce the HCC recurrence rates. Unfortunately, a prospective phase III multicenter RCT showed no significant improvement of the recurrence rate in HCC transplant recipients treated with sirolimus[56].

Some small studies have shown that sorafenib can improve the survival rate of LT patients with a high risk of recurrence after transplantation[33], but there is also evidence against chemotherapy or sorafenib adjuvant therapy after LT[57]. Whether targeted drugs are suitable for LT patients with MVI therefore remains to be verified in the future. Overall, there is no evidence that systemic adjuvant chemotherapy after LT can prevent HCC recurrence[58].

Although ICIs have demonstrated a certain level of efficacy in advanced liver cancer, based on the characteristics of ICIs and the special physical condition of patients after LT, balancing graft-protective immunosuppression and anti-tumor immune enhancement is still an unresolved issue. The use of ICIs as adjuvant therapy in transplant recipients has been the subject of several case reports[58-62], but ICIs may promote allograft injury[63], leading to severe rejection and even death. When systematically evaluating the data of cancer transplant recipients receiving ICIs, 37.5% of the recipients experienced liver allograft rejection, resulting in a 75% incidence of end-stage organ failure[64]. PD-1 inhibitor therapy after LT was reported in eight cases, including two cases of graft rejection[58,60,65]. Even if the treatment strategy of combined ICIs has great prospects, clinicians should be extremely cautious in practical application.

Tumor cell invasion of microscopic blood vessels in the surrounding liver tissue adjacent to the tumor is a histological feature of HCC. In recent years, several studies have intended to classify MVI based on different features[66-68], indicating that MVI can be further classified as MI and microscopic portal vein invasion (MPVI)[69,70], where tumor cells may invade the microvessels at the initial stage of invasion, while the newly formed microvascular structure due to the interaction of liver tissue around the tumor

Table 4 Adjuvant therapy after liver transplantation

Ref.	Interventions	Characteristics	*n*	Result	PMID
Rodríguez-Perálvarez *et al* [53]	Drug: mTOR inhibitors	Multicenter retrospective study	219	Effective	23867318
Vivarelli *et al*[54]	Drug: Cyclosporine	Retrospective study	70	Effective	15838913
Vivarelli *et al*[55]	Drug: Tacrolimus	Retrospective study	139	Ineffective	18948815
Geissler *et al*[56]	Drug: Sirolimus	Phase: 3. Allocation: Randomized. Intervention model: Parallel	525	Ineffective	26555945
Friend *et al*[78]	Drug: Nivolumab	Retrospective study	2	Ineffective	28643391
Biondani *et al*[60]	Drug: Nivolumab	Case report	1	Ineffective	29293878
DeLeon *et al*[61]	Drug: PD-1/PD-L1 inhibitors	Retrospective study	7	Partly effective	30603124
Gassmann *et al*[63]	Drug: Nivolumab	Case report	1	Ineffective	30255136
Varkaris *et al*[65]	Drug: Pembrolizumab	Case report	1	Ineffective	29215617
Iavarone *et al*[79]	Drug: Sorafenib	Multicenter retrospective study	28	Ineffective	31365177

mTOR: Mammalian target of rapamycin; PD-1: Programmed cell death protein 1; PD-L1: Programmed death ligand 1.

is defined as MI. Subsequently, as tumor invasion accelerates, tumor cells float and settle in the portal vein branches farther away from the original tumor, which is defined as MPVI. Unfortunately, MVI can only be definitively diagnosed by examining surgical specimens, limiting its role in guiding individualized treatment. The two types of MVI have different foundations and mechanisms. MPVI is a more advanced form of tumor invasion than MI. Patients with MPVI have more aggressive tumor characteristics, and the two different risk factors for recurrence suggest that the goals should be different when designing adjuvant therapy for each type. For MI, the main strategy should be targeted at disseminated tumor cells that spread from the primary tumor[7]. For MPVI, a potentially systemic treatment strategy is more appropriate. Our preliminary study indicated that postoperative adjuvant therapy could improve long-term outcomes after curative LR in HCC patients with MPVI, but the effect was weaker in MI. At the same time, our studies have shown that in MI, a wider surgical margin can eliminate peripheral intrahepatic micrometastasis, thereby preventing early tumor recurrence. By contrast, the surgical results of MPVI patients are similar regardless of the width of the surgical margin[71].

Therefore, it may not be wise to classify the two types of vascular invasion into one group for research and analysis, while more appropriate treatment strategies should be developed based on different biological and histological characteristics. Several limitations exist in this study. First, the prognosis of HCC is affected by a variety of factors including tumor markers, tumor size, tumor differentiation, and liver cancer staging, here, we only give a systematic review of the prognosis of patients with MVI, not considering other factors. Second, since adjuvant therapy after LT with MVI is relatively limited, the results obtained may not objectively reflect its efficacy. Third, we did not categorize all studies using meta-analysis, so there may still be valid treatment outcomes missed. Thus, more clinical studies may be needed to analyze the postoperative adjuvant therapy for such populations in order to obtain the best treatment strategy.

CONCLUSION

Adjuvant therapy for preventing tumor recurrence after radical resection in HCC patients with MVI is the key to improving the long-term survival rate. Although there is still controversy, after LR, TACE may be an effective choice to improve DFS and OS. As targeted therapy and immunotherapy have been effective in improving the prognosis of patients with advanced liver cancer in many retrospective studies, adjuvant therapy based on molecular targeted drugs needs further study. Many RCT studies evaluating adjuvant ICI after LR are ongoing, and their results may provide additional references for adjuvant therapy. In the future, prospective studies should be carried out to clarify the improvement of prognosis in the MVI subgroup by these two treatments. Moreover, in consideration of the actual drug efficacy, adverse reactions, and patient tolerance, the relationship between efficacy and safety should be balanced in clinical practice. It may be necessary to distinguish potential populations benefiting from each combination therapy, and to assess whether patients have the preconditions to receive effective combination therapy using novel biomarkers and biological characteristics.

FOOTNOTES

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