Front. Med. 2021, 15(2): 155–169
https://doi.org/10.1007/s11684-021-0848-3

REVIEW

Adjuvant treatment strategy after curative resection for hepatocellular carcinoma

Wei Zhang, Bixiang Zhang (✉), Xiao-ping Chen (✉)

Hepatic Surgery Center, Tongji Hospital, Tongji Medical College, Huazhong University of Science and Technology, Wuhan 430030, China

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Abstract **Hepatic resection represents the first-line treatment for patients with resectable hepatocellular carcinoma (HCC). However, the 5-year recurrence rates of HCC after surgery have been reported to range from 50% to 70%. In this review, we evaluated the available evidence for the efficiency of adjuvant treatments to prevent HCC recurrence after curative liver resection. Antiviral therapy has potential advantages in terms of reducing the recurrence rate and improving the overall survival (OS) and/or disease-free survival of patients with hepatitis-related HCC. Postoperative adjuvant transarterial chemoembolization can significantly reduce the intrahepatic recurrence rate and improve OS, especially for patients with a high risk of recurrence. The efficacy of molecular targeted drugs as an adjuvant therapy deserves further study. Adjuvant adoptive immunotherapy can significantly improve the clinical prognosis in the early stage. Randomized controlled trial (RCT) studies evaluating adjuvant immune checkpoint inhibitors are ongoing, and the results are highly expected. Adjuvant hepatic artery infusion chemotherapy might be beneficial in patients with vascular invasion. Huaier granule, a traditional Chinese medicine, has been proved to be effective in prolonging the recurrence-free survival and reducing extrahepatic recurrence. The efficiency of other adjuvant treatments needs to be further confirmed by large RCT studies.**

Keywords hepatocellular carcinoma; adjuvant treatment; hepatic resection; recurrence

Introduction

Hepatocellular carcinoma (HCC) is one of the most common and frequently fatal malignances. HCC is the fourth most frequent cause of cancer-related death and ranks sixth in terms of incident cases worldwide [1,2]. An estimated 392 868 new HCC cases were recorded in China, with an estimated 368 960 deaths in 2018 [1]. Approximately half of the new cases and deaths involving HCC worldwide occurred in China [3]. Patients with HCC commonly have underlying chronic liver disease or cirrhosis, caused by hepatitis B or C virus infection, alcohol abuse, or nonalcoholic steatohepatitis cirrhosis [4].

At present, the potentially curative options for HCC patients mainly include surgical treatment (liver resection and liver transplantation (LT)) and radiofrequency ablation. Theoretically, LT is the best option because it cures both end stage liver disease and HCC. However, LT is hampered by the severe shortage of donor organs. Moreover, patients with well-preserved liver function or those outside the Milan criteria are not eligible for LT. Ablation is a rational treatment option, but its clinical efficacy is limited by tumor size and location [5]. Therefore, surgical resection is still considered as the principal strategy for the treatment of HCC. Unfortunately, the overall survival (OS) of patients with HCC following resection is still very poor because of recurrence and metastasis. The 5-year recurrence rates of HCC following liver resection have been reported to range from 50% to 70% [6–8].

The prevention and effective management of recurrent HCC are undoubtedly essential to improve long-term survival after liver resection for HCC. In the past few decades, encouraging progress has been made in systemic and locoregional treatment options for HCC and the treatment of viral hepatitis. Published studies have shown some evidence of the efficacy of adjunctive therapies in reducing the risk of tumor recurrence following liver

Received September 9, 2020; accepted February 20, 2021
Correspondence: Xiao-ping Chen, chenxpchenxp@163.com;
Bixiang Zhang, bixiangzhang@163.com

resection. These therapies include antiviral therapy, transarterial chemoembolization (TACE), molecular targeted therapy, immunotherapy, regional or systemic chemotherapy, radiolabeled lipiodol therapy, traditional Chinese medicine, and vitamin K2 (VK2) analogs and retinoids. However, whether these strategies can be used to reduce the risk of recurrence and metastasis following liver resection is unclear. In the present review, we evaluated the available evidence for the efficiency of adjuvant treatments to prevent HCC recurrence after curative liver resection.

Methods

An electronic search was performed to identify all studies that explored the efficacy of adjuvant treatments to prevent HCC recurrence in patients following curative liver resection in PubMed, EMBASE, and Cochrane Library up to August 2020. The following keywords were used: hepatocellular carcinoma, hepatic resection, recurrence, adjuvant therapy, antiviral therapy, nucleoside analogs, interferon, direct antiviral agents, transarterial chemoembolization, molecular targeted therapy, immunotherapy, chemotherapy, hepatic artery infusion chemotherapy, iodine-131, iodine-125, radiation therapy, vitamin K2, retinoids, traditional Chinese medicine, Huaier granule, branched chain amino acids, and PI-88. Both retrospective and prospective studies were considered eligible. Studies published in languages other than English with no translation readily available were excluded. Manual searches of references cited by the published original studies and review articles supplemented the database search strategy. The review focused on the outcomes of OS, recurrence-free survival (RFS), disease-free survival (DFS), and recurrence rates.

Antiviral therapy

Nucleoside analogs (NAs)

Previous studies revealed that high viral load was closely correlated with a high risk of HCC recurrence and metastasis after liver resection [9,10]. Therefore, antiviral therapy plays an important role in preventing postoperative recurrence of hepatitis-related HCC. Five prospective randomized controlled trial (RCT) studies investigated the effect of NA treatment on postoperative prognosis of hepatitis B virus (HBV)-related HCC (Table 1) [11–15]. For patients who had high preoperative HBV-DNA levels ($>$ 2000 IU/mL), Huang *et al*. [11] found that the administration of adefovir led to significantly longer RFS and OS after 5-year follow-up. Multivariate analysis showed that antiviral therapy was an independent prognostic factor for long-term survival. More recently, Huang *et al*. [12] investigated the effect of antiviral therapy in patients with low ($<$ 2000 IU/mL) preoperative viral levels. This study showed that antiviral therapy with telbivudine reduced HBV reactivation and late HCC recurrence and eventually improved survival. Huang *et al*. [13] also found that telbivudine can significantly decrease the perioperative reactivation of viral replication. Yin *et al*. [14] reported that lamivudine therapy was associated with significantly improved liver function, decreased HCC recurrence, and longer postoperative survival. By contrast, an RCT from Taiwan, China, which was published as a meeting abstract, demonstrated that adjuvant adefovir did not reduce the postoperative recurrence of HBV-related HCC [15].

Zhang *et al*. [16] conducted a meta-analysis to investigate the prognostic effects of NAs in patients with HBV-related HCC after curative treatment. A total of 21 studies with 8752 patients (2 RCTs and 20 non-RCT studies) were included in the study. The pooled data suggested that NA therapy may reduce the incidence of early recurrence and improve OS. Another meta-analysis of 26 cohort studies, comprising 2546 patients in the antiviral group and 6463 patients in the control group, found that antiviral therapy with NAs confers significant survival benefits, especially in patients with high ($\geqslant$ 20 000 IU/mL) preoperative viral levels [17]. Similar conclusions were obtained in other meta-analyses [18–23]. The mechanisms of NA treatment in improving the prognosis after radical hepatectomy for HBV-related HCC may include inhibiting hepatitis activity, decreasing chronic inflammation in the remnant liver, improving liver reserve function, reducing the risk of developing HBV-related HCC, and increasing further therapeutic opportunities following HCC recurrence [24,25].

Interferon

A total of six RCTs of IFN therapy after liver resection for HCC have been reported (Table 2) [26–31]. Two focused on HCV-related HCC [26,27], three on HBV- and HCV-related HCC [28,30,31], and one on HBV-related HCC [29]. Conflicting conclusions were drawn from these RCT studies. In one study from Taiwan, China with the largest number of subjects, Chen *et al*. [31] found that adjuvant IFNα-2b had no significant effect on the incidence of postoperative recurrence and OS. Mazzaferro *et al*. [28] also reported that no significant difference in RFS was detected between the IFNα and control groups. However, an obvious benefit on late recurrences was observed in HCV-related HCC patients. Another RCT study from Hong Kong, China found no evidence of a significant effect of adjuvant interferon therapy on the overall recurrence rate for the total patient group, but the incidence of early recurrence in patients with pTNM stage III and

Table 1 Prospective RCTs of adjuvant antiviral therapy with NAs for patients with HBV-related HCC

Study	Country/ region	Study design	Arms and intervention	Sample size	Follow-up (month)	Main outcomes
Yin *et al.* (2013) [14]	China	Two-stage longitudinal clinical study (RCT and non-RCT)	NA (lamivudine 100 mg/day, orally within 1 week after resection until hepatitis B surface antigen seroconversion) vs. no therapy	163 in RCT (81 treatment and 82 controls)	39.93	NA treatment significantly improved liver function and decreased HCC recurrence and HCC-related death
Huang *et al.* (2013) [13]	China	RCT	NA (telbivudine 600 mg/day, once daily on day 0 after surgery) vs. no therapy	84 (40 antiviral and 44 controls)	NA	NA treatment significantly decreased the incidence of viral reactivation during the perioperative period and could not facilitate postoperative liver function recovery
Huang *et al.* (2015) [11]	China	RCT	NA (adefovir 10 mg/day, orally starting from 4 to 7 days after resection) vs. no therapy	200 (100 antiviral and 100 controls)	60	Adefovir antiviral therapy reduced late HCC recurrence and significantly improved OS. Antiviral therapy was an independent protective factor of late tumor recurrence
Chen *et al.* (2015) [15]	Taiwan, China	RCT	NA (adefovir 10 mg/day for 3 years) vs. no therapy. In both groups, 18 months of lamivudine would be given when the HBV DNA titer $>$ 20 000 IU/mL and ALT $>$ 2.0$\times$ UNL	117 (58 antiviral and 59 controls)	NA	Three years of adjuvant adefovir did not reduce the postoperative recurrence and late recurrence of HBV-related HCC compared with observation followed by lamivudine when the HBV DNA titer $>$ 20 000 IU/mL and ALT $>$ 2.0$\times$ UNL
Huang *et al.* (2018) [12]	China	RCT	NA (telbivudine 600 mg/day, orally starting from 4 to 7 days after surgery) vs. no therapy	200 (100 antiviral and 100 controls)	60	In patients with low preoperative HBV-DNA levels, antiviral therapy significantly reduced HCC recurrence and improved OS

IVA tumors was significantly reduced [30]. Sun *et al*. [29] found that OS was better in the IFN treatment group than in the control group although adjuvant IFN treatment did not significantly improve DFS. Heterogeneity of the underlying liver disease and liver reserve function and differences in interferon types, dose, and treatment duration may be the reasons for the inconsistent results.

Multiple meta-analyses have been published to explore the effect of adjuvant interferon therapy on the prognosis of hepatitis-related HCC after curative therapy [32–43]. The results of most meta-analyses showed that adjuvant interferon after curative resection or ablation had a significant beneficial effect in terms of survival and tumor recurrence in patients with hepatitis-related HCC. In a recent meta-analysis that only included RCT studies, Xu *et al*. [42] found that adjuvant IFN can improve OS but has no effect on RFS. Subgroup analysis revealed that adjuvant interferon can reduce the recurrence of patients with tumor less than 3 cm. Xu *et al*. [40] reported that IFN therapy was not associated with decreased postoperative recurrence among patients with HBV-related HCC, but efficiently improved OS and reduced the recurrence rate of HCV-related HCC after surgery. Similar findings have also been observed by other investigators [36,39].

Direct antiviral agents (DAAs)

During the past decades, interferon-based treatment has been considered as the gold standard for chronic hepatitis C. Recently, the development of DAAs (also termed as direct-acting antivirals) has revolutionized the treatment of HCV infection. Multiple studies confirmed that the combined use of two or more of these agents can lead to sustained virological responses (SVRs) up to 95% and is well tolerated [44–46]. However, DAA treatment might increase the recurrence rates among patients with HCV-related HCC and complete response after resection, ablation, or TACE [47]. At the same time, Conti *et al*. [48] also reported that the recurrence rate was surprisingly high (28.8%) among cirrhotic patients with a history of surgical resection or locoregional ablation for HCC after a median follow-up of only 5.7 months. Yang *et al*. [49]

Table 2 Prospective RCTs of adjuvant antiviral therapy with IFN for patients with hepatitis-related HCC

Study	Country/ region	Primary treatment	Type (IFN)	Viral hepatitis	Sample size	Follow-up (months)	Main outcomes
Ikeda *et al.* (2000) [26]	Japan	Hepatic resection/ PEI	IFNβ	HCV	20 (10 antiviral and 10 controls)	25	Intermittent administration of IFN suppressed tumor recurrence after treatment with surgery or ethanol injection in patients with HCV-related chronic liver disease
Kubo *et al.* (2002) [27]	Japan	Hepatic resection	IFNα	HCV	30 (15 antiviral and 15 controls)	1817 days	Postoperative interferon therapy seemed to improve the outcome after resection of HCV-related HCC
Sun *et al.* (2006) [29]	China	Hepatic resection	IFNα	HBV	236 (118 antiviral and 118 controls)	NA	IFNα treatment improved the OS of patients with HBV-related HCC after curative resection, probably by postponing recurrence
Mazzaferro *et al.* (2006) [28]	Italy	Hepatic resection	IFNα	HBV/HCV	150 (76 antiviral and 74 controls)	45	IFN does not affect overall prevention of HCC recurrence after resection, but it may reduce late recurrence in HCV-pure patients
Lo *et al.* (2007) [30]	Hong Kong, China	Hepatic resection	IFNα	HBV/HCV	80 (40 antiviral and 40 controls)	NA	Adjuvant interferon therapy showed a trend for survival benefit, primarily in those with pTNM stage III/IVA tumors
Chen *et al.* (2012) [31]	Taiwan, China	Hepatic resection	IFNα	HBV/HCV	268 (133 antiviral and 135 controls)	63.8	Adjuvant IFNα-2b did not reduce the postoperative recurrence of viral hepatitis-related HCC

investigated the prognostic outcomes in patients listed for LT with HCV-associated HCC who were treated with DAA. The results showed a trend toward a higher risk of HCC recurrence in patients who received pre-LT DAA (5/18, 27.8%) than in untreated patients (6/63, 9.5%) (P = 0.06).

On the other hand, three prospective French multicenter cohorts failed to show an increased risk of HCC recurrence after DAA treatment in patients previously treated for HCC using curative procedures [50]. In the largest retrospective study comparing HCC recurrence risk between DAA-treated patients and untreated patients, Singla *et al*. [51] found that DAA-based therapy was not associated with overall or early HCC recurrence and recurrence patterns. Of note, DAA therapy was associated with lower recurrence risk in the subgroup of patients who achieved complete response after resection. Recently, in a prospective real-world multicenter observational study, Cabibbo *et al*. [52] compared the outcomes of 102 patients with BCLC 0/A HCC treated with DAA following curative resection or ablation with 102 DAA-untreated patients. The DAA group showed significantly lower decompensation rate and higher survival rate than the DAA-untreated group. The risk of HCC recurrence was not significantly different between the two groups. In addition, DAA-treated patients who achieved an SVR had better OS and lower risk of tumor recurrence and hepatic decompensation. The available data about the potential risks and benefits of DAA therapy in patients with HCV-related HCC are conflicting. More multicenter prospective studies are needed to provide some insights into this controversial issue.

TACE

TACE is one of the main treatment methods for unresectable HCC, bridging or downstaging therapy before LT. In recent years, TACE is gaining increasing interest as an adjuvant treatment strategy to prevent the recurrence of HCC after surgical resection. The main objective of TACE after liver resection for HCC is to eradicate tumor cells released during surgery due to extrusion and destroy intrahepatic preexisting microscopic carcinomatous foci that preoperative imaging examination failed to detect. Seven RCTs [53–59], comprising one from Japan and six from China, investigated the efficacy of adjuvant TACE in preventing the recurrence of HCC (Table 3). All but one study [55] concluded that adjuvant postoperative TACE significantly reduces the intrahepatic recurrence rate and improves the OS and/or DFS. A recent meta-analysis involving 11 165 patients showed that patients who received adjuvant TACE had statistically significant improvement in OS and DFS compared with those who received curative resection alone [60]. Subgroup analysis revealed that postoperative TACE can improve OS and decrease tumor recurrence for patients with high risk of postoperative recurrence (tumor diameter $>$ 5 cm, microvascular invasion (MVI) positive, or multinodular tumor). Liao *et al*. [61] conducted a

Table 3 Prospective RCTs of adjuvant TACE for patients with HCC after curative resection

Author (year)	Inclusion period	Country	Number of patients (TACE/no TACE)	TACE course	TACE regime	Main outcomes
Izumi *et al.* (1994) [53]	1987–1992	Japan	50 (23/27)	1 course, 3–12 weeks postoperatively	Lipiodol (2–3 mL/m^2), doxorubicin (20 mg/m^2), mitomycin (10 mg/m^2), gelatin sponge	Significantly improved DFS but not OS
Li *et al.* (1995) [54]	1990–1993	China	140 (70/70)	1–3 courses, 3–4 weeks postoperatively	Lipiodol (4–10 mL), doxorubicin (40 mg/m^2), mitomycin (6 mg/m^2)	Significantly reduced intrahepatic recurrence rate and improved OS
Li *et al.* (2006) [55]	1998–2001	China	84 (39/45)	3 courses, 4 weeks postoperatively	Lipiodol (5–10 mL), doxorubicin (30 mg), mitomycin (20 mg), cisplatin (80–100 mg), or carboplatinum (400 mg)	Did not significantly improve DFS
Zhong *et al.* (2009) [56]	2001–2004	China	115 (57/58)	1 course, 4–6 weeks postoperatively	Lipiodol (5–10 mL), carboplatin (200 mg/m^2), mitomycin (6 mg/m^2), epirubicin (40 mg/m^2)	Significantly improved OS and DFS
Peng *et al.* (2009) [57]	1996–2004	China	104 (51/53)	2–5 courses, 3–4 weeks postoperatively	Lipiodol (10–20 mL), 5-fluorouracil (500 mg/m^2), adriamycin (30 mg/m^2), gelatin sponge	Significantly improved OS
Wei *et al.* (2018) [58]	2009–2012	China	250 (125/125)	1–2 courses, 4–6 weeks postoperatively	Iodized oil (4–5 mL), carboplatin (200 mg/m^2), mitomycin (6 mg/m^2), epirubicin (40 mg/m^2)	Significantly improved OS and DFS in patients with solitary tumor $\geqslant$ 5 cm and MVI
Wang *et al.* (2018) [59]	2011–2014	China	280 (140/140)	1 course, 4–6 weeks postoperatively	Adriamycin (20–30 mg/m^2) and lipiodol (3–5 mL)	Significantly reduced tumor recurrence and improved RFS and OS

meta-analysis of 8 RCTs and 12 non-RCT studies including 3325 patients. The results also showed that adjuvant TACE was associated with improved OS and RFS. Repeated TACE interventions did not provide a higher survival benefit compared with a single course. Different combinations of TACE antitumor regimes demonstrated similar survival benefits. Several previous meta-analyses have also suggested a beneficial effect of adjuvant TACE on survival [62–64].

The management of HCC with portal vein tumor thrombosis (PVTT) or hepatic vein tumor thrombus (HVTT) is complicated and controversial. With the development of treatment modalities, many studies have revealed that surgical resection offers a feasible treatment option for HCC with PVTT or HVTT and may provide a chance for long-term survival [65–67]. An early RCT involving 51 patients in the TACE group and 53 patients in the control group reported that the estimated survival rates at 1, 3, and 5 years were better in the postoperative TACE group than the control group. Liver resection combined with PVTT removal and postoperative TACE might be beneficial to the survival of HCC patients with PVTT [57]. In a large retrospective cohort, Liu *et al*. [68] found that postoperative adjuvant TACE was associated with longer OS. In particular, the benefit of adjuvant TACE seemed to be more pronounced in patients with larger extent of tumor thrombus (type II or III PVTT). For patients with HCC and HVTT, Zhang *et al*. [69] found that the OS and RFS were significantly better for patients in the postoperative TACE group than those in the liver resection alone group. Subgroup analysis showed that postoperative TACE may not provide survival benefits for patients with HVTT that extended to the inferior vena cava.

MVI is one of the most prominent prognostic risk factors of HCC prognosis after surgery. A randomized, open-labeled, phase III trial showed that adjuvant TACE after hepatectomy is effective to prevent recurrence and prolong the survival of patients with a solitary tumor $\geqslant$ 5 cm and MVI. Subgroup analysis found that male patients aged $<$ 60 years with the presence of cirrhosis, tumor $>$ 10 cm, and resection margin $<$ 2 cm would benefit most from adjuvant TACE [58]. In a recent meta-analysis involving seven studies with 1869 patients, the patients in the postoperative TACE group had longer OS and DFS than those in the hepatectomy alone group. For HCC larger than 5 cm, postoperative TACE prolonged the DFS, but the difference in OS was not statistically significant [70]. Another two meta-analyses also suggested that adjuvant TACE could improve PFS and OS for patients with HCC and MVI. Subgroup analysis demonstrated that HCC patients with MVI or tumor diameter $>$ 5 cm or multinodular tumors could benefit from adjuvant TACE [71,72].

Molecular targeted therapy

Sorafenib is regarded as a valuable and standard treatment for patients with advanced and unresectable HCC. Recent opinions that adjuvant sorafenib could benefit patients with HCC after liver resection remain controversial. To date, the STORM trial is the only RCT that investigated the efficacy of sorafenib as an adjuvant therapy in patients with HCC after surgical resection or local ablation with curative intent [73]. It included 1114 patients (556 in the sorafenib group and 558 in the placebo group) across 202 sites in 28 countries. After a median duration of about 12.5 months of treatment, sorafenib had no significant treatment effect on RFS, time to recurrence (TTR), or OS. Another European study also showed that adjuvant sorafenib does not confer any substantial clinical benefit in terms of survival [74]. On the contrary, several recent retrospective studies from China demonstrated that sorafenib could reduce recurrence and prolong the survival rate in patients after surgery [75–80]. Of note, all these studies have included patients with high risk of recurrence after surgery. A retrospective study involving a small sample size from Taiwan, China demonstrated that sorafenib effectively prevents early recurrence after curative liver resection in patients with solitary poorly differentiated tumor and/or satellite nodules and/or MVI [75]. Li *et al*. [76] and Xia *et al*. [77] found that adjuvant sorafenib significantly prolonged time to progression, DFS, and OS after curative resection for locally advanced HCC in BCLC stage C patients. For patients with tumors involving a major branch of the portal or hepatic vein, direct invasion of adjacent organs, or tumor ruptures, Liao *et al*. [78] found that patients receiving sorafenib following resection had significantly longer DFS compared with the best supportive care group. Zhuang *et al*. [79] revealed that sorafenib significantly increased OS after hepatectomy in intermediate stage and in advanced stage HCC. Recently, Huang *et al*. [80] evaluated the effect of sorafenib as an adjuvant therapy on the clinical outcomes in HCC patients with MVI. The results indicated that adjuvant sorafenib significantly prolonged both RFS and OS of HCC patients after curative resection. A meta-analysis also found that sorafenib as an adjuvant treatment could improve RFS and reduce the recurrence rate and mortality rate [81].

Immunotherapy

Immunotherapy has shown to be a promising therapy for HCC by stimulating or adjusting the immune function to kill tumor cells. It includes adoptive immunotherapy (lymphokine-activated killer (LAK) cells, cytokine-induced killer (CIK) cells, natural killer (NK) cells), tumor vaccines, immune checkpoint inhibitors (ICIs), and immunomodulators (cytokines, ILs, chemokines) [82]. To date, seven RCTs from Asia evaluated the efficacy of adjuvant adoptive immunotherapy (AIT) with CIK cells or LAK cells after curative treatments for HCC [83–89].

One of the earliest studies by Takayama *et al*. [84] evaluated the therapeutic effect of adjuvant immunotherapy. After a median follow-up of 4.4 years, the patients in the adoptive immunotherapy group had an 18% decreased frequency of recurrence and significantly longer RFS. However, the OS did not differ significantly between groups. Hui *et al.* [85] also found that postoperative immunotherapy with CIK cells may prevent recurrence and metastasis, but it did not affect the OS. For patients with HCC treated by surgical resection, Yu *et al*. [86] found that adjuvant CIK treatment delayed early tumor recurrence, but the 3-year OS and PFS showed no significant differences between the two arms. In 2015, a phase III multicenter RCT study from Korea for the first time demonstrated that adjuvant immunotherapy with commercialized CIK cell agents improves both RFS and OS after potentially curative treatment for HCC [87]. The same research team conducted an extended follow-up study [88]. The results showed that adjuvant CIK cell immunotherapy significantly improves RFS and OS for up to 5 years. Recently, another RCT also showed that CIK cell treatment significantly prolonged the TTR after curative resection, but the treatment did not affect the DFS and OS [89]. The possible explanations for this discrepancy may lie in the differences of the treatment cycle and the durations of AIT therapy. In addition, the length of follow-up and the HCC stage prior to curative treatment varied across the studies. A meta-analysis of the abovementioned RCTs suggested that adoptive immunotherapy can significantly improve the clinical prognosis (recurrence and survival rate) after curative treatment in the early stage (< 3 years) but not in the late stage (5 years) [90–92]. This may mean that adjuvant AIT can eliminate small intrahepatic metastases, but it may have no effect on liver cirrhosis and cannot prevent multicentric recurrence in remnant liver.

The aim of cancer vaccination is to alter the tumor-suppressing microenvironment and trigger tumor-specific immunological effects by inducing effector T-cells, which can induce immunological memory to control tumor recurrence. Kuang *et al*. [93] developed an autologous formalin-fixed tumor vaccine. This vaccine significantly reduced early postoperative recurrence and improved OS compared with the no adjuvant control. Dendritic cells (DCs) are professional antigen-presenting cells, which play a crucial role in both innate and adaptive immunity. Several recent prospective studies assessed the efficacy and safety of adjuvant immunotherapy with DC vaccine in patients with HCC after curative treatments. A phase II multicenter clinical study from Korea found that patients who received DC immunotherapy after surgical resection had significantly better RFS than the control group [94].

Shimizu *et al*. [95] investigated the efficacy of the combination therapy of DC vaccines and CD3-activated T-cell transfer (ATVAC) for postoperative HCC. The results showed that postoperative ATVAC treatment could succeed in improving RFS and OS in patients with HCC.

Recent advances in cancer immunotherapies using ICIs have brought novel and promising opportunities in cancer treatment. CTLA-4 and PD-1 are the most investigated ICIs in HCC [96]. Unfortunately, RCTs assessing the efficacy of ICIs as adjuvant therapy following surgical resection for HCC are lacking. The CheckMate-9DX is an ongoing trial investigating whether nivolumab will improve RFS compared with placebo in patients with HCC who have a high risk of recurrence after hepatic resection or ablation. In a phase III study (KEYNOTE-937), pembrolizumab is being compared with placebo following curative resection or ablation, with RFS as the primary outcome [97]. Another phase III study (IMbrave 050) is currently comparing atezolizumab plus bevacizumab with active surveillance in HCC patients at high risk of recurrence following curative treatment. A phase III trial (EMERALD-2) is also looking at the use of durvalumab plus bevacizumab combination or durvalumab alone in the adjuvant setting. The findings of these trials are highly awaited.

Systemic or regional adjuvant chemotherapy

The benefit of adjuvant chemotherapy is to control tumor growth and reduce recurrence, which has been proven in many solid tumors. Four RCT studies have explored the role of adjuvant systemic chemotherapy in reducing recurrence and metastasis after radical resection for HCC. The earliest RCT conducted by Yamamoto *et al*. [98] in 1996 found that the OS and RFS of patients with mild liver dysfunction in the adjuvant oral carmofur group were significantly higher than those of the control group. However, for patients with moderate liver dysfunction, no significant difference was observed. Hasegawa *et al*. [99] found no evidence to support the survival benefit of oral tegafur/uracil for patients who underwent curative hepatic resection and observed that tegafur/uracil might have some potentially undesirable effects on OS. Another RCT from China found that postoperative adjuvant therapy with capecitabine significantly increased the median TTR of HCC patients after curative resection and reduced the risk of tumor recurrence, but did not improve the OS [100]. A recent RCT involving 117 patients in Japan reported that adjuvant oral tegafur/uracil failed to prolong the OS and RFS compared with surgery alone [101]. A systematic review including the first three RCTs concluded that adjuvant oral systemic chemotherapy did not provide significant benefit regarding OS and DFS [102].

Hepatic artery infusion chemotherapy (HAIC) is considered to result in higher tumor drug concentrations and have less systemic toxicity than standard systemic chemotherapy. To reduce early multiple intrahepatic recurrence after surgical resection for patients with PVTT, researchers in some institutions pay more attention to postoperative adjuvant HAIC. Hamada *et al*. [103] reported that HCC patients with portal vein infiltration who were treated with adjuvant HAIC had a higher OS than those without HAI, but not with tumor-free survival. Another retrospective multi-institutional study from Japan involving 400 HCC patients with PVTT in the first branch or main portal trunk found that adjuvant postoperative HAIC was associated with improved DFS and OS in such patients [104]. For patients with multiple tumors and concomitant MVI, Hsiao *et al*. [105] reported that the OS time was better in the HAIC group. Other retrospective studies have also found that adjuvant HAIC might reduce the risk of postoperative recurrence and improve OS in patients with HCC and PVTT [106–108]. A meta-analysis based on 11 retrospective cohort studies concluded that the combined treatment of surgical resection and adjuvant HAI therapy had improved OS compared with surgery alone. However, stratified analysis showed that resection with adjuvant HAI therapy failed to improve DFS in tumors $\geqslant$ 7 cm [109].

Radiolabeled lipiodol therapy

Lau *et al*. [110] proposed for the first time the use of intra-arterial iodine-131(^{131}I)-labeled lipiodol as an adjuvant treatment after hepatectomy for HCC. The RCT reported that patients who received postoperative intra-arterial ^{131}I-lipiodol had significantly better DFS and OS than those who received hepatic resection alone. A follow-up study based on all 43 randomized patients found that adjuvant intra-arterial ^{131}I-lipiodol could significantly improve the long-term DFS and OS up to 7 years [111]. Subsequently, two French and one Australian nonrandomized studies also demonstrated favorable outcomes with adjuvant ^{131}I-lipiodol after resection of HCC [112–114]. A small case–control study reported that the intrahepatic injection of ^{131}I-lipiodol was beneficial to prevent early recurrence of HCC following curative surgical resection in the short term up to 15 months [115].

However, a recent multicenter RCT involving 103 patients concluded that adjuvant ^{131}I-lipiodol therapy did not provide significant clinical benefit [116]. Another retrospective study of the largest sample to date also reached a similar conclusion [117]. The results from meta-analysis showed that adjuvant ^{131}I-lipiodol significantly reduced the risk of HCC recurrence and improved the DFS and OS [118–120]. Only one RCT evaluated the effects of postoperative iodine-125 (^{125}I) brachytherapy on the

recurrence of HCC. The results indicated that ^{125}I brachytherapy could significantly prolong TTR and OS in HCC patients receiving curative resection [121]. Further larger, multicentered RCTs are warranted to arrive at a conclusive evidence.

Radiation therapy

Radiotherapy (RT) is one of the most important strategies for cancer treatment. Recently, multiple studies have reported positive outcomes of RT with favorable OS and good local control rates in advanced HCC [122,123]. The data on postoperative RT as adjuvant therapy to surgical resection are limited. For centrally located HCC, it is often difficult to gain an adequate resection margin (> 1 cm) during liver resection. A prospective randomized study found that adjuvant RT for centrally located HCC did not improve RFS and OS. Subgroup comparison of patients with small HCC (< 5 cm) showed that RFS was significantly longer in the adjuvant RT group than in the control group [124]. A recent study carried out in HCC patients with MVI and narrow resection margin showed that postoperative RT resulted in significantly superior survival outcomes than in the control group regardless of the degree of MVI classification [125]. Some studies have suggested that adjuvant RT might be better than TACE with respect to RFS and OS for HCC patients with MVI [126,127]. An RCT trial by Sun *et al*. [128] found that postoperative RT significantly improved the DFS and OS outcomes in patients with HCC and PVTT. The survival benefits were limited to patients with HCC and PVTT type I and II.

VK2 analogs and retinoids

VK2 is known as a co-enzyme for γ-carboxylase. VK2 has been shown to induce cell cycle arrest at the G1/S phase, leading to growth inhibition of hepatoma cells, and exert strong anti-angiogenic effects [129,130]. Six RCTs and one cohort study from Japan investigated the effects of VK2 on recurrence and survival in patients with HCC after curative treatment [131–137]. Three of these RCTs reported that VK2 or combination treatment of VK2 and ACEI may be effective in preventing the recurrence of HCC [131,133,134]. However, other studies found no difference in DFS between treatment and control arms [132,135–137]. All seven studies suggested that VK2 analogs had no significant effects on OS after hepatic resection or local ablation. A meta-analysis based on these studies found that VK2 analog therapy significantly reduced the 2- and 3-year tumor recurrence rates and improved the 1-, 2-, and 3-year OS [138].

Analogues of vitamin A (retinoids) can inhibit chemically induced hepatocarcinogenesis in rats [139]. One RCT by Muto *et al*. [140] involving 89 patients found that oral polyprenoic acid was effective in reducing the incidence of recurrent or new hepatomas after surgical resection or the percutaneous injection of ethanol. The research group continued to follow up these patients and found that the preventive effect of acyclic vitamin A lasted up to 199 weeks after randomization [141]. All these studies were conducted in Japan where most patients were infected with hepatitis C virus. Therefore, the effect of VK2 analog and retinoid therapy in other patient populations is still unknown.

Traditional Chinese medicine

Traditional Chinese medicine plays an important role in preventing cancer recurrence and metastasis and prolonging the OS of cancer patients in China [142]. *Perenniporia robiniophila* (Murrill) Ryvarden or Huaier is a sandy beige mushroom that grows on hard wood trees and has been used in China for nearly 1600 years [143]. Huaier exerts antitumor effects by inducing cell cycle arrest at the G0/G1 phase, inhibiting cell proliferation, inducing cell apoptosis, and inhibiting tumor angiogenesis [144–146]. A recent multicenter RCT by our group evaluated the effect of adjuvant application of Huaier granules on long-term prognosis after radical resection of HCC [147]. A total of 1044 patients were randomly assigned to receive Huaier granules and placebo in a 2:1 ratio. A significant prolongation of RFS and reduced extrahepatic recurrence were observed in the Huaier group. Zhai *et al*. [148] conducted a multicenter RCT to compare the clinical efficacy of traditional herbal medicine (THM) treatment and TACE on the recurrence rate of small HCC after radical resection. The results indicated that the RFS and OS in the THM group were significantly superior to those in the TACE group.

Other adjuvant therapies

The administration of branched chain amino acids (BCAAs) is known to correct malnutrition in patients with cirrhosis [149]. Four RCTs from Japan [150–153], one of which was later republished [153], examined the clinical efficiency in terms of tumor recurrence and OS in patients with HCC undergoing hepatic resection. Three of these studies found that BCAA treatment failed to significantly improve OS or reduce tumor recurrence [150–152]. Ichikawa *et al*. [153] found that oral supplementation of BCAA can reduce early recurrence after hepatic resection in patients with HCC.

PI-88 is a compound with antiheparanase activity, which has a direct effect on angiogenic growth factor binding

[154]. A phase II RCT using PI-88 as adjuvant therapy in patients with HCC after curative resection showed that the RFS was marginally higher in the group treated with 160 mg/day PI-88 than the control group ($P = 0.07$) [155]. In the observational follow-up study, Liu *et al*. [156] reported that PI-88 treatment decreased the 3-year TTR probability by 21.8%. However, no significant increase in RFS or OS was observed.

Conclusions

Adjuvant therapy for preventing recurrence after curative treatment is a critical issue for improving the long-term survival of HCC patients. Antiviral therapy has potential benefits with regard to reducing the recurrence rate and improving the OS and/or DFS of patients with hepatitis-related HCC after curative therapy. Whether direct antiviral drugs will increase the recurrence rate of hepatitis C-related HCC remains to be further investigated. Post-operative adjuvant TACE can significantly reduce the intrahepatic recurrence rate and improve OS, especially for patients with a high risk of recurrence (tumor diameter > 5 cm, MVI positive, or multinodular tumors). Although the results of the STROM study did not meet the expected goals, it is too early to believe that molecular targeted drugs are useless in postoperative adjuvant therapy. Based on the recent results of multiple retrospective studies, the efficacy of molecular targeted drugs as an adjuvant therapy deserves further study. Existing evidence suggests that AIT can significantly improve early clinical prognosis (recurrence and survival rate). The long-term efficacy will require further investigation. A number of RCT studies evaluating adjuvant ICI after hepatectomy are ongoing, and the results are highly expected. Current evidence does not support the use of adjuvant chemotherapy to improve survival outcomes. However, adjuvant HAIC might be beneficial in patients with macroscopic or microscopic vascular invasion. The first nationwide multicenter study in China proved the effectiveness of Huaier granule as adjuvant therapy for HCC after liver resection. Other adjuvant treatments such as radiolabeled lipiodol, radiation therapy, VK2 analogs and retinoids, and PI-88 are not routinely used in clinical practices, and further validation from large RCTs is needed.

Acknowledgements

This work is supported by the National Natural Science Foundation of China (No. 81860117).

Compliance with ethics guidelines

Wei Zhang, Bixiang Zhang, and Xiao-ping Chen declare that they have no conflicts of interest. This manuscript is a review article and does not involve a research protocol requiring approval by the relevant institutional review board or ethics committee.

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