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REVIEW

- 1604** Advances in postoperative adjuvant therapy for primary liver cancer
Zeng ZM, Mo N, Zeng J, Ma FC, Jiang YF, Huang HS, Liao XW, Zhu GZ, Ma J, Peng T
- 1622** Immunotherapy for nonalcoholic fatty liver disease-related hepatocellular carcinoma: Lights and shadows
Costante F, Airola C, Santopaolo F, Gasbarrini A, Pompili M, Ponziani FR
- 1637** Emerging role of caldesmon in cancer: A potential biomarker for colorectal cancer and other cancers
Alnuaimi AR, Nair VA, Malhab LJB, Abu-Gharbieh E, Ranade AV, Pintus G, Hamad M, Busch H, Kirfel J, Hamoudi R, Abdel-Rahman WM

MINIREVIEWS

- 1654** Liquid biopsy to detect resistance mutations against anti-epidermal growth factor receptor therapy in metastatic colorectal cancer
Valenzuela G, Burotto M, Marcelain K, González-Montero J
- 1665** Implication of gut microbiome in immunotherapy for colorectal cancer
Koustas E, Trifylli EM, Sarantis P, Papadopoulos N, Aloizos G, Tsagarakis A, Damaskos C, Garmpis N, Garmpi A, Papavassiliou AG, Karamouzis MV

ORIGINAL ARTICLE**Basic Study**

- 1675** Potential of six-transmembrane epithelial antigen of the prostate 4 as a prognostic marker for colorectal cancer
Fang ZX, Li CL, Chen WJ, Wu HT, Liu J

Case Control Study

- 1689** Inverse relations between *Helicobacter pylori* infection and risk of esophageal precancerous lesions in drinkers and peanut consumption
Pan D, Sun GJ, Su M, Wang X, Yan QY, Song G, Wang YY, Xu DF, Wang NN, Wang SK

Retrospective Cohort Study

- 1699** Prognostic impact of tumor deposits on overall survival in colorectal cancer: Based on Surveillance, Epidemiology, and End Results database
Wu WX, Zhang DK, Chen SX, Hou ZY, Sun BL, Yao L, Jie JZ
- 1711** Consolidation chemotherapy with capecitabine after neoadjuvant chemoradiotherapy in high-risk patients with locally advanced rectal cancer: Propensity score study
Sheng XQ, Wang HZ, Li S, Zhang YZ, Geng JH, Zhu XG, Quan JZ, Li YH, Cai Y, Wang WH

Retrospective Study

- 1727 Efficacy and safety of computed tomography-guided microwave ablation with fine needle-assisted puncture positioning technique for hepatocellular carcinoma
Hao MZ, Hu YB, Chen QZ, Chen ZX, Lin HL
- 1739 Clinicopathological characterization of ten patients with primary malignant melanoma of the esophagus and literature review
Zhou SL, Zhang LQ, Zhao XK, Wu Y, Liu QY, Li B, Wang JJ, Zhao RJ, Wang XJ, Chen Y, Wang LD, Kong LF
- 1758 Endoscopic debulking resection with additive chemoradiotherapy: Optimal management of advanced inoperable esophageal squamous cell carcinoma
Ren LH, Zhu Y, Chen R, Shrestha Sachin M, Lu Q, Xie WH, Lu T, Wei XY, Shi RH
- 1771 Nomogram for predicting the prognosis of tumor patients with sepsis after gastrointestinal surgery
Chen RX, Wu ZQ, Li ZY, Wang HZ, Ji JF
- 1785 Efficacy and safety of laparoscopic radical resection following neoadjuvant therapy for pancreatic ductal adenocarcinoma: A retrospective study
He YG, Huang XB, Li YM, Li J, Peng XH, Huang W, Tang YC, Zheng L

Observational Study

- 1798 To scope or not - the challenges of managing patients with positive fecal occult blood test after recent colonoscopy
Rattan N, Willmann L, Aston D, George S, Bassan M, Abi-Hanna D, Anandabaskaran S, Ermerak G, Ng W, Koo JH
- 1808 Clinical implications of interleukins-31, 32, and 33 in gastric cancer
Liu QH, Zhang JW, Xia L, Wise SG, Hambly BD, Tao K, Bao SS
- 1823 Construction and analysis of an ulcer risk prediction model after endoscopic submucosal dissection for early gastric cancer
Gong SD, Li H, Xie YB, Wang XH
- 1833 Percutaneous insertion of a novel dedicated metal stent to treat malignant hilar biliary obstruction
Cortese F, Acquafredda F, Mardighian A, Zurlo MT, Ferraro V, Memeo R, Spiliopoulos S, Inchingolo R

EVIDENCE-BASED MEDICINE

- 1844 Prediction of gastric cancer risk by a polygenic risk score of *Helicobacter pylori*
Wang XY, Wang LL, Liang SZ, Yang C, Xu L, Yu MC, Wang YX, Dong QJ

META-ANALYSIS

- 1856 Dissecting novel mechanisms of hepatitis B virus related hepatocellular carcinoma using meta-analysis of public data
Aljabban J, Rohr M, Syed S, Cohen E, Hashi N, Syed S, Khorfan K, Aljabban H, Borkowski V, Segal M, Mukhtar M, Mohammed M, Boateng E, Nemer M, Panahiazar M, Hadley D, Jalil S, Mumtaz K
- 1874 Prognostic and clinicopathological value of Twist expression in esophageal cancer: A meta-analysis
Song WP, Wang SY, Zhou SC, Wu DS, Xie JY, Liu TT, Wu XZ, Che GW

LETTER TO THE EDITOR

1886 Nutrition deprivation affects the cytotoxic effect of CD8 T cells in hepatocellular carcinoma

Zhang CY, Liu S, Yang M

ABOUT COVER

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Advances in postoperative adjuvant therapy for primary liver cancer

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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 3 and 5 years after liver resection, respectively, and even in Milan-eligible recipients, the recurrence rate is approximately 20% at 5 years after liver transplantation. Therefore, reducing the postoperative recurrence rate is 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.

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INTRODUCTION

Primary liver cancer (PLC) is one of the most common malignancies worldwide. According to the Global Cancer Data (GLOBOCAN) 2020, the annual number of new cases of liver cancer reached 905677 worldwide, ranking seventh in malignant tumors, whereas the annual number of deaths caused by PLC is 830180, ranking second in malignant tumors[1]. 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 fourth most common malignant tumor in China, and its mortality rate ranks second, with a ratio of incidence to mortality rates reaching 1:0.8[2], which seriously threatens the life and health of the population. The predominant histological type of PLC is hepatocellular carcinoma (HCC), which accounts for approximately 85% to 90% of 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[3-6]. 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[7]. 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%[8,9], and even if they receive liver transplantation, the 5-year recurrence rate in recipients who meet the Milan criteria can reach approximately 20%[10]. 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[11].

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 2 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[12]. 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 2 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 [13]. 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[14-16]. 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[14-17]. 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, University of California San Francisco 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[18].

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%-25% from the hepatic artery and 70%-75% from the portal vein, whereas 95%-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[19-23]. These results were confirmed by two recently published RCTs. Wang *et al*[24] 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 TACE or observation groups after radical hepatectomy. Patients in the TACE group had a significantly lower recurrence rate and significantly longer recurrence-free survival (RFS) and OS compared to those of the observation group[24]. In another randomized, open-label, single-center phase III study including 250 cases Wei *et al*[25] randomly assigned 1:1 patients with HCC and tumor diameter > 5 cm with microvascular invasion (MVI) to either adjuvant TACE or non-adjuvant treatment groups. The results showed a median disease-free survival (DFS) of 17.45 mo in the TACE group compared with 9.27 mo in the control group (hazard ratio [HR] = 0.70; $P = 0.020$)[25]. Qi *et al*[26] reported a prospective clinical study in which 200 patients with postoperative pathologically MVI-positive HCC were divided into adjuvant TACE and control groups. The results showed that TACE improved the prognosis of the disease, especially in patients with tumors > 5 cm in diameter or multinodular tumors. Several large single-center retrospective studies[27-31] found that postoperative adjuvant TACE therapy prolonged 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, adjuvant TACE treatment was generally well tolerated, although it increased the incidence of adverse events.

In patients at low risk of recurrence, a retrospective study[32] including 180 patients with hepatectomized HCC reported that the median progression-free survival of patients treated with TACE after surgery was 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 was 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 suggested that patients with low-risk recurrent HCC do not seem to benefit from the adjuvant therapy[33]. 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[34,35]. Huang *et al*[36] 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-year 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[36]. 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 HCC. 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 was significantly better in the postoperative adjuvant HAIC group (5-fluorouracil, oxaliplatin, and mitomycin combination regimen) than in the non-chemotherapy group[37]. 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 were significantly longer in the postoperative adjuvant PVC group ($n = 67$) than in the control group, and the cumulative recurrence rate was significantly lower in the PVC group compared to that of the control group[38]. Hamada *et al*[39] reported that DFS and OS were 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*[40] 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 improved OS and DFS compared to surgical treatment alone[41]. Li *et al*[42] reported a prospective, open-label, phase III, randomized controlled trial that included 127 patients and the results showed that postoperative transarterial infusion chemotherapy (FOLFOX regimen) as adjuvant therapy in patients with HCC with MVI prolonged 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 found that adjuvant radiotherapy for centrally located HCC did not improve RFS and OS; subgroup analysis showed that RFS was significantly longer in the adjuvant radiotherapy group than in the control group in the subgroup of patients with small HCC (< 5 cm)[43]. Another prospective randomized controlled study provided 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 showed no significant difference in RFS between the adjuvant radiotherapy and control groups, while RFS was significantly longer in patients with small HCC (5 cm) and OS was significantly improved in patients with small HCC compared to those of the control group at 2 to 5 years after treatment[44]. By contrast, Wang *et al*[45] showed that in patients with HCC with close to large vessels, postoperative adjuvant radiotherapy led to 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[46]. In patients with positive MVI, the study showed that the postoperative adjuvant radiotherapy group had significantly better RFS and OS than those of the TACE and unadjuvanted groups in patients with HCC combined with MVI [47]. A study of patients with MVI combined with narrow margin HCC showed that postoperative radiotherapy was significantly superior to controls, regardless of the degree of MVI staging[48]. Sun *et al* [49] reported an RCT in which the postoperative radiotherapy significantly prolonged 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 were 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* [50] 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 were significantly better in patients with 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 improved long-term DFS and OS for up to 7 years[51]. Subsequently, several non-randomized studies also confirmed that adjuvant 131I-iodine oil after HCC resection improved DFS and OS after hepatectomy[52-54]. However, a multicenter RCT involving 103 patients showed that the adjuvant 131I-iodine oil treatment did not improve RFS and OS [55]. Another retrospective study with the largest sample to date showed no significant survival improvement with the 131I-iodine oil adjuvant therapy[56]. The results of the meta-analysis showed that intra-arterial instillation of 131I-iodine oil after hepatectomy significantly reduced the risk of HCC recurrence and improved DFS and OS[57,58], 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 improved 5-year RFS in patients with cluster of differentiation 147-expressing tumors after hepatectomy and is well tolerated by patients; subgroup analysis showed that the main effective targets were high-risk recurrent patients with MVI-positive, tumor diameter > 5 cm, poorly differentiated tumors, and incomplete tumor envelope[59]. 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 prolonged TTR and OS in patients with HCC who underwent radical resection[60].

ADJUNCTIVE SYSTEM THERAPY

Postoperative adjuvant targeted therapy

Sorafenib monotherapy is used as a standard treatment option for advanced HCC, but its effectiveness in postoperative adjuvant therapy has been unsatisfactory. The 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 sorafenib treatment or placebo groups[61], which showed no statistical difference in RFS between the two groups (33.3 *vs* 33.7 mo; $P = 0.26$). Conversely, 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[62] 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 had 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 was significantly lower in the sorafenib-treated than in the control group (29.4% *vs* 70.7%; $P = 0.032$)[63]. Li *et al*[64] showed that patients treated with sorafenib within 30 d after surgery had 7 mo longer tumor-free survival than those treated with surgery only, with safe and manageable side effects. A retrospective analysis found that treatment with adjuvant sorafenib is beneficial for patients with postoperative high-risk recurrence HCC. Wang *et al*[65] 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 was significantly higher in the sorafenib group than in the control group. 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 had significantly better OS and RFS than those of the surgery alone group[66]. 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 were better than previous historical ones in terms of the median RFS[64]. Moreover, 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 was 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; $P = 0.0359$) [67]. These results showed 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* [68] 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 6 wk 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 was better in the adjuvant group than in the palliative care and control groups ($P = 0.034, 0.026, \text{ and } 0.011$, respectively), and OS at 24 mo of follow-up show the same trend ($P = 0.031$). Shetty *et al* [69] found a reduction in the overall recurrence rate of HCC in the adjuvant sorafenib treatment group (7 patients) compared to 12 historical control patients (29% *vs* 75%; $P = 0.07$). Huang *et al* [70] 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 was significantly lower in the test group compared to the control group (53.3% *vs* 86.6%; $P < 0.05$) and the OS was significantly longer (28.3 ± 2.5 mo *vs* 17.9 ± 3.5 mo; $P < 0.05$). Han *et al* [71] 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 was 291 [95% confidence interval (CI): 204-516] d, which was significantly longer than that in the control group of 182 (95%CI: 56-537) d ($P = 0.04$); the drug safety and patient tolerability were acceptable.

The aforementioned studies were all single-center, small-sample clinical explorations, and although the credibility of the results was 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 [72], but also favoring immune escape of HCC cells [73]. 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 [74] on the application of secondary immunotherapy after surgery for HCC showed that secondary immunotherapy reduced the risk of recurrence by 41% compared with that of the control group, and RFS and disease-specific survival were significantly better in the immunotherapy group than in the control group, but the difference in OS between the two groups was not statistically significant. A large phase III RCT [75] 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 extended the median RFS time from 30 to 44 mo but also reduced the overall risk of death and had 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 ($P = 0.009$) [76]. 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 cytokine-induced killer (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 [77]. A meta-analysis that included eight RCTs and two cohort studies containing 2120 patients showed that patients with HCC treated with adjuvant overt immunotherapy had significantly lower recurrence rates at 1, 3, and 5 years than those of the surgical treatment alone group [78]. However, another meta-analysis containing eight RCTs showed that CIK reduced the 1- and 3-year postoperative recurrence rates and increased OS from 1 to 5 years in patients with HCC but had no effect on the 5-year recurrence rate and 6-year OS [79]. 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 programmed cell death protein 1 (PD-1) and programmed death-ligand 1 (PD-L1) upregulated tumor-infiltrating lymphocytes in HCC and HCC-associated Kupffer cells [80] 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 United States Food and Drug Administration 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*[81] 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, 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[82]. 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[83]. A recently published prospective RCT[84] 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*[85] 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 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*[86] 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 were 89.7%, 86.2%, and 78.8% in the adjuvant chemotherapy group, respectively, which was 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 showed 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 improved 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[87]. Although earlier studies suggested that adjuvant systemic chemotherapy might be associated with reduced recurrence and prolonged RFS[88], 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

Table 1 Clinical studies of postoperative adjuvant therapy under investigation for hepatocellular carcinoma

NCT	Phase	Treatment option	Patient population	Expected group entry	Primary endpoint	Status
NCT03383458 (CheckMate 9DX)	III	Nivolumab	High-risk recurrent HCC after radical resection/ablation	530	RFS	Follow-up
NCT04233840	I/II	Nivolumab ± P1101	Post-radical resection of HBV-related HCC	72	Phase I: DLT, phase II: RFS	Recruiting
NCT03867084 (KEYNOTE-937)	III	Pembrolizumab	Imaging CR after surgical resection/local ablation	950	RFS, OS	Recruiting
NCT04639180	III	Camrelizumab + apatinib	High-risk recurrent HCC after surgical resection or ablation	674	RFS	Recruiting
NCT03839550	II	Camrelizumab + apatinib	High-risk recurrent HCC after radical surgery	200	RFS	Not yet recruited
NCT04102098 (IMbrave050)	III	Atezolizumab + bevacizumab	High-risk recurrent HCC after surgical resection/ablation	662	RFS	Recruiting
NCT04649489	-	Atezolizumab + bevacizumab	Post hepatectomy with portal vein carcinoma thrombosis HCC	198	TTF	Not yet recruited
NCT03847428 (EMERALD-2)	III	Durvalumab + bevacizumab	High-risk recurrent HCC after radical resection/ablation	888	RFS	Recruiting

CR: Complete response; DLT: Dose-limiting toxicity; HBV: Hepatitis B virus; HCC: Hepatocellular carcinoma; OS: Overall survival; RFS: Recurrence-free survival; TTF: Time to treatment failure.

with chronic hepatitis B, and very few are associated with hepatitis C caused by the HCV. In patients with HBV-associated HCC, higher hepatitis B surface antigen levels[89] and viral load (serum HBV DNA >10⁶ copies/mL) before and after surgery[90,91] 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[92]. Two randomized trials[93,94] supported significantly higher OS and RFS in patients with HCC treated with postoperative adjuvant antiviral therapy. One of these studies[94] showed that the antiviral therapy is an independent prognostic factor for distant recurrence after HCC surgery (HR 0.348) but not for recurrence within 2 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 relative risk (RR) 0.50, 3-year recurrence rate RR 0.70][95] 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 ≥ 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[96,97]. 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 4 years[98], 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 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[99], showing that the DAA treatment did not reduce HCC recurrence rates but significantly improved OS. Studies have shown that the use of DAA, either before or after hepatectomy, can improve the prognosis of the disease[100], 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 (IFN)-free pan-genotypic regimens.

Adjuvant traditional herbal medicine treatment

Traditional herbal medicine exhibits antitumor activity by inhibiting tumor cell growth, inducing apoptosis, inhibiting angiogenesis, and enhancing immune function[101,102]. 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[103]. A retrospective study with a large sample size showed that a comprehensive THM treatment improved OS in patients with HCC[104]. 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 to TACE in preventing recurrence of small HCC and prolonged OS[105]. 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[106]. Lei *et al*[107] 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 were 17.9% and 35.7%, respectively, which were 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 IFN

IFN is considered 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 IFN α [108-115] and IFN β [116]. Ikeda *et al*[116] suggested adjuvant IFN β administration lowered postoperative recurrence rate in patients with HCC after their hepatic resection or ablation. However, RCTs on curative effects of IFN α showed conflicting results. Mazzaferro *et al*[109] reported that IFN α 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*[113] indicated it made no contribution to postoperative recurrence reduction, while Lo *et al*[114] found that patients with pathological tumor-node-metastasis 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 IFN suppressed tumor recurrence and increased overall survival within certain time periods[117-128]. Notwithstanding, IFN α significantly reduced recurrence rate in patients with HCC caused by HCV but not by HBV, according to subgroup analysis[117,125,127].

Adjuvant vitamin K2 analogs and retinoids

As a crucial hydrophobic vitamin, vitamin K2 (VK2) shows substantial anti-angiogenic effects, induce cell cycle arrest, and inhibits the proliferation of HCC cells[129-131]. The effects of VK2 were explored in six RCTs[132-137] and a cohort trial[138] 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*[132], Kakizaki *et al*[134] and Yoshiji *et al*[138] 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[133,135-137]. 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 second and third years, and improved 1-, 2-, and 3-year OS according to the findings of Zhong *et al*[139]. 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[140,141]. It was reported to inhibit the relapse in patients who have undergone hepatectomy through disrupting the

rapid growth of heparanase level after liver resection[142]. Liu *et al*[143] 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 and OS were not significantly improved[144].

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 in HCC patients are tumor protein p53, telomerase reverse transcriptase, and catenin beta 1, which mainly lead to the occurrence and development of HCC[145-147]. 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[148,149], 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.

FOOTNOTES

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REFERENCES

- Sung H**, Ferlay J, Siegel RL, Laversanne M, Soerjomataram I, Jemal A, Bray F. Global Cancer Statistics 2020: GLOBOCAN Estimates of Incidence and Mortality Worldwide for 36 Cancers in 185 Countries. *CA Cancer J Clin* 2021; **71**: 209-249 [PMID: 33538338 DOI: 10.3322/caac.21660]
- Cao W**, Chen HD, Yu YW, Li N, Chen WQ. Changing profiles of cancer burden worldwide and in China: a secondary analysis of the global cancer statistics 2020. *Chin Med J (Engl)* 2021; **134**: 783-791 [PMID: 33734139 DOI: 10.1097/CM9.0000000000001474]
- Ascha MS**, Hanounch IA, Lopez R, Tamimi TA, Feldstein AF, Zein NN. The incidence and risk factors of hepatocellular carcinoma in patients with nonalcoholic steatohepatitis. *Hepatology* 2010; **51**: 1972-1978 [PMID: 20209604 DOI: 10.1002/hep.23527]
- Mittal S**, El-Serag HB, Sada YH, Kanwal F, Duan Z, Temple S, May SB, Kramer JR, Richardson PA, Davila JA. Hepatocellular Carcinoma in the Absence of Cirrhosis in United States Veterans is Associated With Nonalcoholic Fatty Liver Disease. *Clin Gastroenterol Hepatol* 2016; **14**: 124-31.e1 [PMID: 26196445 DOI: 10.1016/j.cgh.2015.07.019]
- Younossi Z**, Stepanova M, Ong JP, Jacobson IM, Bugianesi E, Duseja A, Eguchi Y, Wong VW, Negro F, Yilmaz Y, Romero-Gomez M, George J, Ahmed A, Wong R, Younossi I, Ziaee M, Afendy A; Global Nonalcoholic Steatohepatitis Council. Nonalcoholic Steatohepatitis Is the Fastest Growing Cause of Hepatocellular Carcinoma in Liver Transplant Candidates. *Clin Gastroenterol Hepatol* 2019; **17**: 748-755.e3 [PMID: 29908364 DOI: 10.1016/j.cgh.2018.05.057]
- Ioannou GN**, Green P, Kerr KF, Berry K. Models estimating risk of hepatocellular carcinoma in patients with alcohol or NAFLD-related cirrhosis for risk stratification. *J Hepatol* 2019; **71**: 523-533 [PMID: 31145929 DOI: 10.1016/j.jhep.2019.05.008]
- Ioannou GN**, Splan MF, Weiss NS, McDonald GB, Beretta L, Lee SP. Incidence and predictors of hepatocellular carcinoma in patients with cirrhosis. *Clin Gastroenterol Hepatol* 2007; **5**: 938-945, 945.e1 [PMID: 17509946 DOI: 10.1016/j.cgh.2007.02.039]
- Dhir M**, Melin AA, Douaiher J, Lin C, Zhen WK, Hussain SM, Geschwind JF, Doyle MB, Abou-Alfa GK, Are C. A Review and Update of Treatment Options and Controversies in the Management of Hepatocellular Carcinoma. *Ann Surg* 2016; **263**: 1112-1125 [PMID: 26813914 DOI: 10.1097/SLA.0000000000001556]
- Rahbari NN**, Mehrabi A, Mollberg NM, Müller SA, Koch M, Büchler MW, Weitz J. Hepatocellular carcinoma: current management and perspectives for the future. *Ann Surg* 2011; **253**: 453-469 [PMID: 21263110 DOI: 10.1097/SLA.0b013e31820d944f]
- Mazzaferro V**, Llovet JM, Miceli R, Bhoori S, Schiavo M, Mariani L, Camerini T, Roayaie S, Schwartz ME, Grazi GL, Adam R, Neuhaus P, Salizzoni M, Bruix J, Forner A, De Carlis L, Cillo U, Burroughs AK, Troisi R, Rossi M, Gerunda GE, Lerut J, Belghiti J, Boin I, Gugenheim J, Rochling F, Van Hoek B, Majno P; Metroticket Investigator Study Group. Predicting survival after liver transplantation in patients with hepatocellular carcinoma beyond the Milan criteria: a retrospective, exploratory analysis. *Lancet Oncol* 2009; **10**: 35-43 [PMID: 19058754 DOI: 10.1016/S1470-2045(08)70284-5]
- Heimbach JK**, Kulik LM, Finn RS, Sirlin CB, Abecassis MM, Roberts LR, Zhu AX, Murad MH, Marrero JA. AASLD guidelines for the treatment of hepatocellular carcinoma. *Hepatology* 2018; **67**: 358-380 [PMID: 28130846 DOI: 10.1002/hep.29086]
- Calderaro J**, Petitprez F, Becht E, Laurent A, Hirsch TZ, Rousseau B, Luciani A, Amaddeo G, Derman J, Charpy C, Zucman-Rossi J, Fridman WH, Sautès-Fridman C. Intra-tumoral tertiary lymphoid structures are associated with a low risk of early recurrence of hepatocellular carcinoma. *J Hepatol* 2019; **70**: 58-65 [PMID: 30213589 DOI: 10.1016/j.jhep.2018.09.003]
- Xu XF**, Xing H, Han J, Li ZL, Lau WY, Zhou YH, Gu WM, Wang H, Chen TH, Zeng YY, Li C, Wu MC, Shen F, Yang T. Risk Factors, Patterns, and Outcomes of Late Recurrence After Liver Resection for Hepatocellular Carcinoma: A Multicenter Study From China. *JAMA Surg* 2019; **154**: 209-217 [PMID: 30422241 DOI: 10.1001/jamasurg.2018.4334]
- Wang MD**, Li C, Liang L, Xing H, Sun LY, Quan B, Wu H, Xu XF, Wu MC, Pawlik TM, Lau WY, Shen F, Yang T. Early and Late Recurrence of Hepatitis B Virus-Associated Hepatocellular Carcinoma. *Oncologist* 2020; **25**: e1541-e1551 [PMID: 32472951 DOI: 10.1634/theoncologist.2019-0944]
- Imamura H**, Matsuyama Y, Tanaka E, Ohkubo T, Hasegawa K, Miyagawa S, Sugawara Y, Minagawa M, Takayama T, Kawasaki S, Makuuchi M. Risk factors contributing to early and late phase intrahepatic recurrence of hepatocellular

- carcinoma after hepatectomy. *J Hepatol* 2003; **38**: 200-207 [PMID: 12547409 DOI: 10.1016/s0168-8278(02)00360-4]
- 16 **Sohn W**, Paik YH, Kim JM, Kwon CH, Joh JW, Cho JY, Gwak GY, Choi MS, Lee JH, Koh KC, Paik SW, Yoo BC. HBV DNA and HBsAg levels as risk predictors of early and late recurrence after curative resection of HBV-related hepatocellular carcinoma. *Ann Surg Oncol* 2014; **21**: 2429-2435 [PMID: 24619495 DOI: 10.1245/s10434-014-3621-x]
- 17 **Qu LS**, Liu JX, Zhu J, Lu CH. Risk Factors for Prognosis of Hepatocellular Carcinoma After Curative Resection In Patients with Low Hepatitis B Viral Load. *Ann Hepatol* 2017; **16**: 412-420 [PMID: 28425411 DOI: 10.5604/16652681.1235484]
- 18 **Zheng SS**, Cheng QY, Geng L, Xu X. Tumor recurrence after liver transplantation for hepatocellular carcinoma: recent research progress. *Zhonghua Putong Waikē Zazhi* 2019; **7**: 773-778 [DOI: 10.7659/j.issn.1005-6947.2019.07.001]
- 19 **Zhong C**, Guo RP, Li JQ, Shi M, Wei W, Chen MS, Zhang YQ. A randomized controlled trial of hepatectomy with adjuvant transcatheter arterial chemoembolization versus hepatectomy alone for Stage III A hepatocellular carcinoma. *J Cancer Res Clin Oncol* 2009; **135**: 1437-1445 [PMID: 19408012 DOI: 10.1007/s00432-009-0588-2]
- 20 **Peng BG**, He Q, Li JP, Zhou F. Adjuvant transcatheter arterial chemoembolization improves efficacy of hepatectomy for patients with hepatocellular carcinoma and portal vein tumor thrombus. *Am J Surg* 2009; **198**: 313-318 [PMID: 19285298 DOI: 10.1016/j.amjsurg.2008.09.026]
- 21 **Sylvester RJ**, van der Meijden AP, Oosterlinck W, Witjes JA, Bouffieux C, Denis L, Newling DW, Kurth K. Predicting recurrence and progression in individual patients with stage Ta T1 bladder cancer using EORTC risk tables: a combined analysis of 2596 patients from seven EORTC trials. *Eur Urol* 2006; **49**: 466-5; discussion 475 [PMID: 16442208 DOI: 10.1016/j.eururo.2005.12.031]
- 22 **Izumi R**, Shimizu K, Iyobe T, Ii T, Yagi M, Matsui O, Nonomura A, Miyazaki I. Postoperative adjuvant hepatic arterial infusion of Lipiodol containing anticancer drugs in patients with hepatocellular carcinoma. *Hepatology* 1994; **20**: 295-301 [PMID: 8045490 DOI: 10.1002/hep.1840200205]
- 23 **Li JQ**, Zhang YQ, Zhang WZ, Yuan YF, Li GH. Randomized study of chemoembolization as an adjuvant therapy for primary liver carcinoma after hepatectomy. *J Cancer Res Clin Oncol* 1995; **121**: 364-366 [PMID: 7541051 DOI: 10.1007/BF01225689]
- 24 **Wang Z**, Ren Z, Chen Y, Hu J, Yang G, Yu L, Yang X, Huang A, Zhang X, Zhou S, Sun H, Wang Y, Ge N, Xu X, Tang Z, Lau W, Fan J, Wang J, Zhou J. Adjuvant Transarterial Chemoembolization for HBV-Related Hepatocellular Carcinoma After Resection: A Randomized Controlled Study. *Clin Cancer Res* 2018; **24**: 2074-2081 [PMID: 29420221 DOI: 10.1158/1078-0432.CCR-17-2899]
- 25 **Wei W**, Jian PE, Li SH, Guo ZX, Zhang YF, Ling YH, Lin XJ, Xu L, Shi M, Zheng L, Chen MS, Guo RP. Adjuvant transcatheter arterial chemoembolization after curative resection for hepatocellular carcinoma patients with solitary tumor and microvascular invasion: a randomized clinical trial of efficacy and safety. *Cancer Commun (Lond)* 2018; **38**: 61 [PMID: 30305149 DOI: 10.1186/s40880-018-0331-y]
- 26 **Qi YP**, Zhong JH, Liang ZY, Zhang J, Chen B, Chen CZ, Li LQ, Xiang BD. Adjuvant transarterial chemoembolization for patients with hepatocellular carcinoma involving microvascular invasion. *Am J Surg* 2019; **217**: 739-744 [PMID: 30103903 DOI: 10.1016/j.amjsurg.2018.07.054]
- 27 **Ye JZ**, Chen JZ, Li ZH, Bai T, Chen J, Zhu SL, Li LQ, Wu FX. Efficacy of postoperative adjuvant transcatheter arterial chemoembolization in hepatocellular carcinoma patients with microvascular invasion. *World J Gastroenterol* 2017; **23**: 7415-7424 [PMID: 29151695 DOI: 10.3748/wjg.v23.i41.7415]
- 28 **Wang H**, Du PC, Wu MC, Cong WM. Postoperative adjuvant transarterial chemoembolization for multinodular hepatocellular carcinoma within the Barcelona Clinic Liver Cancer early stage and microvascular invasion. *Hepatobiliary Surg Nutr* 2018; **7**: 418-428 [PMID: 30652086 DOI: 10.21037/hbsn.2018.09.05]
- 29 **Gao Z**, Du G, Pang Y, Fu Z, Liu C, Liu Y, Zhou B, Kong D, Shi B, Jiang Z, Jin B. Adjuvant transarterial chemoembolization after radical resection contributed to the outcomes of hepatocellular carcinoma patients with high-risk factors. *Medicine (Baltimore)* 2017; **96**: e7426 [PMID: 28816936 DOI: 10.1097/MD.00000000000007426]
- 30 **Li C**, Wen TF, Yan LN, Lu WS, Li B, Wang WT, Xu MQ, Yang JY. Liver resection versus liver resection plus TACE for patients with hepatocellular carcinoma beyond Milan criteria. *J Surg Res* 2017; **209**: 8-16 [PMID: 28032575 DOI: 10.1016/j.jss.2016.09.054]
- 31 **Ye JZ**, Xie ZB, Bai T, Chen J, Gong WF, Qi LN, Zhong JH, Ma L, Xiang BD. Necessity of postoperative adjuvant hepatic arterial chemoembolization for patients with early recurrent liver cancer. *Zhonghua Gandan Waikē Zazhi* 2016; **4**: 217-222 [DOI: 10.3760/cma.j.issn.1007-8118.2016.04.001]
- 32 **Xie H**, Tian S, Cui L, Yan J, Bai Y, Li X, Wang M, Zhang F, Duan F. Adjuvant trans-arterial chemoembolization after hepatectomy significantly improves the prognosis of low-risk patients with R0-stage hepatocellular carcinoma. *Cancer Manag Res* 2019; **11**: 4065-4073 [PMID: 31118814 DOI: 10.2147/CMAR.S195485]
- 33 **Cheng X**, Sun P, Hu QG, Song ZF, Xiong J, Zheng QC. Transarterial (chemo)embolization for curative resection of hepatocellular carcinoma: a systematic review and meta-analyses. *J Cancer Res Clin Oncol* 2014; **140**: 1159-1170 [PMID: 24752339 DOI: 10.1007/s00432-014-1677-4]
- 34 **Chen ZH**, Zhang XP, Zhou TF, Wang K, Wang H, Chai ZT, Shi J, Guo WX, Cheng SQ. Adjuvant transarterial chemoembolization improves survival outcomes in hepatocellular carcinoma with microvascular invasion: A systematic review and meta-analysis. *Eur J Surg Oncol* 2019; **45**: 2188-2196 [PMID: 31256949 DOI: 10.1016/j.ejso.2019.06.031]
- 35 **Huang J**, Liu FC, Li L, Yuan SX, Yang Y, Jiang BG, Liu H, Pan ZY. Prognostic Nomogram for Hepatitis B Virus-related Hepatocellular Carcinoma With Adjuvant Transarterial Chemoembolization After Radical Resection. *Am J Clin Oncol* 2020; **43**: 20-27 [PMID: 31633514 DOI: 10.1097/COC.0000000000000619]
- 36 **Huang LF**, Xing X, Wu D, Xia Y, Li J, Wang K, Yan ZL, Wan XY, Shi LH, Yang T, Lau WY, Wu MC, Shen F. A novel scoring system predicts adjuvant chemolipiodolization benefit for hepatocellular carcinoma patients after hepatectomy. *Oncotarget* 2016; **7**: 25493-25506 [PMID: 27027439 DOI: 10.18632/oncotarget.8333]
- 37 **Feng M**, Tang C, Feng W, Bao Y, Zheng Y, Shen J. Hepatic artery-infusion chemotherapy improved survival of hepatocellular carcinoma after radical hepatectomy. *Onco Targets Ther* 2017; **10**: 3001-3005 [PMID: 28652782 DOI: 10.2147/OTT.S136806]

- 38 **Gao Y**, Wang PX, Cheng JW, Sun YF, Hu B, Guo W, Zhou KQ, Yin Y, Li YC, Wang J, Huang JF, Qiu SJ, Zhou J, Fan J, Yang XR. Chemotherapeutic perfusion of portal vein after tumor thrombectomy and hepatectomy benefits patients with advanced hepatocellular carcinoma: A propensity score-matched survival analysis. *Cancer Med* 2019; **8**: 6933-6944 [PMID: 31566899 DOI: 10.1002/cam4.2556]
- 39 **Hamada T**, Yano K, Wada T, Imamura N, Hiyoshi M, Kondo K, Nanashima A. Increased Survival Benefit of Adjuvant Intra-arterial Infusion Chemotherapy in HCC Patients with Portal Vein Infiltration after Hepatectomy. *World J Surg* 2020; **44**: 2770-2776 [PMID: 32318792 DOI: 10.1007/s00268-020-05527-w]
- 40 **Hsiao JH**, Tsai CC, Liang TJ, Chiang CL, Liang HL, Chen IS, Chen YC, Chang PM, Chou NH, Wang BW. Adjuvant hepatic arterial infusion chemotherapy is beneficial for selective patients with Hepatocellular carcinoma undergoing surgical treatment. *Int J Surg* 2017; **45**: 35-41 [PMID: 28728985 DOI: 10.1016/j.ijso.2017.07.071]
- 41 **Moran A**, Ramos LF, Picado O, Pendola F, Sleeman D, Dudeja V, Merchant N, Yakoub D. Hepatocellular carcinoma: resection with adjuvant hepatic artery infusion therapy vs resection alone. A systematic review and meta-analysis. *J Surg Oncol* 2019; **119**: 455-463 [PMID: 30575028 DOI: 10.1002/jso.25338]
- 42 **Li S**, Mei J, Wang Q, Guo Z, Lu L, Ling Y, Xu L, Chen M, Zheng L, Lin W, Zou J, Wen Y, Wei W, Guo R. Postoperative Adjuvant Transarterial Infusion Chemotherapy with FOLFOX Could Improve Outcomes of Hepatocellular Carcinoma Patients with Microvascular Invasion: A Preliminary Report of a Phase III, Randomized Controlled Clinical Trial. *Ann Surg Oncol* 2020; **27**: 5183-5190 [PMID: 32418078 DOI: 10.1245/s10434-020-08601-8]
- 43 **Yu W**, Wang W, Rong W, Wang L, Xu Q, Wu F, Liu L, Wu J. Adjuvant radiotherapy in centrally located hepatocellular carcinomas after hepatectomy with narrow margin (<1 cm): a prospective randomized study. *J Am Coll Surg* 2014; **218**: 381-392 [PMID: 24559953 DOI: 10.1016/j.jamcollsurg.2013.11.030]
- 44 **Rong W**, Yu W, Wang L, Wu F, Zhang K, Chen B, Miao C, Liu L, An S, Tao C, Wang W, Wu J. Adjuvant radiotherapy in central hepatocellular carcinoma after narrow-margin hepatectomy: A 10-year real-world evidence. *Zhongguo Aizheng Yanjiu* 2020; **32**: 645-653 [DOI: 10.21147/j.issn.1000-9604.2020.05.09]
- 45 **Wang WH**, Wang Z, Wu JX, Zhang T, Rong WQ, Wang LM, Jin J, Wang SL, Song YW, Liu YP, Ren H, Fang H, Wang WQ, Liu XF, Yu ZH, Li YX. Survival benefit with IMRT following narrow-margin hepatectomy in patients with hepatocellular carcinoma close to major vessels. *Liver Int* 2015; **35**: 2603-2610 [PMID: 25939444 DOI: 10.1111/liv.12857]
- 46 **Chen B**, Wu JX, Cheng SH, Wang LM, Rong WQ, Wu F, Wang SL, Jin J, Liu YP, Song YW, Ren H, Fang H, Tang Y, Li N, Li YX, Wang WH. Phase 2 Study of Adjuvant Radiotherapy Following Narrow-Margin Hepatectomy in Patients With HCC. *Hepatology* 2021; **74**: 2595-2604 [PMID: 34097307 DOI: 10.1002/hep.31993]
- 47 **Wang L**, Wang W, Yao X, Rong W, Wu F, Chen B, Liu M, Lin S, Liu Y, Wu J. Postoperative adjuvant radiotherapy is associated with improved survival in hepatocellular carcinoma with microvascular invasion. *Oncotarget* 2017; **8**: 79971-79981 [PMID: 29108379 DOI: 10.18632/oncotarget.20402]
- 48 **Wang L**, Wang W, Rong W, Li Z, Wu F, Liu Y, Zheng Y, Zhang K, Siqin T, Liu M, Chen B, Wu J. Postoperative adjuvant treatment strategy for hepatocellular carcinoma with microvascular invasion: a non-randomized interventional clinical study. *BMC Cancer* 2020; **20**: 614 [PMID: 32611327 DOI: 10.1186/s12885-020-07087-7]
- 49 **Sun J**, Yang L, Shi J, Liu C, Zhang X, Chai Z, Lau WY, Meng Y, Cheng SQ. Postoperative adjuvant IMRT for patients with HCC and portal vein tumor thrombus: An open-label randomized controlled trial. *Radiother Oncol* 2019; **140**: 20-25 [PMID: 31176205 DOI: 10.1016/j.radonc.2019.05.006]
- 50 **Lau WY**, Leung TW, Ho SK, Chan M, Machin D, Lau J, Chan AT, Yeo W, Mok TS, Yu SC, Leung NW, Johnson PJ. Adjuvant intra-arterial iodine-131-labelled lipiodol for resectable hepatocellular carcinoma: a prospective randomised trial. *Lancet* 1999; **353**: 797-801 [PMID: 10459961 DOI: 10.1016/s0140-6736(98)06475-7]
- 51 **Lau WY**, Lai EC, Leung TW, Yu SC. Adjuvant intra-arterial iodine-131-labeled lipiodol for resectable hepatocellular carcinoma: a prospective randomized trial-update on 5-year and 10-year survival. *Ann Surg* 2008; **247**: 43-48 [PMID: 18156922 DOI: 10.1097/SLA.0b013e3181571047]
- 52 **Partensky C**, Sassolas G, Henry L, Paliard P, Maddern GJ. Intra-arterial iodine 131-labeled lipiodol as adjuvant therapy after curative liver resection for hepatocellular carcinoma: a phase 2 clinical study. *Arch Surg* 2000; **135**: 1298-1300 [PMID: 11074884 DOI: 10.1001/archsurg.135.11.1298]
- 53 **Boucher E**, Corbinais S, Rolland Y, Bourguet P, Guyader D, Boudjema K, Meunier B, Raoul JL. Adjuvant intra-arterial injection of iodine-131-labeled lipiodol after resection of hepatocellular carcinoma. *Hepatology* 2003; **38**: 1237-1241 [PMID: 14578862 DOI: 10.1053/jhep.2003.50473]
- 54 **Chua TC**, Saxena A, Chu F, Butler SP, Quinn RJ, Glenn D, Morris DL. Hepatic resection with or without adjuvant iodine-131-lipiodol for hepatocellular carcinoma: a comparative analysis. *Int J Clin Oncol* 2011; **16**: 125-132 [PMID: 21061140 DOI: 10.1007/s10147-010-0143-9]
- 55 **Chung AY**, Ooi LL, Machin D, Tan SB, Goh BK, Wong JS, Chen YM, Li PC, Gandhi M, Thng CH, Yu SW, Tan BS, Lo RH, Htoo AM, Tay KH, Sundram FX, Goh AS, Chew SP, Liau KH, Chow PK, Tan YM, Cheow PC, Ho CK, Soo KC. Adjuvant hepatic intra-arterial iodine-131-lipiodol following curative resection of hepatocellular carcinoma: a prospective randomized trial. *World J Surg* 2013; **37**: 1356-1361 [PMID: 23463394 DOI: 10.1007/s00268-013-1970-4]
- 56 **Furtado RV**, Ha L, Clarke S, Sandroussi C. Adjuvant Iodine (131) Lipiodol after Resection of Hepatocellular Carcinoma. *J Oncol* 2015; **2015**: 746917 [PMID: 26713092 DOI: 10.1155/2015/746917]
- 57 **Gong L**, Shi L, Sun J, Yuan WS, Chen JF, Liu P, Gong F, Dong JH. Comparative survival analysis of adjuvant therapy with iodine-131-labeled lipiodol to hepatic resection of primary hepatocellular carcinoma: a meta-analysis. *Nucl Med Commun* 2014; **35**: 484-492 [PMID: 24492679 DOI: 10.1097/MNM.0000000000000081]
- 58 **Furtado R**, Crawford M, Sandroussi C. Systematic review and meta-analysis of adjuvant i(131) lipiodol after excision of hepatocellular carcinoma. *Ann Surg Oncol* 2014; **21**: 2700-2707 [PMID: 24743904 DOI: 10.1245/s10434-014-3511-2]
- 59 **Li J**, Xing J, Yang Y, Liu J, Wang W, Xia Y, Yan Z, Wang K, Wu D, Wu L, Wan X, Yang T, Gao C, Si A, Wang H, Wu M, Lau WY, Chen Z, Shen F. Adjuvant ¹³¹I-metuximab for hepatocellular carcinoma after liver resection: a randomised, controlled, multicentre, open-label, phase 2 trial. *Lancet Gastroenterol Hepatol* 2020; **5**: 548-560 [PMID: 32164877 DOI: 10.1016/S2468-1253(19)30422-4]

- 60 **Chen K**, Xia Y, Wang H, Xiao F, Xiang G, Shen F. Adjuvant iodine-125 brachytherapy for hepatocellular carcinoma after complete hepatectomy: a randomized controlled trial. *PLoS One* 2013; **8**: e57397 [PMID: 23468980 DOI: 10.1371/journal.pone.0057397]
- 61 **Bruix J**, Takayama T, Mazzaferro V, Chau GY, Yang J, Kudo M, Cai J, Poon RT, Han KH, Tak WY, Lee HC, Song T, Roayaie S, Bolondi L, Lee KS, Makuuchi M, Souza F, Berre MA, Meinhardt G, Llovet JM; STORM investigators. Adjuvant sorafenib for hepatocellular carcinoma after resection or ablation (STORM): a phase 3, randomised, double-blind, placebo-controlled trial. *Lancet Oncol* 2015; **16**: 1344-1354 [PMID: 26361969 DOI: 10.1016/S1470-2045(15)00198-9]
- 62 **Shang J**, Xu S, Zhang J, Ran X, Bai L, Tang H. Efficacy of sorafenib in patients with hepatocellular carcinoma after resection: a meta-analysis. *Oncotarget* 2017; **8**: 109723-109731 [PMID: 29312642 DOI: 10.18632/oncotarget.21299]
- 63 **Wang SN**, Chuang SC, Lee KT. Efficacy of sorafenib as adjuvant therapy to prevent early recurrence of hepatocellular carcinoma after curative surgery: A pilot study. *Hepatol Res* 2014; **44**: 523-531 [PMID: 23672310 DOI: 10.1111/hepr.12159]
- 64 **Li J**, Hou Y, Cai XB, Liu B. Sorafenib after resection improves the outcome of BCLC stage C hepatocellular carcinoma. *World J Gastroenterol* 2016; **22**: 4034-4040 [PMID: 27099447 DOI: 10.3748/wjg.v22.i15.4034]
- 65 **Wang D**, Jia W, Wang Z, Wen T, Ding W, Xia F, Zhang L, Wu F, Peng T, Liu B, Zhou C, Zheng Q, Miao X, Peng J, Huang Z, Dou K. Retrospective analysis of sorafenib efficacy and safety in Chinese patients with high recurrence rate of post-hepatic carcinectomy. *Onco Targets Ther* 2019; **12**: 5779-5791 [PMID: 31410023 DOI: 10.2147/OTT.S168447]
- 66 **Zhang XP**, Chai ZT, Gao YZ, Chen ZH, Wang K, Shi J, Guo WX, Zhou TF, Ding J, Cong WM, Xie D, Lau WY, Cheng SQ. Postoperative adjuvant sorafenib improves survival outcomes in hepatocellular carcinoma patients with microvascular invasion after R0 liver resection: a propensity score matching analysis. *HPB (Oxford)* 2019; **21**: 1687-1696 [PMID: 31153833 DOI: 10.1016/j.hpb.2019.04.014]
- 67 **Chen JH**, Lu L, Wen TF, Huang ZY, Zhang T, Zeng YY, Li XC, Xiang BD, Lu CD, Xu X. Adjuvant lenvatinib in combination with TACE for hepatocellular carcinoma patients with high risk of postoperative relapse (LANCE): Interim results from a multicenter prospective cohort study. *J Clin Oncol* 2020; **38** (15_suppl): 4580-4580 [DOI: 10.1200/JCO.2020.38.15_suppl.4580]
- 68 **Teng CL**, Hwang WL, Chen YJ, Chang KH, Cheng SB. Sorafenib for hepatocellular carcinoma patients beyond Milan criteria after orthotopic liver transplantation: a case control study. *World J Surg Oncol* 2012; **10**: 41 [PMID: 22339891 DOI: 10.1186/1477-7819-10-41]
- 69 **Shetty K**, Dash C, Laurin J. Use of adjuvant sorafenib in liver transplant recipients with high-risk hepatocellular carcinoma. *J Transplant* 2014; **2014**: 913634 [PMID: 24818010 DOI: 10.1155/2014/913634]
- 70 **Huang L**, Su GM, Zhu JY, Li Z, Li T, Leng XS. Preliminary application of sorafenib in patients with super-Milan standard liver transplantation. *Zhonghua Gandan Waikie Zazhi* 2012; **5**: 350-353 [DOI: 10.3760/cma.j.issn.1007-8118.2012.05.010]
- 71 **Han B**, Ding H, Zhao S, Zhang Y, Wang J, Gu J. Potential Role of Adjuvant Lenvatinib in Improving Disease-Free Survival for Patients With High-Risk Hepatitis B Virus-Related Hepatocellular Carcinoma Following Liver Transplantation: A Retrospective, Case Control Study. *Front Oncol* 2020; **10**: 562103 [PMID: 33365268 DOI: 10.3389/fonc.2020.562103]
- 72 **Jenne CN**, Kubes P. Immune surveillance by the liver. *Nat Immunol* 2013; **14**: 996-1006 [PMID: 24048121 DOI: 10.1038/ni.2691]
- 73 **Kim HY**, Park JW. Current immunotherapeutic strategies in hepatocellular carcinoma: recent advances and future directions. *Therap Adv Gastroenterol* 2017; **10**: 805-814 [PMID: 29051790 DOI: 10.1177/1756283X17722061]
- 74 **Takayama T**, Sekine T, Makuuchi M, Yamasaki S, Kosuge T, Yamamoto J, Shimada K, Sakamoto M, Hirohashi S, Ohashi Y, Kakizoe T. Adoptive immunotherapy to lower postsurgical recurrence rates of hepatocellular carcinoma: a randomised trial. *Lancet* 2000; **356**: 802-807 [PMID: 11022927 DOI: 10.1016/S0140-6736(00)02654-4]
- 75 **Lee JH**, Lee JH, Lim YS, Yeon JE, Song TJ, Yu SJ, Gwak GY, Kim KM, Kim YJ, Lee JW, Yoon JH. Adjuvant immunotherapy with autologous cytokine-induced killer cells for hepatocellular carcinoma. *Gastroenterology* 2015; **148**: 1383-91.e6 [PMID: 25747273 DOI: 10.1053/j.gastro.2015.02.055]
- 76 **Lee JH**, Lee JH, Lim YS, Yeon JE, Song TJ, Yu SJ, Gwak GY, Kim KM, Kim YJ, Lee JW, Yoon JH. Sustained efficacy of adjuvant immunotherapy with cytokine-induced killer cells for hepatocellular carcinoma: an extended 5-year follow-up. *Cancer Immunol Immunother* 2019; **68**: 23-32 [PMID: 30232520 DOI: 10.1007/s00262-018-2247-4]
- 77 **Xu L**, Wang J, Kim Y, Shuang ZY, Zhang YJ, Lao XM, Li YQ, Chen MS, Pawlik TM, Xia JC, Li SP, Lau WY. A randomized controlled trial on patients with or without adjuvant autologous cytokine-induced killer cells after curative resection for hepatocellular carcinoma. *Oncoimmunology* 2016; **5**: e1083671 [PMID: 27141337 DOI: 10.1080/2162402X.2015.1083671]
- 78 **Yuan BH**, Li RH, Yuan WP, Yang T, Tong TJ, Peng NF, Li LQ, Zhong JH. Harms and benefits of adoptive immunotherapy for postoperative hepatocellular carcinoma: an updated review. *Oncotarget* 2017; **8**: 18537-18549 [PMID: 28061472 DOI: 10.18632/oncotarget.14507]
- 79 **Wang J**, Shen T, Wang Q, Zhang T, Li L, Wang Y, Fang Y. The long-term efficacy of cytokine-induced killer cellular therapy for hepatocellular carcinoma: a meta-analysis. *Immunotherapy* 2019; **11**: 1325-1335 [PMID: 31578914 DOI: 10.2217/imt-2019-0079]
- 80 **Wu K**, Kryczek I, Chen L, Zou W, Welling TH. Kupffer cell suppression of CD8+ T cells in human hepatocellular carcinoma is mediated by B7-H1/programmed death-1 interactions. *Cancer Res* 2009; **69**: 8067-8075 [PMID: 19826049 DOI: 10.1158/0008-5472.CAN-09-0901]
- 81 **Kudo M**, Ueshima K, Nakahira S, Nishida N, Ida H, Minami Y, Nakai T, Wada H, Kubo S, Ohkawa K. Adjuvant nivolumab for hepatocellular carcinoma (HCC) after surgical resection (SR) or radiofrequency ablation (RFA)(NIVOLVE): A phase 2 prospective multicenter single-arm trial and exploratory biomarker analysis. *J Clin Oncol* 2021; **39** (15_suppl): 4070 [DOI: 10.1200/JCO.2021.39.15_suppl.4070]
- 82 **Hasegawa K**, Takayama T, Ijichi M, Matsuyama Y, Imamura H, Sano K, Sugawara Y, Kokudo N, Makuuchi M. Uracil-

- tegafur as an adjuvant for hepatocellular carcinoma: a randomized trial. *Hepatology* 2006; **44**: 891-895 [PMID: 17006925 DOI: 10.1002/hep.21341]
- 83 **Xia Y**, Qiu Y, Li J, Shi L, Wang K, Xi T, Shen F, Yan Z, Wu M. Adjuvant therapy with capecitabine postpones recurrence of hepatocellular carcinoma after curative resection: a randomized controlled trial. *Ann Surg Oncol* 2010; **17**: 3137-3144 [PMID: 20602260 DOI: 10.1245/s10434-010-1148-3]
- 84 **Ishizuka M**, Kubota K, Nemoto T, Shimoda M, Kato M, Iso Y, Tago K. Administration of adjuvant oral tegafur/uracil chemotherapy post hepatocellular carcinoma resection: A randomized controlled trial. *Asian J Surg* 2016; **39**: 149-154 [PMID: 26123137 DOI: 10.1016/j.asjsur.2015.04.008]
- 85 **Zhang Q**, Chen H, Li Q, Zang Y, Chen X, Zou W, Wang L, Shen ZY. Combination adjuvant chemotherapy with oxaliplatin, 5-fluorouracil and leucovorin after liver transplantation for hepatocellular carcinoma: a preliminary open-label study. *Invest New Drugs* 2011; **29**: 1360-1369 [PMID: 21809025 DOI: 10.1007/s10637-011-9726-1]
- 86 **Wang LT**, Zhang Q, Chen H, Tian Y, Mao S, Bai L. Safety study of adjuvant chemotherapy with oxaliplatin and 5-Fu and CF after liver transplantation for hepatocellular carcinoma. *Wujing Yixue* 2013; **24**: 289-292 [DOI: 10.3969/j.issn.1004-3594.2013.04.005]
- 87 **Wu J**, Sun H, Han Z, Peng Z. A single center experience: post-transplantation adjuvant chemotherapy impacts the prognosis of hepatocellular carcinoma patients. *Zhonghua Yixue Zazhi* 2014; **127**: 430-434 [DOI: 10.3760/cma.j.issn.0366-6999.20120126]
- 88 **Yamamoto M**, Arii S, Sugahara K, Tobe T. Adjuvant oral chemotherapy to prevent recurrence after curative resection for hepatocellular carcinoma. *Br J Surg* 1996; **83**: 336-340 [PMID: 8665186 DOI: 10.1002/bjs.1800830313]
- 89 **Qiu JF**, Ye JZ, Feng XZ, Qi YP, Ma L, Yuan WP, Zhong JH, Zhang ZM, Xiang BD, Li LQ. Pre- and post-operative HBsAg levels may predict recurrence and survival after curative resection in patients with HBV-associated hepatocellular carcinoma. *J Surg Oncol* 2017; **116**: 140-148 [PMID: 28628729 DOI: 10.1002/jso.24628]
- 90 **Kubo S**, Hirohashi K, Tanaka H, Tsukamoto T, Shuto T, Yamamoto T, Ikebe T, Wakasa K, Nishiguchi S, Kinoshita H. Effect of viral status on recurrence after liver resection for patients with hepatitis B virus-related hepatocellular carcinoma. *Cancer* 2000; **88**: 1016-1024 [PMID: 10699889 DOI: 10.1002/(SICI)1097-0142(20000301)88:5<1016::AID-CNCR10>3.0.CO;2-V]
- 91 **Wu JC**, Huang YH, Chau GY, Su CW, Lai CR, Lee PC, Huo TI, Sheen IJ, Lee SD, Lui WY. Risk factors for early and late recurrence in hepatitis B-related hepatocellular carcinoma. *J Hepatol* 2009; **51**: 890-897 [PMID: 19747749 DOI: 10.1016/j.jhep.2009.07.009]
- 92 **Singal AK**, Salameh H, Kuo YF, Fontana RJ. Meta-analysis: the impact of oral anti-viral agents on the incidence of hepatocellular carcinoma in chronic hepatitis B. *Aliment Pharmacol Ther* 2013; **38**: 98-106 [PMID: 23713520 DOI: 10.1111/apt.12344]
- 93 **Yin J**, Li N, Han Y, Xue J, Deng Y, Shi J, Guo W, Zhang H, Wang H, Cheng S, Cao G. Effect of antiviral treatment with nucleotide/nucleoside analogs on postoperative prognosis of hepatitis B virus-related hepatocellular carcinoma: a two-stage longitudinal clinical study. *J Clin Oncol* 2013; **31**: 3647-3655 [PMID: 24002499 DOI: 10.1200/JCO.2012.48.5896]
- 94 **Huang G**, Lau WY, Wang ZG, Pan ZY, Yuan SX, Shen F, Zhou WP, Wu MC. Antiviral therapy improves postoperative survival in patients with hepatocellular carcinoma: a randomized controlled trial. *Ann Surg* 2015; **261**: 56-66 [PMID: 25072444 DOI: 10.1097/SLA.0000000000000858]
- 95 **Yuan P**, Chen P, Qian Y. Evaluation of Antiviral Therapy Performed after Curative Therapy in Patients with HBV-Related Hepatocellular Carcinoma: An Updated Meta-Analysis. *Can J Gastroenterol Hepatol* 2016; **2016**: 5234969 [PMID: 27446846 DOI: 10.1155/2016/5234969]
- 96 **Wang GQ**, Wang FS, Zhuang H, Li TS, Zheng SJ, Zhao H, Duan ZP, Hou JL, Jia JD, Xu XY. Guidelines for prevention and Treatment of Chronic Hepatitis B (2019 Edition). *Gan Zang* 2019; **24**: 6-27
- 97 **The Hepatitis Group, Chinese Society of Hepatology, Chinese Medical Association**. An expert consensus for the adjustment of treatment strategies in patients with chronic hepatitis B treated with non-first-line nucleos(t)ide analogues. *Zhonghua Ganzhangbing Zazhi* 2019; **35**: 1212-1214
- 98 **Singal AG**, Rich NE, Mehta N, Branch AD, Pillai A, Hoteit M, Volk M, Odewole M, Scaglione S, Guy J, Said A, Feld JJ, John BV, Frenette C, Mantry P, Rangnekar AS, Oloruntoba O, Leise M, Jou JH, Bhamidimarri KR, Kulik L, Ioannou GN, Huang A, Tran T, Samant H, Dhanasekaran R, Duarte-Rojo A, Salgia R, Eswaran S, Jalal P, Flores A, Satapathy SK, Kagan S, Gopal P, Wong R, Parikh ND, Murphy CC. Direct-Acting Antiviral Therapy for Hepatitis C Virus Infection Is Associated With Increased Survival in Patients With a History of Hepatocellular Carcinoma. *Gastroenterology* 2019; **157**: 1253-1263.e2 [PMID: 31374215 DOI: 10.1053/j.gastro.2019.07.040]
- 99 **Cabibbo G**, Celsa C, Calvaruso V, Petta S, Cacciola I, Cannavò MR, Madonia S, Rossi M, Magro B, Rini F, Distefano M, Larocca L, Prestileo T, Malizia G, Bertino G, Benanti F, Licata A, Scalisi I, Mazzola G, Di Rosolini MA, Alaimo G, Aversa A, Cartabellotta F, Alessi N, Guastella S, Russello M, Scifo G, Squadrito G, Raimondo G, Trevisani F, Craxi A, Di Marco V, Cammà C; Rete Sicilia Selezione Terapia – HCV (RESIST-HCV) and Italian Liver Cancer (ITA. LI.CA.) Group. Direct-acting antivirals after successful treatment of early hepatocellular carcinoma improve survival in HCV-cirrhotic patients. *J Hepatol* 2019; **71**: 265-273 [PMID: 30959157 DOI: 10.1016/j.jhep.2019.03.027]
- 100 **Okamura Y**, Sugiura T, Ito T, Yamamoto Y, Ashida R, Ohgi K, Uesaka K. The Achievement of a Sustained Virological Response Either Before or After Hepatectomy Improves the Prognosis of Patients with Primary Hepatitis C Virus-Related Hepatocellular Carcinoma. *Ann Surg Oncol* 2019; **26**: 4566-4575 [PMID: 31602577 DOI: 10.1245/s10434-019-07911-w]
- 101 **Qu L**, Zhang H, Yang Y, Yang G, Xin H, Ling C. Corosolic acid analogue, a natural triterpenoid saponin, induces apoptosis on human hepatocarcinoma cells through mitochondrial pathway in vitro. *Pharm Biol* 2016; **54**: 1445-1457 [PMID: 26810384 DOI: 10.3109/13880209.2015.1104699]
- 102 **Shu G**, Zhao W, Yue L, Su H, Xiang M. Antitumor immunostimulatory activity of polysaccharides from *Salvia chinensis* Benth. *J Ethnopharmacol* 2015; **168**: 237-247 [PMID: 25858511 DOI: 10.1016/j.jep.2015.03.065]
- 103 **Tsai TY**, Livneh H, Hung TH, Lin IH, Lu MC, Yeh CC. Associations between prescribed Chinese herbal medicine and risk of hepatocellular carcinoma in patients with chronic hepatitis B: a nationwide population-based cohort study. *BMJ Open* 2017; **7**: e014571 [PMID: 28122837 DOI: 10.1136/bmjopen-2016-014571]

- 104 **Liu X**, Li M, Wang X, Dang Z, Yu L, Jiang Y, Yang Z. Effects of adjuvant traditional Chinese medicine therapy on long-term survival in patients with hepatocellular carcinoma. *Phytomedicine* 2019; **62**: 152930 [PMID: [31128485](#) DOI: [10.1016/j.phymed.2019.152930](#)]
- 105 **Zhai XF**, Liu XL, Shen F, Fan J, Ling CQ. Traditional herbal medicine prevents postoperative recurrence of small hepatocellular carcinoma: A randomized controlled study. *Cancer* 2018; **124**: 2161-2168 [PMID: [29499082](#) DOI: [10.1002/ncr.30915](#)]
- 106 **Chen Q**, Shu C, Laurence AD, Chen Y, Peng BG, Zhen ZJ, Cai JQ, Ding YT, Li LQ, Zhang YB, Zheng QC, Xu GL, Li B, Zhou WP, Cai SW, Wang XY, Wen H, Peng XY, Zhang XW, Dai CL, Bie P, Xing BC, Fu ZR, Liu LX, Mu Y, Zhang L, Zhang QS, Jiang B, Qian HX, Wang YJ, Liu JF, Qin XH, Li Q, Yin P, Zhang ZW, Chen XP. Effect of Huaier granule on recurrence after curative resection of HCC: a multicentre, randomised clinical trial. *Gut* 2018; **67**: 2006-2016 [PMID: [29802174](#) DOI: [10.1136/gutjnl-2018-315983](#)]
- 107 **Lei JY**, Yan LN, Zhu JQ, Wang WT. Hepatocellular Carcinoma Patients May Benefit From Postoperative Huaier Aqueous Extract After Liver Transplantation. *Transplant Proc* 2015; **47**: 2920-2924 [PMID: [26707314](#) DOI: [10.1016/j.transproceed.2015.10.045](#)]
- 108 **Sun HC**, Tang ZY, Wang L, Qin LX, Ma ZC, Ye QH, Zhang BH, Qian YB, Wu ZQ, Fan J, Zhou XD, Zhou J, Qiu SJ, Shen YF. Postoperative interferon alpha treatment postponed recurrence and improved overall survival in patients after curative resection of HBV-related hepatocellular carcinoma: a randomized clinical trial. *J Cancer Res Clin Oncol* 2006; **132**: 458-465 [PMID: [16557381](#) DOI: [10.1007/s00432-006-0091-y](#)]
- 109 **Mazzaferro V**, Romito R, Schiavo M, Mariani L, Camerini T, Bhoori S, Capussotti L, Calise F, Pellicci R, Belli G, Tagger A, Colombo M, Bonino F, Majno P, Llovet JM; HCC Italian Task Force. Prevention of hepatocellular carcinoma recurrence with alpha-interferon after liver resection in HCV cirrhosis. *Hepatology* 2006; **44**: 1543-1554 [PMID: [17133492](#) DOI: [10.1002/hep.21415](#)]
- 110 **Nishiguchi S**, Tamori A, Kubo S. Effect of long-term postoperative interferon therapy on intrahepatic recurrence and survival rate after resection of hepatitis C virus-related hepatocellular carcinoma. *Intervirolgy* 2005; **48**: 71-75 [PMID: [15785093](#) DOI: [10.1159/000082098](#)]
- 111 **Lin SM**, Lin CJ, Hsu CW, Tai DI, Sheen IS, Lin DY, Liaw YF. Prospective randomized controlled study of interferon-alpha in preventing hepatocellular carcinoma recurrence after medical ablation therapy for primary tumors. *Cancer* 2004; **100**: 376-382 [PMID: [14716774](#) DOI: [10.1002/ncr.20004](#)]
- 112 **Shiratori Y**, Shiina S, Teratani T, Imamura M, Obi S, Sato S, Koike Y, Yoshida H, Omata M. Interferon therapy after tumor ablation improves prognosis in patients with hepatocellular carcinoma associated with hepatitis C virus. *Ann Intern Med* 2003; **138**: 299-306 [PMID: [12585827](#) DOI: [10.7326/0003-4819-138-4-200302180-00008](#)]
- 113 **Chen LT**, Chen MF, Li LA, Lee PH, Jeng LB, Lin DY, Wu CC, Mok KT, Chen CL, Lee WC, Chau GY, Chen YS, Lui WY, Hsiao CF, Whang-Peng J, Chen PJ; Disease Committee of Adjuvant Therapy for Postoperative Hepatocellular Carcinoma, Taiwan Cooperative Oncology Group, National Health Research Institutes, Zhunan, Taiwan. Long-term results of a randomized, observation-controlled, phase III trial of adjuvant interferon Alfa-2b in hepatocellular carcinoma after curative resection. *Ann Surg* 2012; **255**: 8-17 [PMID: [22104564](#) DOI: [10.1097/SLA.0b013e3182363ff9](#)]
- 114 **Lo CM**, Liu CL, Chan SC, Lam CM, Poon RT, Ng IO, Fan ST, Wong J. A randomized, controlled trial of postoperative adjuvant interferon therapy after resection of hepatocellular carcinoma. *Ann Surg* 2007; **245**: 831-842 [PMID: [17522506](#) DOI: [10.1097/01.sla.0000245829.00977.45](#)]
- 115 **Kubo S**, Nishiguchi S, Hirohashi K, Tanaka H, Shuto T, Kinoshita H. Randomized clinical trial of long-term outcome after resection of hepatitis C virus-related hepatocellular carcinoma by postoperative interferon therapy. *Br J Surg* 2002; **89**: 418-422 [PMID: [11952580](#) DOI: [10.1046/j.0007-1323.2001.02054.x](#)]
- 116 **Ikeda K**, Arase Y, Saitoh S, Kobayashi M, Suzuki Y, Suzuki F, Tsubota A, Chayama K, Murashima N, Kumada H. Interferon beta prevents recurrence of hepatocellular carcinoma after complete resection or ablation of the primary tumor-A prospective randomized study of hepatitis C virus-related liver cancer. *Hepatology* 2000; **32**: 228-232 [PMID: [10915728](#) DOI: [10.1053/jhep.2000.9409](#)]
- 117 **Zhuang L**, Zeng X, Yang Z, Meng Z. Effect and safety of interferon for hepatocellular carcinoma: a systematic review and meta-analysis. *PLoS One* 2013; **8**: e61361 [PMID: [24069133](#) DOI: [10.1371/journal.pone.0061361](#)]
- 118 **Zhong JH**, Li H, Li LQ, You XM, Zhang Y, Zhao YN, Liu JY, Xiang BD, Wu GB. Adjuvant therapy options following curative treatment of hepatocellular carcinoma: a systematic review of randomized trials. *Eur J Surg Oncol* 2012; **38**: 286-295 [PMID: [22281155](#) DOI: [10.1016/j.ejso.2012.01.006](#)]
- 119 **Xu J**, Li J, Chen J, Liu ZJ. Effect of adjuvant interferon therapy on hepatitis b/c virus-related hepatocellular carcinoma after curative therapy - meta-analysis. *Adv Clin Exp Med* 2015; **24**: 331-340 [PMID: [25931368](#) DOI: [10.17219/acem/29760](#)]
- 120 **Xu JB**, Qi FZ, Xu G, Chen GF, Huang MD, Zhang JH. Adjuvant interferon therapy after surgical treatment for hepatitis B/C virus-related hepatocellular carcinoma: A meta-analysis. *Hepatol Res* 2014; **44**: 209-217 [PMID: [23578168](#) DOI: [10.1111/hepr.12109](#)]
- 121 **Wang J**, He XD, Yao N, Liang WJ, Zhang YC. A meta-analysis of adjuvant therapy after potentially curative treatment for hepatocellular carcinoma. *Can J Gastroenterol* 2013; **27**: 351-363 [PMID: [23781519](#) DOI: [10.1155/2013/417894](#)]
- 122 **Singal AK**, Freeman DH Jr, Anand BS. Meta-analysis: interferon improves outcomes following ablation or resection of hepatocellular carcinoma. *Aliment Pharmacol Ther* 2010; **32**: 851-858 [PMID: [20659285](#) DOI: [10.1111/j.1365-2036.2010.04414.x](#)]
- 123 **Shen YC**, Hsu C, Chen LT, Cheng CC, Hu FC, Cheng AL. Adjuvant interferon therapy after curative therapy for hepatocellular carcinoma (HCC): a meta-regression approach. *J Hepatol* 2010; **52**: 889-894 [PMID: [20395009](#) DOI: [10.1016/j.jhep.2009.12.041](#)]
- 124 **Miyake Y**, Takaki A, Iwasaki Y, Yamamoto K. Meta-analysis: interferon-alpha prevents the recurrence after curative treatment of hepatitis C virus-related hepatocellular carcinoma. *J Viral Hepat* 2010; **17**: 287-292 [PMID: [19732321](#) DOI: [10.1111/j.1365-2893.2009.01181.x](#)]
- 125 **Miao RY**, Zhao HT, Yang HY, Mao YL, Lu X, Zhao Y, Liu CN, Zhong SX, Sang XT, Huang JF. Postoperative adjuvant

- antiviral therapy for hepatitis B/C virus-related hepatocellular carcinoma: a meta-analysis. *World J Gastroenterol* 2010; **16**: 2931-2942 [PMID: 20556841 DOI: 10.3748/wjg.v16.i23.2931]
- 126 **Jiang S**, Liu Y, Wang L, Duan C, Liu M. A meta-analysis and systematic review: adjuvant interferon therapy for patients with viral hepatitis-related hepatocellular carcinoma. *World J Surg Oncol* 2013; **11**: 240 [PMID: 24060218 DOI: 10.1186/1477-7819-11-240]
- 127 **Huang TS**, Shyu YC, Chen HY, Yuan SS, Shih JN, Chen PJ. A systematic review and meta-analysis of adjuvant interferon therapy after curative treatment for patients with viral hepatitis-related hepatocellular carcinoma. *J Viral Hepat* 2013; **20**: 729-743 [PMID: 24010648 DOI: 10.1111/jvh.12096]
- 128 **Breitenstein S**, Dimitroulis D, Petrowsky H, Puhon MA, Müllhaupt B, Clavien PA. Systematic review and meta-analysis of interferon after curative treatment of hepatocellular carcinoma in patients with viral hepatitis. *Br J Surg* 2009; **96**: 975-981 [PMID: 19672926 DOI: 10.1002/bjs.6731]
- 129 **Wang Z**, Wang M, Finn F, Carr BI. The growth inhibitory effects of vitamins K and their actions on gene expression. *Hepatology* 1995; **22**: 876-882 [PMID: 7657295 DOI: 10.1002/hep.1840220327]
- 130 **Hitomi M**, Nonomura T, Yokoyama F, Yoshiji H, Ogawa M, Nakai S, Deguchi A, Masaki T, Inoue H, Kimura Y, Kurokohchi K, Uchida N, Kuriyama S. In vitro and in vivo antitumor effects of vitamin K5 on hepatocellular carcinoma. *Int J Oncol* 2005; **26**: 1337-1344 [PMID: 15809726]
- 131 **Hitomi M**, Yokoyama F, Kita Y, Nonomura T, Masaki T, Yoshiji H, Inoue H, Kinekawa F, Kurokohchi K, Uchida N, Watanabe S, Kuriyama S. Antitumor effects of vitamins K1, K2 and K3 on hepatocellular carcinoma in vitro and in vivo. *Int J Oncol* 2005; **26**: 713-720 [PMID: 15703828]
- 132 **Mizuta T**, Ozaki I, Eguchi Y, Yasutake T, Kawazoe S, Fujimoto K, Yamamoto K. The effect of menatetrenone, a vitamin K2 analog, on disease recurrence and survival in patients with hepatocellular carcinoma after curative treatment: a pilot study. *Cancer* 2006; **106**: 867-872 [PMID: 16400650 DOI: 10.1002/ncr.21667]
- 133 **Hotta N**, Ayada M, Sato K, Ishikawa T, Okumura A, Matsumoto E, Ohashi T, Kakumu S. Effect of vitamin K2 on the recurrence in patients with hepatocellular carcinoma. *Hepatogastroenterology* 2007; **54**: 2073-2077 [PMID: 18251162]
- 134 **Kakizaki S**, Sohara N, Sato K, Suzuki H, Yanagisawa M, Nakajima H, Takagi H, Naganuma A, Otsuka T, Takahashi H, Hamada T, Mori M. Preventive effects of vitamin K on recurrent disease in patients with hepatocellular carcinoma arising from hepatitis C viral infection. *J Gastroenterol Hepatol* 2007; **22**: 518-522 [PMID: 17376044 DOI: 10.1111/j.1440-1746.2007.04844.x]
- 135 **Yoshida H**, Shiratori Y, Kudo M, Shiina S, Mizuta T, Kojiro M, Yamamoto K, Koike Y, Saito K, Koyanagi N, Kawabe T, Kawazoe S, Kobashi H, Kasugai H, Osaki Y, Araki Y, Izumi N, Oka H, Tsuji K, Toyota J, Seki T, Osawa T, Masaki N, Ichinose M, Seike M, Ishikawa A, Ueno Y, Tagawa K, Kuromatsu R, Sakisaka S, Ikeda H, Kuroda H, Kokuryu H, Yamashita T, Sakaida I, Katamoto T, Kikuchi K, Nomoto M, Omata M. Effect of vitamin K2 on the recurrence of hepatocellular carcinoma. *Hepatology* 2011; **54**: 532-540 [PMID: 21574174 DOI: 10.1002/hep.24430]
- 136 **Ishizuka M**, Kubota K, Shimoda M, Kita J, Kato M, Park KH, Shiraki T. Effect of menatetrenone, a vitamin k2 analog, on recurrence of hepatocellular carcinoma after surgical resection: a prospective randomized controlled trial. *Anticancer Res* 2012; **32**: 5415-5420 [PMID: 23225445]
- 137 **Keiko H**, Jun-ichi O, Masahiko K, Yoshikazu M. Vitamin K2 has no preventive effect on recurrence of hepatocellular carcinoma after effective treatment. *Yonago Acta Med* 2008; **51**: 91-95
- 138 **Yoshiji H**, Noguchi R, Toyohara M, Ikenaka Y, Kitade M, Kaji K, Yamazaki M, Yamao J, Mitoro A, Sawai M, Yoshida M, Fujimoto M, Tsujimoto T, Kawaratani H, Uemura M, Fukui H. Combination of vitamin K2 and angiotensin-converting enzyme inhibitor ameliorates cumulative recurrence of hepatocellular carcinoma. *J Hepatol* 2009; **51**: 315-321 [PMID: 19501932 DOI: 10.1016/j.jhep.2009.04.011]
- 139 **Zhong JH**, Mo XS, Xiang BD, Yuan WP, Jiang JF, Xie GS, Li LQ. Postoperative use of the chemopreventive vitamin K2 analog in patients with hepatocellular carcinoma. *PLoS One* 2013; **8**: e58082 [PMID: 23505456 DOI: 10.1371/journal.pone.0058082]
- 140 **Kudchadkar R**, Gonzalez R, Lewis KD. PI-88: a novel inhibitor of angiogenesis. *Expert Opin Investig Drugs* 2008; **17**: 1769-1776 [PMID: 18922112 DOI: 10.1517/13543784.17.11.1769]
- 141 **Ferro V**, Dredge K, Liu L, Hammond E, Bytheway I, Li C, Johnstone K, Karoli T, Davis K, Copeman E, Gautam A. PI-88 and novel heparan sulfate mimetics inhibit angiogenesis. *Semin Thromb Hemost* 2007; **33**: 557-568 [PMID: 17629854 DOI: 10.1055/s-2007-982088]
- 142 **Liao BY**, Wang Z, Hu J, Liu WF, Shen ZZ, Zhang X, Yu L, Fan J, Zhou J. PI-88 inhibits postoperative recurrence of hepatocellular carcinoma via disrupting the surge of heparanase after liver resection. *Tumour Biol* 2016; **37**: 2987-2998 [PMID: 26415733 DOI: 10.1007/s13277-015-4085-8]
- 143 **Liu CJ**, Lee PH, Lin DY, Wu CC, Jeng LB, Lin PW, Mok KT, Lee WC, Yeh HZ, Ho MC, Yang SS, Lee CC, Yu MC, Hu RH, Peng CY, Lai KL, Chang SS, Chen PJ. Heparanase inhibitor PI-88 as adjuvant therapy for hepatocellular carcinoma after curative resection: a randomized phase II trial for safety and optimal dosage. *J Hepatol* 2009; **50**: 958-968 [PMID: 19303160 DOI: 10.1016/j.jhep.2008.12.023]
- 144 **Liu CJ**, Chang J, Lee PH, Lin DY, Wu CC, Jeng LB, Lin YJ, Mok KT, Lee WC, Yeh HZ, Ho MC, Yang SS, Yang MD, Yu MC, Hu RH, Peng CY, Lai KL, Chang SS, Chen PJ. Adjuvant heparanase inhibitor PI-88 therapy for hepatocellular carcinoma recurrence. *World J Gastroenterol* 2014; **20**: 11384-11393 [PMID: 25170226 DOI: 10.3748/wjg.v20.i32.11384]
- 145 **Shibata T**. Genomic landscape of hepatocarcinogenesis. *J Hum Genet* 2021; **66**: 845-851 [PMID: 33958712 DOI: 10.1038/s10038-021-00928-8]
- 146 **Wang S**, Shi H, Liu T, Li M, Zhou S, Qiu X, Wang Z, Hu W, Guo W, Chen X, Guo H, Shi X, Shi J, Zang Y, Cao J, Wu L. Mutation profile and its correlation with clinicopathology in Chinese hepatocellular carcinoma patients. *Hepatobiliary Surg Nutr* 2021; **10**: 172-179 [PMID: 33898558 DOI: 10.21037/hbsn.2019.09.17]
- 147 **Pinyol R**, Torrecilla S, Wang H, Montironi C, Piqué-Gili M, Torres-Martin M, Wei-Qiang L, Willoughby CE, Ramadori P, Andreu-Oller C, Taik P, Lee YA, Moeini A, Peix J, Faure-Dupuy S, Riedl T, Schuehle S, Oliveira CP, Alves VA, Boffetta P, Lachenmayer A, Roessler S, Minguez B, Schirmacher P, Dufour JF, Thung SN, Reeves HL, Carrilho FJ,

- Chang C, Uzilov AV, Heikenwalder M, Sanyal A, Friedman SL, Sia D, Llovet JM. Molecular characterisation of hepatocellular carcinoma in patients with non-alcoholic steatohepatitis. *J Hepatol* 2021; **75**: 865-878 [PMID: 33992698 DOI: 10.1016/j.jhep.2021.04.049]
- 148 Xie DY, Fan HK, Ren ZG, Fan J, Gao Q. Identifying Clonal Origin of Multifocal Hepatocellular Carcinoma and Its Clinical Implications. *Clin Transl Gastroenterol* 2019; **10**: e00006 [PMID: 30829920 DOI: 10.14309/ctg.0000000000000006]
- 149 Wang XH, Liao B, Hu WJ, Tu CX, Xiang CL, Hao SH, Mao XH, Qiu XM, Yang XJ, Yue X, Kuang M, Peng BG, Li SQ. Novel Models Predict Postsurgical Recurrence and Overall Survival for Patients with Hepatitis B Virus-Related Solitary Hepatocellular Carcinoma ≤ 10 cm and Without Portal Venous Tumor Thrombus. *Oncologist* 2020; **25**: e1552-e1561 [PMID: 32663354 DOI: 10.1634/theoncologist.2019-0766]



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