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Current status and prospect of treatment for recurrent hepatocellular carcinoma

Yang YQ *et al*. Treatment for recurrent HCC

Abstract

Owing to its heterogeneous and highly aggressive nature, hepatocellular carcinoma (HCC) has a high recurrence rate, which is a non-negligible problem despite the increasing number of available treatment options. Recent clinical trials have attempted to reduce the recurrence and develop innovative treatment options for patients with recurrent HCC. In the event of liver remnant recurrence, the current available treatment options include repeat hepatectomy, salvage liver transplantation, tumor ablation, transcatheter arterial chemoembolization, stereotactic body radiotherapy, systemic therapies, and combination therapy. In this review, we summarize the strategies to reduce recurrence of high-risk tumors and aggressive therapies for recurrent HCC. Additionally, we discuss methods to prevent HCC recurrence and prognostic models constructed based on predictors of recurrence to develop an appropriate surveillance program.

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Core Tip: The current rate of recurrence after initial hepatocellular carcinoma treatment remains unsatisfactory. Repeat hepatectomy and salvage liver transplantation are the preferred options for patients who meet the criteria. However, for patients whose clinical situation do not allow these treatments, non-surgical treatment can also provide survival benefit. Additionally, adjuvant treatment strategies to prevent recurrence and proper surveillance are effective tools to improve overall patient survival. This review summarizes the existing literature to help guide clinical decision-making and provide directions for further research.

INTRODUCTION

Hepatocellular carcinoma (HCC), a heterogeneous disease with multiple etiologies, is the major subtype of primary malignancies of the liver, accounting for 70%-85% of primary liver cancers[1]. Globally, HCC is the third most common cause of cancer-related mortality, and its incidence is rising[2]. Treatment options for HCC have improved, but frequent recurrence after treatment is a major concern. International guidelines provide detailed treatment options for each stage of HCC, and depending on the patient's liver function and tumor burden, treatment options vary from radical treatment options, such as resection, transplantation, ablation, and combination therapy, to palliative treatment options, such as transcatheter arterial chemoembolization (TACE), systemic therapy, and supportive care. Although hepatectomy is the preferred option for patients with HCC who meet the criteria, 67.6% of patients develop tumor recurrence or metastasis after hepatectomy[3]. Moreover, few patients can undergo radical hepatectomy due to insufficient liver function reserve, vascular invasion, extrahepatic metastases, and the size and number of lesions[4]. With the continuous development and maturation of transplantation technology, liver transplantation has become the best long-term treatment for patients with early-stage HCC. However, liver transplantation also has limitations, including a 25% risk of recurrence even if the patient meets the strict Milan criteria and a lack of donor organs, which limit the use of transplantation[5]. Ablation is another way to treat patients with small HCC who are not candidates for surgery due to comorbidities, liver dysfunction, or tumor location. However, the risk of recurrence after ablative therapy is as high as 80%; therefore, this option is limited to patients who cannot undergo surgical resection but are suitable for liver-directed therapy[6]. The combination of TACE and ablation is one of the most widespread and efficacious combination therapies. The latest version of the Barcelona Clinic Liver Cancer (BCLC) guidelines suggests that the combination of TACE and ablation as a radical treatment solution for 3-5 cm masses has the advantage of reducing heat deposition and expanding the scope of ablation compared to a single

treatment option[7]. Nevertheless, 76.4% of patients undergoing TACE with ablation develop recurrence, probably because of the presence of portal vein collateral circulation and high alpha-fetoprotein (AFP) levels[8]. Finally, palliative care options mostly play a role in improving the symptoms and quality of life of patients with advanced HCC but are not curative. Given the high risk of recurrence with radical treatment regimens, refining and optimizing treatment options for recurrent liver cancer are urgent issues.

In addition to differences in recurrence risk, various treatment modalities have varying patterns of recurrence, which affects the choice of treatment options for recurrent HCC. In general, hepatectomy is mostly associated with intrahepatic recurrence, with few extrahepatic metastases, most probably due to residual minuscule lesions. Lee *et al*[9] observed that tumor recurrence after resection was detected in the liver in 80.1% of patients and suggested that curative therapeutic results might be achieved through repeat hepatectomy or local ablation. In addition, HCC recurrence can be classified into early and late recurrence, depending on the time of recurrence after surgery. It is generally believed that early recurrence may be associated with tiny preoperative or intraoperative metastases and the continued growth of tiny postoperative residual lesions, mostly close to surgically resected lesions. Late recurrences are mostly new tumors arising from the malignant transformation of normal liver cells due to latent cancer-causing factors in the liver, such as frequent recurrent inflammation of the liver and cirrhotic fibrosis[10]. There is no consensus on the dividing line between early and late recurrences; however, a 2-year cutoff after resection has been widely used to distinguish between the two types of HCC recurrence[11]. Treatment options for recurrent HCC after resection vary according to the type of recurrence pattern and timing. The best treatment plan should be developed by fully integrating multiple treatments and following the principle of the maximum benefit to the recipient.

Similarly, with the demarcation line being set at 2 years, HCC recurrence after liver transplantation can be divided into early and late recurrence. A higher original tumor

burden and more aggressive features may account for early recurrence in patients who undergo liver transplantation[12]. A high primary tumor burden predisposes to missed or undetectable extrahepatic metastases before transplantation, leading to recurrence of HCC. Similarly, more aggressive tumors tend to trigger the engraftment and growth of circulating HCC cell clones in the target organ after transplantation[12].

Early recurrent HCC tends to involve multiple organs and has a poor prognosis; therefore, its treatment plan should be selected carefully[13]. In contrast, late recurrence appears to be the result of transplantation of a small number of latent advanced HCC cells, and patients tend to have more favorable tumor characteristics at this time; thus, TACE and local ablation may be capable of achieving positive outcomes[5]. Radiofrequency ablation (RFA) is one of the main applications of ablation therapy, which is typically performed for unresectable solitary tumors < 3 cm in diameter and has comparatively high safety and efficacy. However, RFA is prone to leaving residual tumor cells owing to incomplete ablation, thus causing local recurrence[4]. Heat dissipation effects and tumor size are the primary limiting factors for RFA, and combination therapy may be a solution[4].

Prevention and treatment of recurrent HCC has become an urgent issue. In this review, we evaluate the available evidence on the effectiveness of adjuvant therapy, summarize the treatment options for the recurrence of primary liver cancer after treatment, and describe appropriate monitoring protocols for predictors of liver cancer recurrence to ultimately identify the optimal management strategy for patients with recurrent liver cancer.

ADJUVANT THERAPY TO PREVENT RECURRENCE OF PRIMARY LIVER CANCER

Given the high recurrence rate after HCC treatment, adjuvant therapy has been proposed to reduce the risk of HCC recurrence and further improve the long-term survival of patients with liver cancer. Nonsurgical therapy, including antiviral therapy, TACE, systemic therapy, radiation therapy, and other strategies, may be performed

preoperatively to improve liver function or postoperatively to improve patient survival outcomes.

Antiviral therapy

Previous studies have shown that high hepatitis B virus (HBV) levels, HBV e-antigen positivity, and HBV reactivation are strongly associated with a high risk of recurrence of HBV-related liver cancer after resection[14]. Similarly, a recent study showed that in HCC patients with viral infection who underwent living liver transplantation, HBV recurrence tended to cause HCC recurrence, and hepatitis D virus infection was considered an independent risk factor for HBV-HCC co-occurrence after transplantation[15]. This suggests that antiviral therapy plays an essential role in the prevention of postoperative recurrence of viral hepatitis-related HCC.

Currently, the primary antiviral treatments include nucleoside analogs (NAs), interferons, and direct antiviral agents (DAAs)[16]. NAs can significantly reduce the incidence of HBV-associated HCC by lowering the patient's HBV load. Several studies have confirmed the effectiveness of NAs in preventing liver cancer[17,18]. The Asian Pacific Association for the Study of the Liver guidelines on the management of HCC state that NAs can be utilized as secondary prevention for the development of HBV-associated HCC[19]. Interferons are broad-spectrum antiviral agents that act mainly through the action of cell surface receptors to produce antiviral proteins, thereby improving the body's immune regulation ability, inhibiting the replication of HBV, and enhancing antiviral ability[20]. Interferons conjugated to polyethylene glycol are particularly effective in preventing HBV-associated HCC[21]. A meta-analysis demonstrated that interferon therapy reduced recurrence in patients with hepatitis-associated HCC whose tumors did not exceed 3 cm in diameter[22]. Moreover, a randomized controlled trial published by Lo *et al*[23], in patients with HBV-related HCC showed that the 5-year survival rate was improved from 24% to 68% ($P = 0.038$) in patients receiving postoperative adjuvant interferon therapy, particularly in those with pTNM stage III/IVA tumors. DAAs effectively inhibit viral replication and are highly

efficacious in the treatment of HCC caused by hepatitis C virus (HCV) infection. A systematic review that included 24 studies reported that patients treated with DAAs had an acceptable risk of recurrence, with a recurrence rate of 21.9% [95% confidence interval (CI): 16.2-28.3)[24]. Combinations of multiple antiviral therapies are also a worthwhile adjuvant treatment option for patients with HBV-associated recurrent HCC, with combination strategies significantly improving the antiviral efficacy and long-term patient survival compared with monotherapy[25,26].

TACE

TACE is the standard of care for intermediate to advanced HCC and the primary method of bridging or step-down therapy before liver transplantation[27]. Many studies have shown that TACE as an adjuvant therapy has certain advantages in improving the prognosis of patients with HCC and preventing cancer recurrence. Liu *et al*[28] systematically analyzed the outcomes of 117 patients with HCC who underwent hepatectomy between 2010 and 2014 and received postoperative TACE and found that postoperative TACE improved the 1-year disease-free survival (DFS) in patients with HCC compared to surgical resection only (64.5% *vs* 45.5%, *P* = 0.04). In addition, they recommend postoperative TACE for patients with tumors > 5 cm with microvascular invasion or satellite nodules[28]. Other studies also support this view and conclude that postoperative TACE is a safe intervention to prevent tumor recurrence in patients with BCLC early- and intermediate-stage HCC with microvascular invasion[29-31]. However, preoperative TACE is controversial, and a meta-analysis of randomized controlled trials based in Asia showed that preoperative TACE did not improve the long-term prognosis of patients with resectable HCC, possibly because of the risk of tumor progression or deterioration of liver function in patients undergoing TACE[32].

Radiation therapy

Because HCC is a relatively radiation-sensitive tumor, radiation therapy is one of the commonly used treatments for liver cancer. A recent systematic review evaluating the

impact of different postoperative treatments on patients with HCC with microvascular invasion after radical resection revealed that postoperative radiotherapy is more effective in reducing recurrence than postoperative TACE[33]. Yoon *et al*[34] shared the same view and concluded that the combination of TACE and radiotherapy is a promising treatment option to alleviate symptoms in patients with HCC and portal vein tumor thrombosis. A narrow-margin (< 1 cm) hepatectomy is prone to residual microscopic lesions that can spread through intrahepatic vessels and lead to recurrence due to detailed control issues during the procedure. However, a prospective randomized study found that adjuvant radiotherapy for central HCC after narrow-margin hepatectomy is technically feasible and relatively safe. Subgroup analysis showed that adjuvant radiotherapy significantly improved recurrence-free survival (RFS) in patients with HCC ≤ 5 cm in diameter, although there was no difference in overall survival (OS)[35]. An additional prospective phase 2 study concurred with this finding and suggested that intraoperative electron radiotherapy was more beneficial for survival in patients with microvascular infiltration after resection[36].

In 1999, Lau *et al*[37] first proposed that adjuvant therapy with intra-arterial administration of 1850 MBq of ^{131}I-labeled lipiodol after radical resection significantly reduced recurrence in patients with HCC and improved DFS and OS. However, Chung *et al*[38] found that administration of adjuvant intra-arterial ^{131}I-labeled lipiodol after resection showed negligible improvement in controlling HCC tumor recurrence and that patients were at risk for hypothyroidism and hepatic artery dissection during angiography. Conversely, several meta-analyses have positively evaluated the efficacy of adjuvant treatment with intra-arterial ^{131}I-lipiodol[39-41]. A systematic review including three case-control studies and two randomized controlled trials showed robust evidence that adjuvant ^{131}I-labeled lipiodol prolongs DFS and OS by up to 5 years after resection in patients with sound liver function and low microvascular invasion[40]. Therefore, more well-designed, randomized pilot studies are required to draw solid evidence.

Adjuvant chemotherapy

Chemotherapy is the most widely administered cancer treatment. Generally speaking, chemotherapy is mostly utilized in the systemic treatment of primary liver cancer; however, with the development of modern technology, regional adjuvant chemotherapy also plays an important role in the prevention of liver cancer recurrence. However, chemotherapy has its limitations, as many drugs kill both cancer and healthy cells[42]. Therefore, chemotherapy is also utilized in combination with other therapies, such as surgery, radiotherapy, and immunotherapy, which have shown positive synergistic effects. As early as 1996, Yamamoto *et al*[43] systematically analyzed the efficacy of oral adjuvant chemotherapy in 67 patients with HCC who underwent radical resection between 1988 and 1990. They found that the OS and RFS were significantly higher in patients who received adjuvant oral 1-hexylcarbamoyl-5-fluorouracil than those who did not among patients with mild hepatic dysfunction, but no significant differences in survival were observed in patients with moderate hepatic dysfunction[43]. A subsequent randomized controlled trial had a different conclusion on the controversial question of whether adjuvant chemotherapy after resection can prevent recurrence of HCC. This trial showed similar relapse-free survival rates in the postoperative oral uracil-tegafur (UFT) and no adjuvant therapy groups and a significantly higher proportion of late recurrence in the UFT group than in the control group (74% *vs* 53%, P = 0.02)[44]. Interestingly, Ueda *et al*[45] discovered that adjuvant chemotherapy with UFT after TACE significantly prolonged the time to treatment failure in patients with advanced HCC, and no serious adverse events were observed with this regimen. This regimen may have adjuvant and anti-angiogenic functions in the treatment of advanced HCC. In addition, Nagano *et al*[46] found that adjuvant interferon-α/5-fluorouracil could benefit patients with advanced HCC after palliative hepatectomy. Therefore, combining chemotherapy with another treatment may be a solution to the poor efficacy of adjuvant chemotherapy when applied alone. Similarly, adjuvant chemotherapy after liver transplantation can provide survival benefits. A systematic evaluation and meta-analysis showed that implementing adjuvant

chemotherapy early after liver transplantation in patients with advanced HCC can significantly prolong patient survival and delay liver cancer recurrence[47].

Hepatic arterial infusion chemotherapy (HAIC) is a type of chemotherapy primarily administered to patients with advanced intrahepatic HCC, such as those with major portal vascular invasion and intrahepatic multinodular lesions with Child-Pugh class B liver function[48]. As patients with HCC with vascular invasion tend to have a poor prognosis after surgical resection, the postoperative administration of HAIC has been increasingly emphasized by investigators. A retrospective study that included 73 patients with HCC with visible vascular invasion found that DFS was significantly higher in the hepatic resection with HAIC group than in the control group without HAIC (33.1% *vs* 11.8%, *P* = 0.029) after 5 years of follow-up; however, there was no significant difference in OS between the two groups[49]. Hsiao *et al*[50] had similar findings and suggested that patients with HCC with multiple small nodules in close proximity to each other or a single large tumor with several satellite nodules could achieve greater benefit when HAIC was performed as an adjuvant treatment after resection. Preoperative HAIC can also be a means of downstaging before resection in patients with advanced HCC. Lee *et al*[51] showed that the median survival time and response rate of patients with advanced HCC who underwent hepatectomy after preoperative HAIC were 14 ± 1.7 mo and 26.4%, respectively.

The drug combinations for HAIC are also being continuously explored by scholars in various countries. A Japanese HAIC study compared the outcomes of 476 patients with HCC who received HAIC (5-fluorouracil and cisplatin) with 1466 patients who did not receive active treatment and showed that the median survival time was longer in patients who received chemotherapy (14.0 mo) than in those who did not receive active treatment (5.2 mo, *P* < 0.0001)[52]. However, several cisplatin (DDP)-based HAIC regimens are dose limited by renal, neurological, and gastrointestinal toxicity, making it difficult to achieve the desired outcomes[53]. In contrast, with the publication of the EACH study[54], oxaliplatin is coming into the limelight as a systemic chemotherapeutic agent. The study explored whether infusional fluorouracil, leucovorin, and oxaliplatin

(FOLFOX4) as palliative chemotherapy for patients with advanced HCC provides survival benefit and efficacy compared to doxorubicin, and found that this regimen may offer some benefit to Asian patients[54]. Subsequently, Chinese scholars modified and applied the FOLFOX regimen to HAIC and achieved stunning results. In the ASCO 2021 meeting, Li *et al*[55] firstly explored the efficacy of comparing neoadjuvant HAIC (FOLFOX regimen) (NT group) with direct surgery (OP group) in patients with HCC with ultra-Milan standard BCLC stage A/B and found that the ORR in the NT group reached 63.6% and DCR reached 96.0%. Furthermore, the team found that this protocol was also effective in HCC patients with microvascular invasion. The study showed that patients who received one or two cycles of postoperative adjuvant arterial perfusion chemotherapy had significantly better OS and DFS compared to patients without any adjuvant therapy (97.7% *vs* 78.5%; 58.7% *vs* 38.6%; P = 0.037 and 0.023)[56]. Thus, HAIC based on the FOLFOX regimen is gaining more and more attention in the academic community for its high ORR and surgical conversion rate.

Systemic therapy

The liver tumor microenvironment has complex immune tolerance capabilities[57]. Immunotherapy can enhance the body's immune response, break the immune tolerance of the tumor microenvironment, and reactivate immune cells to recognize and kill tumor cells. Immunotherapies mainly include adoptive cell transfer-based therapies, tumor vaccines, and immune checkpoint inhibitors (ICIs)[58]. Adoptive cell transfer-based therapy is used to isolate immunocompetent cells from the bodies of cancer patients. Through cytokine stimulation, *in vitro* culture, or tumor antigen loading, a large number of amplifications and functional identifications are performed *in vitro,* and then cells are injected back into the patient's body. These cells are now primed to enhance the patient's immune function and kill tumor cells. Cytokine-induced killer cells (CIKs) and genetically modified natural killer or T cells are the main immune cells used for this process in liver cancer[58]. A randomized trial published by Takayama *et al*[59] in 2000 first demonstrated the safety and efficacy of adoptive immunotherapy in

reducing recurrence and improving patient survival after HCC resection. A study of patients with HCC undergoing curative therapy also showed that adjuvant injection of activated CIKs improved RFS and OS[60]. However, other studies have shown a limited effect of adoptive T cell therapy in solid tumors, possibly due to the poor persistence of adoptive T cells *in vivo*, their cytotoxicity, and other defects[61]. Tumor vaccines are immunotherapies in which the patient's tumor antigens are infused back into the patient in various forms to enhance immunogenicity, thereby activating the patient's immune system to attack tumor cells. This is the theoretical basis of tumor vaccine treatment for liver cancer[61]. Repáraz *et al*[62] indicated that tumor vaccines have significant potential in combination with ICIs for the prevention and treatment of HCC. A recent review that included 31 clinical trials worldwide held the same opinion and concluded that HBV-associated HCC may benefit more from tumor vaccines than HCV-associated HCC[63]. Currently, tumor vaccines for patients with HCC mainly include dendritic cell (DC) vaccines, AFP vaccines, and other vaccines. DC vaccines, a common tumor vaccine, can provide clinical benefits to patients with HCC by stimulating antitumor T cell responses without significantly increasing toxicity[64]. AFP vaccines are peptide-based tumor vaccines used in HCC and are characterized by low immunogenicity and tolerance to the host immune system[62]. Immune checkpoints play a protective role in the body's immune system by preventing excessive activation of T cells from damaging the body's tissues. Cytotoxic T lymphocyte-associated antigen-4 and programmed death 1 are the two main immune checkpoints considered in the treatment of HCC, and ICIs developed against these checkpoint molecules have been widely adopted clinically for liver cancer. Numerous studies have reported ICIs as an appropriate therapy option pre- and post-transplantation, but most of these studies are retrospective or case reports; therefore, ICIs should be administered to patients undergoing liver transplantation with caution[65]. Similarly, there is a shortage of randomized controlled trials of ICIs after HCC resection or ablation, although several relevant trials are underway, testing drugs such as pembrolizumab (KEYNOTE-937, NCT03867084), nivolumab (CheckMate 9DX, NCT03383458), and atezolizumab plus

bevacizumab (IMbrave050, NCT04102098), which are expected to yield promising results.

Molecular targeted therapy is of epoch-making significance in the field of cancer treatment and is mainly based on the pathways involved in the pathogenesis of cancer. The development of molecular targeted therapeutics can cause death specifically in tumor cells. Sorafenib is an approved multi-target tyrosine kinase inhibitor for the treatment of patients with advanced and unresectable HCC[66]. Numerous retrospective studies have shown that adjuvant sorafenib treatment improves recurrence and prolongs survival, especially in patients at high risk of postoperative recurrence[67-69]. However, a phase 3, randomized, double-blind, placebo-controlled trial (STORM trial) evaluating the efficacy of adjuvant sorafenib after resection or ablation of HCC found no difference in the median RFS between the adjuvant sorafenib and placebo groups (33.3 mo vs 33.7 mo, P = 0.26)[70]. Sorafenib treatment in the perioperative period of liver transplantation is equally ineffective and strongly associated with a worse prognosis[71]. In contrast, lenvatinib has shown promising results as an adjuvant therapy for patients who have undergone liver transplantation. A retrospective case-control study showed that adjuvant lenvatinib can prolong DFS in patients with high-risk HBV-related HCC following liver transplantation[72]. Bevacizumab, an angiogenesis inhibitor, has shown poor results as adjuvant therapy in patients with HCC. Pinte *et al*[73] found that patients treated with adjuvant bevacizumab after TACE not only had no improvement in OS but also developed sepsis and vascular side effects. Consequently, for the prophylactic treatment of patients with HCC, adjuvant treatment strategies with molecularly targeted drugs should be carefully selected.

TREATMENT FOR RECURRENT HCC

The treatment of recurrent liver cancer is mostly based on the diagnosis and treatment guidelines for primary liver cancer[74] combined with clinical experience. Multiple studies have shown that surgical resection, liver transplantation, and non-surgical treatment (such as ablation and TACE) for recurrent HCC can lead to survival benefits

comparable to those of the first treatment[75-79]. However, most of these are small-sample studies at a single institution, the evidence is weak, and the results are difficult to generalize. Ideally, treatment strategies for recurrent HCC can be based on the same criteria as those for primary cancer; however, given the intratumoral heterogeneity and different clonal lineages between primary and recurrent HCC, it is still advisable to perform a comprehensive overview of the tumor before choosing the best treatment modality. In addition, patient characteristics (such as sex, age, and psychological state), conditions of the first operation (such as surgical area and main blood vessels severed during the first operation), and basic liver function status should also be comprehensively evaluated. A suggested flowchart to guide treatment decision-making in the setting of recurrent HCC is presented in Figure 1.

Repeat hepatectomy

Hepatectomy remains a safe and effective treatment for recurrent HCC. Reoperation in patients with HCC with good liver function significantly prolongs survival, especially in patients exhibiting recurrence within 2 years and those with a primary tumor burden exceeding the Milan criteria[80,81]. Yoh *et al*[3] observed similar findings; in their study, 128 patients who underwent repeat surgery had better liver function and a significantly longer time to recurrence than 548 patients who did not undergo reoperation (16.5 mo *vs* 11.4 mo; *P* < 0.001). Although repeat hepatectomy is most commonly performed for patients with intrahepatic metastases, surgical resection can also provide benefit to patients with recurrent extrahepatic lesions under conditions of limited isolation of metastases, preservation of liver function, and adequate control of the primary tumor[82]. Repeat hepatectomy is also a recommended treatment option for patients with recurrent HCC occurring more than 18 mo after the initial resection, and survival rates are significantly higher for patients with multiple distant metastases than for those with intrahepatic metastases[83]. Numerous retrospective studies have suggested that appropriately selected patients undergoing partial hepatectomy can achieve long-term survival after both initial hepatectomy and liver transplantation, with 5-year OS and

RFS rates ranging from 22%-84% and from 10%-43%, respectively (Table 1). Third repeat hepatectomy is also a promising technique for recurrent tumors, and it has been reported that three or more repeat hepatectomies for recurrent HCC are reasonable and safe; however, they should be performed with caution because of the high recurrence rate, long operative duration, and high patient selectivity of resection[84,85]. For recurrent HCC after liver transplantation, patients who undergo repeat hepatectomy tend to have worse prognosis and are more susceptible to deterioration in liver function. Therefore, an alternative, less invasive laparoscopic approach can be applied for repeat hepatectomy in these patients. Recurrent HCC was previously considered a contraindication to laparoscopic surgery; however, recent studies have shown that laparoscopic surgery for recurrent HCC is reliable, and there is no significant difference in tumor recurrence or survival after laparoscopic surgery compared with open surgery[86,87]. In contrast, the advantages of laparoscopic liver resection include shorter operation time, less intraoperative bleeding, and faster recovery compared to traditional surgery; therefore, laparoscopic liver resection can be a safe alternative to open surgery.

Salvage liver transplantation

Salvage liver transplantation (SLT) is an appropriate treatment for recurrent HCC complicated by severe cirrhosis and liver decompensation. Available studies suggest that SLT in patients with recurrence after initial hepatectomy is a highly applicable strategy with long-term survival outcomes comparable to those of early liver transplantation[88-90]. SLT is a proven curative treatment technique for patients with recurrent HCC who meet the Milan criteria, with 5-year OS and RFS rates ranging from 42% to 67% and from 32% to 68%, respectively (Table 2). An intention-to-treat analysis study of curative SLT in patients with cirrhosis and HCC by de Haas *et al*[89] showed that SLT had a favorable curative potential and that a model for end-stage liver disease score > 10 and the absence of TACE were predictors of successful SLT. In addition, Lim *et al*[90] compared the prognosis of 77 patients with HCC who underwent SLT with that of 314 patients with HCC who underwent a second surgery. They found that the 5-year

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intention-to-treat OS rates calculated from the time of the first hepatectomy were similar between the two groups (SLT, 72%; second surgery, 77%; *P* = 0.57), and the 5-year DFS rate after transplantation was much higher than that after a second hepatectomy (SLT, 72%; second surgery, 18%; *P* < 0.001)[90]. However, owing to organ shortages and cancer progression while on waiting lists, SLT can provide benefit to only a limited number of patients, making it far less widely used than repeat liver resection. Therefore, secondary resection of recurrent HCC may be considered a better therapeutic option than SLT in the current context of organ shortage. Nevertheless, given adequate organ reserves, SLT remains the preferred option for patients with cirrhosis after primary HCC resection or for those who undergo inoperable resection but meet the criteria for liver transplantation. It is worth pointing out that the existing international consensus suggests that SLT is not amenable for the treatment of HCC recurrence after transplantation[91].

Tumor ablation

Non-surgical treatment is typically proposed for recurrent HCC in the setting of inadequately preserved liver function or advanced tumor stage. Ablation therapy, such as RFA, has also been studied in the setting of recurrent HCC, with 5-year OS rates ranging from 9%-33% and 5-year RFS rates ranging from 32%-68% (Table 3). An updated meta-analysis showed that RFA is the preferred choice for recurrent HCC meeting the Milan criteria, with OS and DFS rates being similar to those of patients undergoing resection[92,93]. One study showed that 297 patients with isolated HCC ≤ 5 cm who underwent percutaneous ultrasonography-guided RFA following recurrence of liver cancer had similar OS to 263 patients who underwent initial RFA during the same period[94]. Similarly, Yang *et al*[95] concluded that RFA is generally effective and safe for the treatment of HCC recurrence after hepatectomy and that ablation is more effective in patients who relapsed 1 year after resection. RFA is also an advantageous alternative to prolong patient survival when surgical resection is contraindicated or technically infeasible[96]. Microwave ablation (MWA) is another commonly used modality for

tumor ablation. Compared to RFA, MWA can reduce the time required for ablation by 60% and is more effective in eradicating tumors 3-5 cm in size[97]. As both RFA and repeat hepatectomy are indicated for HCC tumors with similar characteristics, a randomized controlled trial compared repeat hepatectomy and RFA for recurrent HCC. After a randomized 1:1 assignment of 217 patients with the same tumor characteristics to repeat hepatectomy or percutaneous RFA, the study found no statistically significant difference in survival outcomes between the two treatment strategies for patients with early-stage recurrent HCC. However, subgroup analysis found that repeat hepatectomy may be correlated with better local disease control and long-term survival in patients with tumor diameters > 3 cm or AFP levels > 200 ng/mL. In addition, because of cirrhosis, multifocal lesions, and vascular invasion, repetitive hepatectomy for recurrent HCC is limited, and only 15%-30% of patients are eligible[98]. Ablation therapy has the advantages of less trauma, less impact on liver function, and fewer complications than surgical treatment. Therefore, RFA remains a potential treatment option for patients with recurrent HCC who are unsuitable for repeat resection or salvage transplantation. However, salvage ablation is usually only appropriate for small recurrences that are detected early.

TACE

Most recurrent HCC cases are not amenable to curative treatment techniques, including repeat resection, transplantation, and ablation. Therefore, TACE is the most common treatment modality for recurrent HCC after primary resection. TACE exerts a combined antitumor effect by embolizing tumor vessels and increasing local drug concentrations[99-101]. Although numerous studies have shown that TACE is inferior to repeat hepatectomy and SLT[102-104], according to a prospective cohort study, TACE is more appropriate for patients with multifocal disease and early (≤ 1 year) recurrence than other treatment techniques, such as repetitive hepatectomy and RFA[105]. Similarly, it has been proposed that TACE is a more effective treatment for prolonging patient survival in patients with BCLC stage 0 or A recurrent HCC with microvascular

invasion, especially those who developed recurrence < 1 year after surgical resection[106]. Furthermore, two randomized controlled trials demonstrated that TACE is the only transarterial embolization modality that offers a survival advantage over best supportive care for patients with HCC who cannot receive curative treatment techniques[107,108].

Selective internal radiotherapy with yttrium-90 is also an available solution for patients with intermediate-to-advanced HCC with portal vein thrombosis as a safe alternative to TACE[109]. However, there are no experimental data on the application of yttrium-90 in the treatment of recurrent HCC. Both regimens can be used for the treatment of recurrent tumors after liver transplantation in patients with multiple lesions[110], but there are few relevant studies, and more robust evidence is needed to demonstrate the safety and efficacy of this regimen.

Stereotactic body radiotherapy
Stereotactic body radiotherapy (SBRT) is an emerging treatment option for HCC, where it is mainly performed for the local control of small HCCs. A matched-pair study demonstrated that 36 patients receiving SBRT had better OS than 138 patients with relapsed HCC who received other treatments or no treatment (2-year OS, 72.6% *vs* 42.1%; P = 0.013)[111]. A review evaluating the efficacy and prognosis of five different strategies for the treatment of recurrent intrahepatic HCC indicated that SBRT was superior to TACE in terms of OS and DFS but less effective than curative treatment techniques. In contrast, the prognostic efficacy of SBRT was better than those of ablation and TACE among patients with tumors > 3 cm and second only to repeat hepatectomy[102]. In addition, a small, single-center, retrospective study evaluating six patients with recurrent intrahepatic HCC after liver transplantation treated with SBRT found no local progression or death in patients at a median follow-up of 15.5 mo, which may imply that SBRT is safe for use in this setting[112]. Notably, a study by Eriguchi *et al*[112] suggested that repeated stereotactic radiotherapy is feasible for the treatment of HCC. The 3-year OS rate of patients with HCC treated with SBRT at least twice between

2012 and 2019 was 62.8% after the second course of treatment. However, there are few prospective studies on the application of SBRT for recurrent HCC.

Systemic therapies

In recent years, systemic therapies, such as molecular targeted drug therapy and immunotherapy, have become a major focus in the treatment of intermediate and advanced liver cancer. Multiple studies have revealed that sorafenib, a representative molecular targeted therapy, prolongs the survival of patients with recurrent HCC after liver transplantation[114-116]. A case-control study showed that 15 patients with HCC treated with sorafenib had a better prognosis than 24 patients who relapsed after liver transplantation on supportive care (median survival for relapse: 21.3 mo *vs* 11.8 mo, *P* = 0.0009)[116]. Martin *et al*[116] also demonstrated a similar safety profile for sorafenib in patients with HCC who developed recurrence after resection. Regorafenib, another molecular targeted therapy, has gained attention as an option for the treatment of recurrent HCC after liver transplantation. In sorafenib-resistant patients who develop disease progression, the application of regorafenib for recurrent tumors after liver transplantation is safe and significantly prolongs patient OS compared with supportive therapy (13.1 mo *vs* 5.5 mo; *P* < 0.01)[118]. Regorafenib and lenvatinib are currently approved for the treatment of recurrent HCC in Japan[119]. However, many patients have *de novo* or acquired resistance to monotherapy; therefore, drug combinations are gradually gaining recognition among investigators. Immunotherapy, such as ICIs, has also proven to be advantageous in the treatment of recurrent HCC when combined with tyrosine kinase inhibitors. One study suggested that the combination of lenvatinib plus pembrolizumab for patients with postoperative refractory recurrent metastatic HCC resulted in partial remission and OS of up to 60 mo after surgery[120]. Similarly, the combination of mammalian target of rapamycin target inhibitors and sorafenib is safe and effective in patients with post-transplant relapsed HCC[121]. Nevertheless, studies on systemic therapy for the treatment of recurrent HCC after resection are still

insufficient, and more data are needed to confirm the therapeutic value of this strategy in the relevant populations.

Combination therapy

A combination of nonsurgical treatments for recurrent HCC is being tested in multiple studies, with the combination of TACE and ablation being the most promising. Heat dissipation may be the reason for the poor ablation effect of RFA. Applying both RFA and TACE can block the blood supply to the tumor, expand the tumor ablation margin to destroy satellite lesions, and minimize the heat loss caused by the heat sink effect, whereas the effect of chemotherapeutic anticancer agents on cancer cells is enhanced by the heat therapy effect[122]. Song *et al*[122] analyzed the outcomes of 96 patients with recurrent HCC ≤ 5 cm treated with a combination regimen of TACE-RFA and found that TACE-RFA as a first-line local therapy led to better DFS than TACE alone. This was also confirmed by a prospective randomized trial in which sequential TACE-RFA was more effective than RFA alone in patients with recurrent HCC ≤ 5 cm in diameter[124]. Furthermore, the combination TACE-RFA regimen was superior in prolonging patient survival compared with sorafenib alone for advanced recurrent HCC. This study revealed that the median OS (14.0 mo *vs* 9.0 mo; *P* < 0.001) and time to progression (7.0 mo *vs* 4.0 mo; *P* < 0.001) were significantly longer in the TACE-RFA combination group than in the sorafenib group[125]. In another study, although the combined TACE-RFA group had similar OS and DFS to the repeat hepatectomy group for patients with recurrent HCC, the combined TACE-RFA group had fewer major complications and shorter hospital stays[126]. In addition to the TACE-RFA combination, the combination of sorafenib and TACE is effective in patients with recurrent intermediate-stage HCC and microvascular invasion, and this treatment strategy yields a longer survival time than TACE alone[127]. Similarly, TACE combined with camrelizumab was reported to have an acceptable safety profile, although its efficacy was comparable to that of TACE alone[128]. Hence, TACE combined with systemic therapy has outstanding potential for recurrent liver cancer, but the variety of combination therapies is relatively small.

Larger prospective clinical studies are needed to optimize the treatment sequence and identify the appropriate combination therapy regimens. The strategy of ablation combined with systemic therapy for the treatment of recurrent HCC is currently being studied in different institutions, including in phase III clinical trials (ClinicalTrials.gov numbers: NCT05444478, NCT05277675, and NCT04663035).

PREDICTORS AND SURVEILLANCE OF RECURRENT HCC

The previous sections highlighted the high risk of recurrence of liver cancer and the limitations of available treatments. For example, surgical resection is the most effective treatment. However, owing to the low sensitivity and specificity of resection caused by the technical level and unclear diagnosis, it is likely that some patients with early recurrence of HCC will be unable to undergo the optimal treatment. Therefore, predicting and monitoring for recurrence of HCC after the initial treatment is key to prolonging survival and avoiding harm to the life and health of patients due to tumor progression. Although there are some treatment measures to prevent the recurrence of HCC, these preventive treatments are not targeted, which can easily lead to overtreatment and increase patients' economic burden and decrease quality of life. Therefore, more accurate indicators are needed to supplement the stratification of prognostic and the risks of postoperative metastasis and tumor recurrence in patients with HCC[129]. The use of molecular biological methods to study and identify effective molecular markers is one of the key means to assist clinical diagnosis, guide clinical intervention, and provide early warning of cancer.

Recurrence and metastasis are the main reasons for the poor prognosis of HCC. However, there is no sensitive and specific method for predicting early recurrence and metastasis of HCC. Several molecular markers or their combinations have been published or reported for the diagnosis or prediction of HCC; however, there is still a lack of molecular markers or combinations that can be used to predict HCC recurrence and metastasis.

Influencers and predictors of recurrent HCC

Pathological factors: Owing to the high malignancy of HCC cells, the rapid growth of cancerous tissue, and the rich blood supply to the liver, cancer cells can easily invade the blood vessels of the liver and metastasize to other parts of the liver hematogenously. Therefore, many pathological factors associated with primary tumor characteristics and the underlying liver are intimately related to the recurrence of HCC, including the size and number of tumors, tumor capsule, portal vein tumor thrombus, staging and differentiation of the tumor, and degree of cirrhosis[130,131]. The size and number of tumors are important factors affecting recurrence after surgery. Some people regard the integrity of the tumor capsule as an indicator of tumor invasiveness; however, the capsule of liver cancer is actually a pseudocapsule (usually constructed from connective fibrous tissue) formed by squeezing the surrounding normal liver tissue during tumor growth[132,133]. Cancerous infiltrates are often found in the liver tissue outside the intact capsule, and there is little evidence of a clear relationship between capsule integrity and postoperative recurrence. However, the existence of an intact capsule has a certain significance in the determination of the surgical margin during radical resection[134]. For patients with a tumor diameter > 3 cm and incomplete imaging of the tumor capsule, a wide resection margin is preferred[134]. The presence of intrahepatic portal vein tumor thrombus is another important factor associated with the postoperative recurrence of liver cancer, and intrahepatic metastasis is easily formed in patients with intrahepatic portal vein tumor thrombus. It is generally believed that the stage and classification of the tumor are strongly correlated with prognosis: The lower the differentiation of a malignant tumor, the more invasive it is. Therefore, primary liver cancers with poor differentiation are prone to early metastasis, resulting in incomplete resection and postoperative recurrence. A retrospective analysis of clinical and pathological factors in 112 patients undergoing partial hepatectomy by Arii *et al*[128] found that factors such as tumor size, number of tumors, cancer cell infiltration of the fibrous capsule of the tumor, portal involvement, and tumor stage may affect the recurrence of HCC; these factors could be utilized as predictors of recurrence, allowing for early diagnosis[130].

Cirrhosis may affect recurrence, because it limits the size of the resection margin, thereby reducing the rate of radical resection. In addition, spleen stiffness measurements directly related to the degree of liver disease and portal hypertension, as assessed using transient elastography, appear to be the only predictors of late recurrence of HCC[131]. Finally, factors related to surgery are also strongly associated with the recurrence of HCC, including tumor margins[135], intraoperative bleeding and blood transfusion[136], and intraoperative compression of the tumor[137]. Tumor margin is the most important factor in the criteria for radical resection of liver cancer. A larger resection margin is associated with a lower detection rate of tumor thrombus and a lower recurrence rate after surgery[135]. Intraoperative bleeding and blood transfusion reflect the degree of surgical trauma, and the magnitude of intraoperative estimated blood loss is related to the biological characteristics of the tumor and the extent of surgery[136]. Moreover, estimated blood loss during HCC resection can affect the postoperative course of hepatitis and the recovery of immune function. Intraoperative compression of the tumor may cause shedding of cancer tissue or tumor cells, resulting in intrahepatic metastasis or distant dissemination and becoming an important source of postoperative recurrence[137].

Serum biomarkers: Serum AFP and albumin levels were the earliest serological markers used to assist in the diagnosis of HCC. Serum AFP ≥ 400 ng/mL is highly suggestive of HCC if pregnancy, chronic or active liver disease, gonad embryonic-derived tumors, and other gastrointestinal tumors can be ruled out. AFP L3 can be used as a prognostic indicator of HCC recurrence. Additionally, in patients with chronic HBV infection and those at a high risk of cirrhosis, AFP L3 can be an early indicator of HCC. After radical resection of HCC, a lack of obvious decrease in AFP L3 indicates the presence of metastasis or residual carcinoma[138]. In addition, given the high false-negative rate of AFP in the detection of early or small HCC, prothrombin induced by vitamin K deficiency or antagonist-II (PIVKA-II) can be used as a complement to AFP. As early as 1984, Liebman et al[137] found abnormally elevated levels of de-γ-carboxy

prothrombin in patients with primary HCC and proposed its use for the laboratory diagnosis of HCC. Many have since studied this serum marker further and compared it with the traditional diagnostic marker AFP. Feng *et al*[138] evaluated the diagnostic efficacy of AFP and PIVKA-II when used separately and in combination in patients with primary and recurrent HCC and observed that the combination of both markers dramatically improved the diagnostic efficiency compared to either marker alone. Conversely, a recent retrospective cohort study indicated that preoperative PIVKA-II positivity, but not preoperative AFP positivity, was an independent risk factor for early recurrence of HCC[141]. This suggests that PIVKA-II is equally effective as a serum diagnostic biomarker and can be considered an alternative to AFP.

Inflammatory markers: C-reactive protein (CRP), which is synthesized by hepatocytes and regulated by interleukin-1 (IL-1) and IL-6, has important clinical value as a marker of acute and chronic inflammation. Several recent studies have found that CRP is an independent risk factor for tumor recurrence in patients with HCC who exceed the Milan criteria after liver transplantation[142,143]. Similarly, elevated postoperative serum CRP may be a prognostic indicator for patients with HCC after elective hepatectomy[144]. Further, the peripheral blood neutrophil-to-lymphocyte ratio (NLR) and platelet-to-lymphocyte ratio (PLR) are correlated with the prognosis of malignant tumors. Halazun *et al*[143] followed up 150 patients who underwent liver transplantation for HCC and found that the tumor recurrence rate of 13 patients with an NLR ≥ 5 was 62%, and the 5-year OS and DFS rates after surgery were significantly lower than those in patients with an NLR < 5. Further, multivariate analysis showed that a high NLR was a risk factor affecting the DFS rate of recipients (hazards ratio = 19.98; *P* = 0.005). Another study of 865 patients who underwent liver transplantation for HCC found that the risk of HCC recurrence increased 1.89 times for each logarithmic unit increase in the NLR[146]. A meta-analysis conducted by Lai *et al*[145] revealed that an elevated PLR was associated with an increased risk of HCC recurrence after liver transplantation (odds ratio = 3.33; 95%CI: 1.78-6.25; *P* < 0.001). Although these studies show the predictive

potential of these inflammatory markers, there is heterogeneity and poor reproducibility. In addition, the cutoff values of inflammatory markers vary greatly between studies; therefore, the optimal cutoff requires further study, and it is difficult to use these as biomarkers widely in clinical practice.

Immunohistochemical indicators: Patients with liver cancer often have a history of HBV or HCV infection, liver cirrhosis, and other backgrounds, and the resulting inflammatory response often leads to large numbers of lymphocytes in or around the lesion. The ratio of CD4/CD8+ T cells in the tumor is associated with recurrence after liver transplantation, and more CD4+ T cell infiltration reduces the risk of recurrence after liver transplantation[148]. Further, tumor or peripheral blood regulatory T (Treg) cells are associated with tumor invasion, and Treg cells reduce the antitumor effect of effector T cells, which promotes tumor immune escape[149,150]. The imbalance between regulatory and cytotoxic T cells in HCC is also expected to be an effective prognostic factor. Clinical studies have found that Treg cells are significantly higher in HCC tissues than in non-cancerous liver tissues, suggesting that Treg cell infiltration in HCC can inhibit antitumor immunity and high Treg cell infiltration in HCC is a predictor of poor prognosis[151].

Genomic biomarkers: In the process of tumor invasion and metastasis, tumor cells need to break through the barriers of the extracellular matrix and basement membrane. Matrix metalloproteinase (MMP)-9 can degrade the extracellular matrix; therefore, tumors with high expression of MMP-9 have stronger invasion and metastasis abilities. Most patients with high MMP-9 expression in liver cancer tissues and plasma have portal vein tumor thrombus or intrahepatic metastasis[152]. The level of serum vascular endothelial growth factor (VEGF) in patients with liver cancer is significantly higher than that in patients with benign liver disease and healthy individuals. High VEGF is closely related to portal vein tumor tether, tumor size, and TNM stage[153]. VEGF plays an important role in the invasion and metastasis of liver cancer, and preoperative

examination of serum VEGF levels is of great significance in predicting the invasion and metastasis of liver cancer[154]. *AFP* mRNA in circulating blood can be used to detect the presence of circulating cancer cells. Reverse transcription-polymerase chain reaction indicated *AFP* mRNA in the peripheral blood of 59.7% of patients with liver cancer[155]. Therefore, the presence of disseminated HCC cells in the blood circulation can be detected before treatment is initiated. The positive rate of *AFP* mRNA in the peripheral blood is significantly correlated with the clinical stage and postoperative recurrence of liver cancer, and 57% of patients with postoperative recurrence have *AFP* mRNA in the peripheral blood[156]. Therefore, *AFP* mRNA expression in the systemic circulation can be used to assess the risk of recurrence and metastasis.

Surveillance of recurrent HCC

The establishment of prognostic models based on predictors is important in the field of HCC recurrence prevention and monitoring. Hwang *et al*[156] integrated three variables (tumor size > 5 cm, high AFP, and high des-γ-carboxy prothrombin) by direct multiplication and constructed the ADV score as a comprehensive proxy for predicting prognosis after isolated HCC resection. This score had a sensitivity of 73.9% and specificity of 66.7%[157]. This team then performed preoperative evaluation and postoperative follow-up of 526 patients with isolated HCC ≥ 8 cm treated with hepatectomy, which led to the development of a comprehensive, predictive surrogate marker that is equally valid in patients with very large HCC. The PPM prediction model constructed in that study is based on four factors, including AFP ≥ 100 ng/mL, hypermetabolic 2-18F-fluoro-2-deoxy-D-glucose positron emission tomography (FDG-PET) findings, microvascular invasion, and satellite nodules, and had C-indexes of 0.66 for tumor recurrence and 0.69 for patient survival. In contrast, in the new version of the PPM prediction model constructed based on two previously studied factors, ADV7 log and FDG-PET, the C-indexes for tumor recurrence and patient survival were 0.64 and 0.70, respectively[158].

The construction of a reliable risk score for recurrence of HCC after liver transplantation could vastly improve surveillance strategies and help identify patients who may benefit from adjuvant therapy. The RETREAT score constructed by Mehta *et al*[157] is effective in predicting recurrence after transplantation in patients with HCC who meet the Milan criteria. The score includes three main factors: Microvascular invasion, post-transplant AFP, and the sum of the maximum diameter and number of surviving tumors. Compared with the Milan criteria, the RETREAT score improved the prediction of HCC recurrence at 1 (0.40, $P = 0.001$) and 5 (0.31, $P < 0.001$) years after liver transplant[159]. Based on the RETREAT score, Costentin *et al*[158] recently proposed a novel composite prediction tool, the R3-AFP score, to optimize the prediction of HCC recurrence after liver transplantation. In addition to the factors included in RETREAT, the model also incorporated pre-transplant AFP and pathological variables, which led to the classification of patients into four risk groups, with a 5-year survival rate of 77.2% for patients in the very low-risk group[160].

In addition to these traditional Cox proportional hazard prediction models based on linearity assumption, the construction of prediction models by machine learning algorithms has become an important method for predicting tumor recurrence. Given the complex, multidimensional, nonlinear relationships between clinical data, machine learning models outperform traditional regression models in predicting HCC progression[161]. The XGBoost model based on clinical data is effective in predicting the risk of early recurrence in patients after MWA, with an area under the curve of 0.75 (95%CI: 0.72-0.78)[162]. Moreover, incorporating magnetic resonance imaging (MRI) data in a machine learning model for recurrent HCC after transplantation can effectively improve the predictive performance of the model compared to incorporating clinical parameters alone[163]. Therefore, appropriate monitoring protocols can be developed to maximize the prevention of recurrence and prolong patient survival after HCC resection.

The main methods currently used for the clinical monitoring of HCC recurrence are serum AFP monitoring, regular abdominal ultrasonography, and computed

tomography (CT). In addition, MRI has strong soft tissue resolution and can reflect the changes in blood flow and enhancement at the lesion site and has been widely used in clinical practice to monitor the recurrence of liver cancer. Gadoxetic acid (Gd-EOB-DTPA) is a relatively safe and well-tolerated liver-specific contrast agent that adequately combines the properties of conventional extracellular contrast agents and hepatocyte-specific magnetic resonance contrast agents with the higher soft tissue resolution of MRI. Therefore, EOB-MRI has better detection and diagnostic efficacy for HCC than CT[164]. The apparent diffusion coefficient (ADC) in magnetic resonance diffusion-weighted imaging (DWI) can quantify the overall diffusion of a lesion. Chuang *et al*[165] revealed that tumor recurrence after liver transplantation could be effectively predicted by analyzing the correlation between tumor recurrence, explant pathologic findings, and the ADC. Furthermore, several lines of evidence suggest that Gd-EOB-DTPA and DWI are more advantageous in detecting small liver lesions than CT[166,167]. Therefore, clinicians may be able to select more appropriate monitoring methods based on the combination of imaging and prognostic models to identify patients at high risk of recurrence and determine the optimal treatment.

CONCLUSION

In conclusion, since HCC has varied recurrence patterns and timing, the choice of treatment option after treatment for primary HCC varies. Repeat hepatectomy is the treatment of choice for recurrent HCC; laparoscopic surgery techniques are becoming increasingly sophisticated and offer a novel, safe, and effective surgical option for hepatectomy in patients with recurrent disease. However, the clinical application of repeat hepatectomy is limited due to the small number of eligible patients. Liver transplantation is preferable for patients with recurrent HCC complicated by severe cirrhosis and hepatic decompensation, and it has a better RFS than repeated hepatectomy; however, a shortage of organ donors and long wait times are two major factors that limit the utilization of SLT. In patients with recurrent HCC who are not candidates for resection or transplantation, nonsurgical treatment options are worth

considering. Whether HCC recurs after resection or transplantation, ablative therapy, especially RFA, has become another treatment alternative advocated by many researchers, owing to its minimally invasive nature and convenient advantages. However, salvage ablation is recommended only for patients with early recurrence of tumors ≤ 3 cm in diameter. Although TACE does not provide the same survival benefit as repeat hepatectomy and SLT for recurrent HCC, it should be considered in patients with early recurrence with microvascular invasion or multiple lesions. Similarly, SBRT can provide good disease control and a modest survival benefit in patients with small HCC who relapse after operative treatment. Systemic therapy, including molecular targeted therapy and immunotherapy, is also gaining attention as an emerging therapeutic strategy for clinical application in recurrent liver cancer. Systemic therapy can provide benefit to patients with advanced recurrent HCC either as a single agent or in combination with other therapies. Combination therapy is a promising way to optimize therapeutic efficacy by combining different treatment options to reduce complications and prolong survival, and this may be a key research direction for the future. The flexible combination of systemic therapies and other complementary therapies may offer a breakthrough in the clinical efficacy of HCC treatment. Finally, despite the promising results of most of these studies, future prospective randomized controlled studies are still needed to provide more rigorous clinical evidence to develop and optimize treatment options for recurrent HCC.

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