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REVIEW

Recent advances in recurrent hepatocellular carcinoma therapy

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Abstract

Hepatocellular carcinoma (HCC) is the most prevalent form of primary liver cancer, accounting for 75%-85% of cases. Although treatments are given to cure early-stage HCC, up to 50%-70% of individuals may experience a relapse of the illness in the liver after 5 years. Research on the fundamental treatment modalities for recurrent HCC is moving significantly further. The precise selection of individuals for therapy strategies with established survival advantages is crucial to ensuring better outcomes. These strategies aim to minimize substantial morbidity, support good life quality, and enhance survival for patients with recurrent HCC. For individuals with recurring HCC after curative treatment, no approved therapeutic regimen is currently available. A recent study presented novel approaches, like immunotherapy and antiviral medication, to improve the prognosis of patients with recurring HCC with the apparent lack of data to guide the clinical treatment. The data supporting several neoadjuvant and adjuvant therapies for patients with recurring HCC are outlined in this review. We also discuss the potential for future clinical and translational investigations.

Key Words: Recurrent hepatocellular carcinoma; Liver transplantation; Therapy; Immunotherapy; Neoadjuvant and adjuvant therapy

Core Tip: Hepatocellular carcinoma (HCC) is the most prevalent form of primary liver cancer, and up to 50%-70% of individuals may experience a relapse of the illness in the liver after 5 years. This review will provide novel approaches to improve the prognosis of patients with recurring HCC with the apparent lack of data to guide the clinical treatment. Neoadjuvant and/or adjuvant therapy methods potentially elevate the opportunity of cure in refractory patients with recurrent HCC and contribute to a better long-term prognosis.

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INTRODUCTION

With an expected 906000 new cases and over 800000 fatalities, primary liver cancer is ranked as the sixth most commonly diagnosed malignancy and the third most prevalent cause of cancer-related deaths worldwide in 2020[1]. Hepatocellular carcinoma (HCC) accounts for 75%-85% of cases of primary liver cancer[2]. As medical care has improved, liver transplantation (LT) has emerged as the best option for individuals with HCC that is either incurable or who have progressive liver damage as a result of their HCC[3]. Although patients receive treatments for early stage HCC intending to cure the disease, up to 50%-70% of patients may experience disease relapse in the liver after 5 years[4,5]. This is not only related to the inadequacy of the surgery (*i.e.*, positive surgical margin) but is also frequently associated with the development of *de novo* tumors as the disease progresses. Additionally, 70% of patients with recurrent HCC experience an early relapse within 2 years of surgery, which is nearly incurable and has been linked to apoor prognosis[6]. The molecular mechanisms underlying the prompt relapse of HCC are still unclear.

In a small percentage of HCC patients with multifocal intra or extrahepatic relapse, liver function impairment, and tumors that cannot be removed, rehepatectomy is necessary[7]. According to reports, HCC patients with tumors that meet the Milan criteria had excellent 5-year survival rates and minimal risks of relapse after LT[8]. Until the disease worsened or tolerance was established, monotherapy was thought to be the only course of therapy. At least two treatments administered simultaneously or within 4 wk of each other were considered multimodal therapy[9]. Preclinical findings suggest that neoadjuvant and adjuvant dosages should be used in combination instead of using either of them individually[10].

Therefore, it is crucial to devise the best treatment plans and fully comprehend the mechanism of HCC relapse. As a result of these problems, numerous researchers have looked into the benefits of neoadjuvant and adjuvant therapeutic approaches to lower relapse rates and enhance prognosis. Adjuvant therapy is not typically advised following curative treatment since its benefits are unclear[11]. It is clear that some additional treatment modalities are necessary, and in this regard, either neoadjuvant or adjuvant approaches are mostly taken into consideration. These include adjuvant antiviral therapy, repeated excision, transarterial chemoembolization (TACE), transarterial radioembolization, radiofrequency ablation (RFA), LT, tyrosine kinase inhibitors, and immunotherapy. Here, we will discuss the current state of knowledge on and recent advances in the therapy of recurrent HCC in this narrative review.

MECHAMISM OF RECURRENT HCC

Up to 70% of early HCC recurrence cases were thought to manifest within the first two years following curative therapy; relapses that occur after this point are referred to as late HCC recurrences[12]. Malignant, immunological, and stromal cells are made up of heterogeneous cell types that interact spatiotemporally in complex tumor ecosystems[13]. Recent research has found similarities between the genetic variants of primary and early recurrent HCC[14]. Nevertheless, explanations for differences between the cellular ecosystems of primary and recurrent HCC are still being sought after. Early-relapse HCC displayed decreased regulatory T cells (Tregs) and higher dendritic cells (DCs) and CD8+ T cells compared to primary HCC, which were associated with a poor prognosis[15], as shown in Figure 1. Treg recruitment is a characteristic of the immunosuppressive milieu of primary HCC[16]. In contrast to the traditional depletion state in primary HCC, CD8+ T cells in relapsed HCC displayed higher CD161

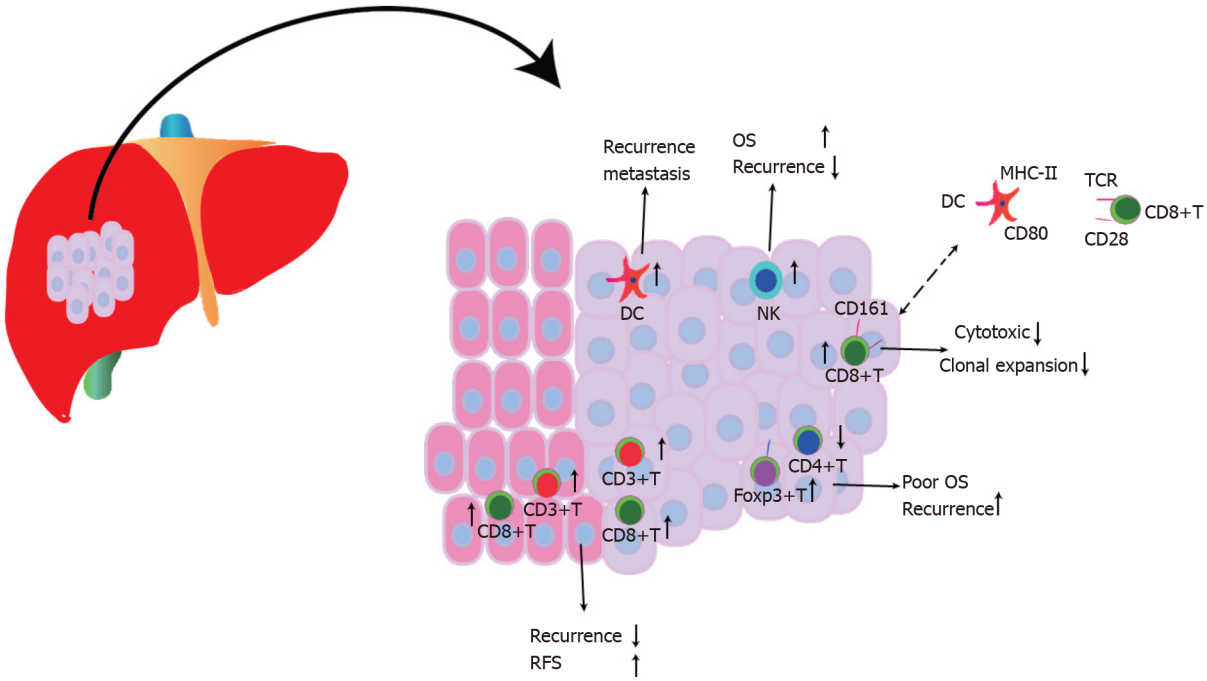

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Figure 1 Mechanism of action of immune cells under investigation for recurrence of hepatocellular carcinoma. Early-relapse hepatocellular carcinoma displays decreased regulatory T cells, and higher dendritic cells and CD8+T cells. FoxP3(+) regulatory T cells encourage a gradual decline in CD4+ cytotoxic T cells, which contributes to poorer survival and high recurrence rates. OS: Overall survival; RFS: Relapse-free survival; DC: Dendritic cells; NK: Natural killer cell.

expression, a low cytotoxic state that was innate, and reduced clonal expansion. This is significant because the immune escape mechanism underlying HCC relapse was connected to the inhibition of DC antigen presentation and infiltration of innate-like CD8+ T cells[15], which caused intrahepatic dissemination of HCC. Tregs and intragraft Toll-like receptor 4/C-X-C motif chemokine 10/CXCR3 C-X-C motif chemokine receptor 3 levels were higher in patients with HCC recurrence following LT, which was further substantiated in a rat transplantation model[17].

According to a meta-analysis, HCC patients with high Foxp3+ T cell infiltration had worse 1-, 3-, and 5-year survival rates and a greater rate of recurrence than patients with low Foxp3+ T cell infiltration [18]. The frequency of CD8+ tumor-infiltrating lymphocytes in the intratumor and margin area was positively correlated with overall survival (OS) and disease-free survival (DFS) in two HCC cohorts (a combined total of 449), and a larger proportion of CD8+ tumor-infiltrating lymphocytes was associated with a lower recurrence rate[19]. As a result of their inflammatory condition, increased densities of CD8+T lymphocytes that infiltrate the liver in HCC patients contribute to tumor recurrence and carcinogenesis[20]. High CD3+ and CD8+ T cell densities were associated with minimal relapse and extended relapse-free survival in both the tumor center and margin[21]. In HCC patients, increased FoxP3(+) regulatory T cells encouraged a gradual decline in CD4+ cytotoxic T cells, which contributed to poorer survival and high recurrence rates[22]. A high Foxp3/CD8 ratio indicated a higher Edmondson-Steiner nuclear grade, relapse, and shorter OS and DFS, along with worse differentiation[23]. In HCC patients who received LT but not Foxp3+ T-lymphocytes, a correlation between CD4/CD8 ratio and tumor recurrence was established[24]. After surgical excision, high DC infiltration in HCC nodules can be used as a predictor of the recurrence and metastasis of the disease[25]. The response to sorafenib improved relapse-free survival, and OS in patients was significantly influenced by the increased density of natural killer (NK) cells[26].

In HCC patients after surgery, higher interleukin (IL-11) levels enhanced tumor expansion, and in genetic mouse model, suppression of IL-11-STAT3 signaling greatly reduced cell proliferation and post-surgical recurrences of HCC tumors[27]. Local recurrence is caused by the invasion of local tumor blood flow and peritumoral diffusion, whereas systemic dissemination is caused by the "rehoming" of circulating tumor cells that have spread from the initial nodules[28]. HCC recurrence can occur as a result of tumor cells that are circulating or at rest, evading the host's immune responses. The total somatic mutations and copy number depletion of WNK2 (WNK lysine deficient protein kinase 2) were associated with low levels of WNK2 protein expression, premature tumor relapse, and poor cumulative survival in patients with HCC following curative excision, indicating a tumor-suppressor role of WNK2 [29]. WNK2 inactivation results in the recruitment of tumor-associated macrophages, ERK1/2 signaling activation, tumor growth, and metastasis.

Following therapy, HCC shows pathological modifications; therapy induced pathological variation, particularly sarcomatous transformation, results in random and frequent recurrences after RFA[30]. It is generally accepted that recurrent HCC following curative therapy was caused by both initial incomplete treatment as well as current technological and biomarker limitations that make it difficult to detect preexisting microscopic tumors[31]. Occasionally, local therapies like TACE result in the direct diffusion of tumor cells from the RFA needle, which eventually causes a relapse of HCC[32]. However, multicentric origin HCC developed from *de novo* carcinogenic effect following curative excision, and the latter has a better OS than the former[33], consistent with the results of Kuo *et al*[34]. The incidence of intrahepatic metastasis and multicentric recurrent HCC was 59.4% and 27.5%, respectively, which were accompanied by loss of heterozygosity (63.8%) and microsatellite instability (30.0%) between primary and recurrent tumors[34]. Concerning previously unidentified circulating tumor cells or preexisting metastasis caused by the current technology that contribute to extrahepatic relapse, metastatic tumor lesions in the graft are originally formed from circulating cells or extrahepatic locales, providing a greater potential for biological advancement[35].

ADJUVANT ANTIVIRAL TREATMENT

Adjuvant antiviral therapy has been shown to decrease multicentric HCC recurrence, which in turn reduces post-treatment recurrence[33]. However, the ideal time for starting therapy with direct-acting antivirals (DAAs) for hepatitis C virus (HCV)-related HCC patients following surgical resection, and the impact of DAA on HCC recurrence remain unclear. Low risk of HCC recurrence after DAA treatment was suggested in some studies, while others have reported contrasting outcomes. Furthermore, there is conflicting evidence concerning HCV-related HCC recurrence in previously cured patients following virus elimination with DAAs. With a 5.7-mo follow-up in 20 DAA-treated HCV patients, a high rate of early HCV-related HCC recurrence was observed[36]. Even though DAA treatment was not associated with HCC or early HCC recurrence, a higher proportion of DAA-treated patients accepted potential curative therapy for recurrent HCV-related HCC compared to untreated patients (32.0% *vs* 24.6%) and developed a non-significant complete or partial response (45.3% *vs* 41.0%)[37]. A systematic review has highlighted an association of HCC recurrence with the status of previous HCC recurrences and the shorter interval between HCV-related HCC complete response and initiation of DAA treatment, and similar recurrences in patients treated with DAAs, those treated with interferon, or untreated patients [38]. HCV-related HCC patients, who had a shorter interval between HCC treatment and DAA therapy (less than 4 mo), appeared to be at greater risk, with a relapse rate of 41.2%[39]. DAA treatment following curative HCC therapy was not associated with early or advanced cancer recurrence[40]. DAA treatment is not associated with a high risk of recurrence in LT patients with HCV and HCC who achieved an original complete response to local-regional therapy, but rather involves a low risk of waitlist dropout due to cancer aggression or death[41]. In three separate prospective cohorts, no increased risk of HCC recurrence following DAA therapy was found, particularly in patients who received curative treatment, such as LT[42].

Even though the impact of DAAs on HCV-related HCC recurrence remains debatable, the results of anti-hepatitis B virus (HBV) treatment following HCC therapy showed that NAs might potentially inhibit HCC recurrence after curative hepatectomy in patients with HBV-related HCC[43]. Managing viral conditions and reactivation of viral replication plays a major role in suppressing HCC recurrence, maintaining liver function, and improving survival for HBV-related HCC post-therapy[44]. After curative therapy, NAs significantly improved recurrence-free survival and OS in HBV-related HCC patients, and entecavir was on par with other NAs, including lamivudine and adefovir, in this regard [45]. Another study discovered that after curative therapy, antiviral therapy with NA could increase survival and reduce early recurrence in patients with HBV-related HCC[46]. NA with or without anti-HBs immunoglobulins was significantly effective in inhibiting post-LT HBV recurrence[47]. In a limited sample cohort, NA did not lower the short-term recurrence rate but increased the elimination of postoperative serum HBV and remnant liver volume, which resulted in significantly improved tolerance to follow-up treatment for HCC recurrence[48]. In a large cohort of 4569 patients with HBV-related HCC who underwent curative resection, the anti-HBV therapy cohort had a significantly lower 6-year HCC recurrence rate than the control cohort [anti-HBV therapy, 45.6%; 95% confidence interval (CI): 36.5%-54.6% *vs* control, 54.6%; 95%CI: 52.5%-56.6%][49]. According to a previous study, recipients who accepted LT by removing HBV-infected initial liver at undetected serum HBV DNA levels continue to have an elevated risk for posttransplant recurrent HBV due to the absence of any particular treatment [50]. In comparison to lamivudine for HCC after curative therapy, entecavir is associated with a four-fold higher one-year OS rate and lower HCC recurrence, suggesting that entecavir may be more suitable for HBV-related HCC patients[51].

REPEAT RESECTION

Only a small proportion of patients with recurrent HCC are candidates for repeat hepatectomy due to recurrent multifocal tumors and compromised liver function[52]. Twenty-two patients with recurrent HCC following LT (2 intrahepatic HCC patients and 20 extrahepatic HCC patients) received complete hepatectomy and had a longer median survival of 35 mo than unresected patients with a median survival of 15 mo[53], suggesting a less aggressive tumor biology. According to a retrospective cohort study, 15 patients with HCC recurrence who underwent LT had a better 5-year OS rate and 5-year DFS rate than the patients with RFA treatment (35% *vs* 28%, and 16% *vs* 0%, respectively)[54]. A recent study reported that repeat laparoscopic liver resection (LR) for recurrent HCC is both feasible and suitable with promising short-term results[55]. Laparoscopic repeat LR was associated with shorter hospitalization and prolonged operation time compared to open repeat LR for recurrent HCC but they had similar perioperative results for primary HCC except for a longer operation time[56]. Patients who underwent wedge resection during laparoscopic repeat LR showed a significantly lower postoperative complication rate than open repeat LR (7.2% *vs* 21.8%)[57]. Even though patients with open LR have a higher morbidity rate than those who underwent LR for primary HCC, there are no striking differences in the clinical characteristics of repeat laparoscopic LR based on prior resection method (open or laparoscopic) or tumor location (segments 7 and 8 or other)[55].

A meta-analysis of 767 patients, 334 of who had repeat laparoscopic hepatectomy and 433 of whom had repeat open hepatectomy, discovered that repeat laparoscopic hepatectomy resulted in less intraoperative blood loss, fewer major complications, shortened hospitalization, and a higher rate of R0 resection[58]. The repeat-surgery group had better liver function, long recurrence-free survival (16.5 mo *vs* 11.4 mo), and better 5-year survival after recurrence (repeat surgery group *vs* non-surgery group: overall, 53.0% *vs* 25.7%; intrahepatic recurrence, 73.8% *vs* 37.2%; extrahepatic recurrence, 30.0% *vs* 0%; intrahepatic and extrahepatic recurrence, 34.1% *vs* 10.6%) compared to the non-surgery group[59] for recurrent HCC. Patients with recurrences within 6 mo of resection had poor survival outcomes than those who experienced recurrences later, and patients with intrahepatic-only recurrences had a better prognosis than those with either extrahepatic-only or intra and extrahepatic recurrences[60]. Additionally, repeated resection of recurrences with a remediable objective produced better outcomes than other therapy options[60]. After 18 mo of initial hepatectomy, repeat hepatectomy may be suggested as a treatment for recurrent HCC. When compared to patients with intrahepatic metastasis, repeat hepatectomy improves survival rates in HCC patients with multicentric occurrence[61]. Although RFA is associated with lower grade 3 morbidity and shorter hospital stay, repeated hepatic resection resulted in a longer median recurrence-free survival *vs* RFA (23.6 mo *vs* 15.2 mo) in patients with recurrent HCC[62]. Resection can be advised as a treatment option for patients with extrahepatic recurrent HCC in conjunction with local treatment for intrahepatic recurrent HCC due to the superior outcomes[63]. At the third (71.3% *vs* 65.7%), fifth (59.9% *vs* 45.4%), and tenth (35.4% *vs* 32.2%) year follow-up, repeat hepatectomy improved long-term OS more than RFA and showed a late survival advantage for patients with recurrent HCC despite a higher morbidity rate[64].

LT

According to reports, the results of salvage LT (SLT) for recurrent HCC following hepatectomy are comparable to the outcomes of initial transplantation, even when examined on an intention-to-treat basis[65]. LT seems to be the most effective treatment for HCC patients to remove both tumors and underlying liver diseases, but the scarcity of organ donors available globally and stringent criteria for patients who are not eligible for transplantation are the major challenges. However, recurrent HCC patients following LT have a poorer prognosis, with a median OS of 10-13 mo as opposed to 2-3 years for patients who had hepatectomy[66-68]. In 2000, Majno *et al*[69] made the first suggestion for SLT, which was used in patients with recurrent HCC or liver dysfunction following primary hepatectomy as initial treatment. Fortunately, liver transplants were an option for 80% of patients with recurrent HCC following curative hepatectomy[70]. A case of salvage living donor LT in a patient with tumor recurrence following surgical resection of combined HCC and cholangiocarcinoma has multiple tumor recurrences after 21 mo due to the more aggressive tumor biology of this type of cancer[71]. The patients receiving SLT therapy demonstrated better DFS than those receiving re-resection or RFA, which is a beneficial strategy for intrahepatic recurrent HCC, particularly for patients with multicentric occurrence that is related to better long-term outcomes than the intrahepatic metastasis pattern[72].

SLT (n = 16) revealed poorer short-term perioperative results than repeat LR (n = 16), with a higher incidence of morbidity (57.8% *vs* 5.4%), reoperations (39.1% *vs* 0%), renal dysfunction (30.1% *vs* 3%), bleeding (19.8% *vs* 2.2%), prolonged intensive care unit stay (4 d *vs* 0 d), and hospitalization (19.8 d *vs* 7.1 d) but significantly decreased recurrence (15.4% *vs* 70.3%) and 5-year cumulative incidence of recurrences (19.4% *vs* 68.4%) to improve long-term survival outcomes for recurrent HCC[73]. SLT was found in a meta-analysis to have higher blood loss, longer hospital stays and surgeries, increased DFS, and elevated risk of postoperative morbidity than repeat LR, while there was no clear difference in

postoperative mortality or OS[74] for recurrent HCC. In terms of disease-specific and recurrence-free survival of patients with intrahepatic HCC recurrence, SLT with transplantable patients is superior to repeat resection, even in patients with Child-Pugh class A liver cirrhosis[75]. Only 56% of cases can be cured using the SLT strategy. A successful SLT strategy is predicted by higher end-stage liver disease scores at the start of the strategy and the absence of pre-resection TACE[76]. Even though SLT is associated with a higher rate of surgical complications, SLT for recurrent HCC following primary hepatic resection is still an efficient and safe treatment that increases survival and reduces tumor recurrence compared to patients with HCC exceeding the Milan criteria who accepted primary orthotopic LT[77]. After hepatectomy, HCC patients with larger tumor sizes were more likely to experience relapse, even with SLT. As a result, LT should be recommended as soon as possible, ideally within a year, for patients with recurrent HCC after LR, followed by meeting the requirements for transplantation[78]. For patients with recurrent HCC after hepatectomy, SLT has a poorer OS and RFS, as well as a higher risk of recurrence and death compared to primary LT, particularly for those who meet the Milan criteria[79]. Another study discovered no difference between patients receiving primary LT and SLT for HCC recurrence following primary treatment with LR or RFA in terms of the 5-year risk of recurrence and 5-year actuarial survival[80]. SLT for relapsed HCC patients after initial LR followed by SLT showed overall and recurrence-free survival rates on par with primary LT. Despite this, there are higher rates of Child-Pugh class A, more than three transplant treatments, and reoperation for postsurgical bleeding[81]. Patient background possibly has various effects on therapy, as Hong Kong patients with recurrent HCC following LR who received SLT, but not Roman patients, showed an increased recurrence rate[82].

RFA

Clinical therapy for HCC frequently involves ablation. Following ablation, the tumor experiences residual and local recurrence due to asymmetrical heat diffusion and heat absorption *via* circulating blood or air around the tumor[83]. For HCC patients who experience recurrence but cannot undergo a suitable operation, ablation is used as a safe and efficient therapy[84]. With ablation alone, the 5-year recurrence rate of HCC patients was 70%[85]. Although a small set of 11 patients with relapsing HCC following LT embraced microwave ablation without serious side effects, this safe technique still needs to be validated in larger studies or compared with other treatment options[86]. RFA and repeat resection are better choices for late-relapsing HCC patients post-curative hepatectomy who meet the Milan criteria[87]. Although the 1-, 3-, and 5-year OS (90.7%, 69.04%, and 55.6% *vs* 87.7%, 62.9%, and 38.1%, respectively) and progression-free survival (PFS) (56.5%, 27.9%, and 14.6% *vs* 50.2%, 21.9%, and 19.2%, respectively) were comparable between the RFA and repeat resection groups for locally recurrent HCC following primary resection, the former was superior to the latter in term of complications and hospitalization[88]. In a different study, repeat resection was found to increase survival for recurrent HCC, particularly for patients who had relapsed within two years and whose primary tumor burden exceeded the Milan criteria[89]. Primary HCC (94.8%, 75.7%, 61.6%, and 47.3%, respectively) and recurrent HCC (91.9%, 71.2%, 58.7%, and 45.2%, respectively) did not differ in the 1-, 3-, 5-, or 10-year OS rate[90]. RFA offers comparable long-term survival whether treatment is for the first-time or recurrent HCC that is 5 cm or less. Although LR with long-term survival results is superior to RFA for recurrent HCC patients, RFA is a good alternative to LR in patients with small-sized recurrence or patients with a limited number of recurrent nodules, even though LR has better long-term survival outcomes for patients with recurrent HCC[91]. Multiprobe stereotactic RFA as first-line therapy for recurrent HCC following LR has such low morbidity that the OS and DFS rates at 1, 3, and 5 years were 94.0%, 70.2%, and 53.3%, and 52.6%, 19.7%, and 15.8%, respectively[92]. RFA is beneficial and effective for intrahepatic recurrent HCC with 1-, 3-, and 5-year OS rates of 68.5%, 40.3%, and 40.3%, respectively, particularly for recurrent HCC following LT in the absence of finite extrahepatic metastases[93]. Due to its advantages of being less invasive, extreme selectivity, and reproducibility, RFA is suggested as a better therapy for intrahepatic HCC recurrence given that it is associated with a lower recurrence-free survival than LT[94].

In patients with recurrent HCC (tumor size < 3 cm, tumor number ≤ 2), a phase III non-inferiority trial found that the 2-, 3-, and 4-year local PFS of proton beam radiotherapy was comparable to that for RFA. However, the most common adverse outcomes were radiation pneumonitis (32.5%) and decreased leukocyte counts (23.8%) for proton beam radiotherapy, and increased alanine aminotransferase levels (96.4%) and abdominal pain (30.4%) for RFA[95], which suggested that proton beam radiotherapy was tolerable and safe with long PFS values comparable to those of RFA.

TACE

TACE is generally considered a standard therapeutic method for patients with unresectable HCC[11]. The most widely used treatment for postoperative recurrence is TACE, especially when there is a large mass or multifocal relapsed HCC[96]. The outcomes of TACE in the neoadjuvant setting are debatable.

OS showed no difference between 71 patients treated with TACE before surgery and 21 patients who underwent surgery without TACE[97]. In a retrospective study, 1457 patients were evaluated, of whom 120 were treated with preoperative TACE, and it was found that 5-year DFS was improved in patients treated with TACE[98]. Patients with primary HCC who undergo embolization have a strikingly higher chance of survival than those with recurrent HCC. A study revealed that primary HCC patients who received TACE had a median survival of 30 mo and a 29% 3-year survival rate[99]. The results of treating patients with recurrent HCC, however, showed a low median survival time of 19 mo and an 11% survival rate. Patients with primary HCC and microvascular invasion (MVI) experience recurrence after resection, and TACE treatment is more effective than resection and RFA for recurrent HCC[100]. There was no significant difference in prognostic factors or OS between the initial and recurrent TACE groups[101]. TACE was administered to 28 patients with recurrent HCC following LT; 19 of these patients (67.9%) experienced tumor-shrinking by over 25%. However, the 1-, 3-, and 5-year survival rates were lower (47.9%, 6.0%, and 0%, respectively) due to extrahepatic metastases or intrahepatic recurrences[102]. According to a different study, patients who underwent chemoembolization without experiencing any serious side effects had a significantly longer OS time following the diagnosis of HCC recurrence post-LT than those who did not receive the treatment[103]. The 1-, 3-, and 5-year OS rates did not significantly differ between the repeat resection or RFA and the TACE groups, suggesting that TACE likely was as effective as repeat resection or RFA for preventing early intrahepatic relapse following curative resection of HCC[87]. Although there is no obvious difference between RFA and TACE treatment for isolated intrahepatic recurrent HCC following LT in terms of 2-year DFS rate (20% *vs* 14%) and 4-year OS rate (33% *vs* 25%), TACE treatment seems to be more beneficial in isolated intrahepatic recurrent HCC patients following LT when RFA therapy is not suitable[104]. In contrast to TACE-alone treatment for intrahepatic recurrent HCC after hepatectomy, apatinib, a vascular endothelial growth factor receptor 2 inhibitor, in conjunction with TACE significantly improved the median PFS, short-term objective responses, and disease control rate, and had a tendency of increasing the 1- and 2-year OS rates[105]. The patients who received TACE-RFA for recurrent HCC that was less than 5 cm following LT had a higher DFS than those who received TACE alone[106]. After a follow-up of 24 mo, the median OS for patients with the first recurrence of HCC treated with multimodality therapy was 40 mo (range 8-85 mo), far exceeding that of patients with LR/ablation (27 mo, range 4-75 mo), TACE/XRT (13 mo, range 4-68 mo), and systemic treatments (26 mo, range 3-59 mo)[9].

SORAFENIB

Sorafenib, a multitarget tyrosine kinase inhibitor (TKI) and the first approved drug for HCC patients, is most frequently used as an adjuvant therapy in resected HCC patients[107] and as a frontline systemic treatment in patients with HCC recurrence after LT. However, the current data are mainly based on observational research due to the exclusion of Randomized Protocol studies and Asia-Pacific trials of sorafenib from the registered studies for HCC[107,108]. Sorafenib has a few drawbacks, including poor oral bioavailability and drug toxicities, and its OS is only marginally improved by 2.8 mo[107,109]. The impacts of sorafenib in patients with recurrent HCC who underwent an incurable liver transplant have been estimated in several retrospective studies. Based on a retrospective cohort study of 50 patients with recurrent HCC following liver transplants who initially accepted sorafenib, an objective response rate of 16% and stable disease in 50% of this population were observed, and the median OS was 18 mo[110]. Patients with HCC recurrence following LT treated with sorafenib had a better median survival of 42 mo compared to 16.2 mo for patients not receiving sorafenib, supporting the notion that sorafenib increases survival[111].

According to this study, patients with relapsed HCC have a better chance of longer OS and a better prognosis by receiving the sorafenib treatment. For patients with recurrent HCC, sorafenib-lenvatinib continuous treatment and radical resection together with nonoperative therapy were both independent favorable factors for post-recurrence survival[112]. According to Lee *et al*[113], sorafenib for recurrent HCC is associated with a better prognosis because it involves smaller intrahepatic HCC combined with favorable liver function in LT recipients, which may explain why the median OS (16.8 mo *vs* 7.1 mo) and time to development were higher in 42 HCC patients in the LT group than in 790 non-LT patients. Sequential sorafenib treatments are similarly common in recurrent HCC patients following LT. These treatments improve OS compared to non-LT treatments and do not suppress systemic treatments with concurrent antirejection strategy[35]. Treatment with sorafenib and TACE was associated with a higher 5-year OS and PFS compared to those treated with TACE alone in patients with recurrent intermediate-stage HCC and lesions positive for MVI, but patients with MVI-negative lesions did not show a survival benefit from combined therapy[114]. Treatment with sorafenib plus TACE improves hepatic reserve, leads to a better OS, and results in longer intervals between TACE rounds in TACE-refractory patients with recurrent advanced HCC than repeated TACE treatments[115]. The RFA plus sorafenib treatment resulted in a significantly improved OS than RFA alone (1-, 3-, and 5-year OS rates of RFA-sorafenib *vs* RFA: 97.7%, 83.7%, and 54.7% *vs* 93.1%, 61.3%, and 30.9%, respectively), suggesting that adjuvant sorafenib combined with RFA was superior to RFA alone in improving survival results in patients with

recurrent HCC who meet the Milan criteria after initial LT[116]. Prussian blue (PB) nanomaterial is safe and has multiple roles as an antidote to thallium poisoning[83]. With minimal injury to surrounding healthy tissues, photothermal therapy is a highly effective and noninvasive therapeutic option[117]. By using human and mouse HCC cell lines, Zhou *et al*[118] developed HCC-targeted SP94 peptide and cyanine (Cy) 5.5-conjugated PB nanoparticles loaded with sorafenib for HCC-targeted multimodality imaging and combined photothermal therapy/sorafenib treatment. These nanoparticles accumulated in HCC tumor sites and then controlled the release of sorafenib to eradicate the tumor without any local recurrence and with a minimal amount of toxic side effects.

OTHER TKIS

The United States and Europe approved lenvatinib in the first line, cabozantinib, and ramucirumab in the second line as a potential systemic therapeutic approach for liver transplant recipients with relapsed HCC. A retrospective multicenter study discovered that regorafenib, a multitarget TKI, was safe and effective for patients with recurrent HCC following LT who were tolerable to sorafenib, with a median OS of 12.9 mo[119]. Lenvatinib, as a TKI, has been used as an optional frontline treatment strategy. Patients with recurrent HCC treated with lenvatinib who are tolerable to sorafenib have a longer median OS (19.5 mo), far exceeding those who are receiving intermittent sorafenib or regorafenib following sorafenib failure (12 mo)[112]. Cabozantinib, a TKI of vascular endothelial growth factor receptor 2 (VEGFR2), is used as an effective and safe monotherapy to proceed with third-line systemic therapies in advanced HCC[120]. Patients with recurrent HCC who received lenvatinib treatment had decreased expression of programmed death ligand 1 (PD-L1) and Treg infiltration in the tumor compared to the matched primary tumor, suggesting that lenvatinib targets fibroblast growth factor receptor 4 to increase the antitumor immune response of anti-programmed cell death-1 (PD-1) treatment, which is accompanied by decreased expression of tumor PD-L1 and Treg infiltration[121]. As a multi-kinase inhibitor, cabozantinib is expected to be an effective treatment for advanced HCC patients with sorafenib tolerance[122]. A case study identified a patient with recurrent HCC who had more than 10 years of survival after receiving an intensive multimodal therapeutic strategy that included surgery, RFA, and systemic therapy with cabozantinib as the second-line therapy in living-donor LT[123]. In patients with HCC recurrence following LT with sorafenib tolerance, regorafenib treatment resulted in a longer median OS (28.8 mo) than best supportive care (15.3 mo). This makes regorafenib a safe and effective second-line treatment option[124].

IMMUNE CHECKPOINT INHIBITORS

Although the importance of immune evasion in the progression of HCC recurrence was widely acknowledged, the lack of effective medications to reverse cancer-related immune suppression remained an untreatable condition until recently. Programmed cell death receptors on T cells and their ligands PDL-1 and PDL-2 on tumor cells are the targets of immune checkpoint inhibitors (ICPIs). Only 15–20% of patients benefit from anti-PD-L1 monoclonal antibodies (mAbs), which block interactions with PD-1 and PD-L1 and restore the roles of T cells in the tumor microenvironment[125,126]. Stimulation-induced immune surveillance has notable antitumoral outcomes in advanced and recurrent HCC, with significant response rates and even complete responses. Despite their promising prospects, ICPIs must be used with caution in transplant patients due to the complexity of HCC. In particular, HCC patients with multifocal tumors, higher AFP levels, larger tumor volume, and poorer differentiation presented a high risk of post-LT relapse when given neoadjuvant ICPIs[127]. The perioperative nivolumab *vs* ipilimumab/nivolumab combination had fine effects, according to a phase II study, with a 29% complete response rate[128]. The immune checkpoint blockade remedy resulted in only 16%-20% response rates among patients with advanced HCC[129]. Combination therapy with anti-PD-1 plus RFA for recurrent HCC achieved a superior recurrence-free survival compared to RFA monotherapy[130]. By combining anti-PD-L1 mAb with SP94-PB-sorafenib-Cy5.5 nanoparticles plus near-infrared therapy, Zhou *et al*[118] also observed the production of extraordinary results, such as suppression of distant metastases and obstruction of cancer relapse. Note that, different from primary HCC, the therapeutic strategy for recurrent HCC following LT has to be discrete due to the higher risk of allograft rejection or graft loss[131,132]. For early HCC recurrence after radical resection, TKIs combined with PD-1 therapy demonstrated a better survival benefit than TKIs alone[133]. In a patient with recurrent, refractory, metastatic HCC following LT, PD-1 inhibitor eliminated lung metastases and resulted in a partial radiological response of metastatic retroperitoneal lymph nodes after 13 cycles[134].

HBV-SPECIFIC T-CELL IMMUNOTHERAPY

Chimeric or classical T-cell receptors (TCRs)-redirected T cells target HBV antigens/epitopes expressed on HBV-infected hepatocytes or in HCC cells as an immunotherapeutic approach. According to a case study, the HBV antigen was expressed in the metastases of a patient with HBV-related HCC after LT [135]. To treat extrahepatic metastases of chemotherapy resistance, HCC autologous T cells were genetically redirected to express an HBsAg-specific T cell receptor. This resulted in decreased HBsAg levels without worsening liver inflammation or other toxicity[135]. In two patients with metastatic recurrence of HBV-related HCC after LT, immunotherapy of HBV-specific TCRs was safe and did not cause any damage to liver function over a year[136]. Notably, a patient appeared to have a reduced volume in 5 of 6 pulmonary metastases during the first year of T-cell management[136]. HBV-specific TCR T-cells transiently escape the immunosuppressive effects of tacrolimus and mycophenolate mofetil owing to the activation of CD39+ Ki67+ peripheral blood mononuclear cells, which are positively correlated to clinical outcomes in patients with HBV-related HCC relapses following LT[137].

OTHER IMMUNOTHERAPIES

Cytokine-induced killing (CIK) cell-based immunotherapy has gained popularity as a promising new adjuvant therapy approach. CIK cells are a mixture of T lymphocytes, which are *ex vivo* amplified with cytokines and comprised of CD3+/CD56+ and CD3+/CD56- T cells, as well as CD3-/CD56+ NK cells, which have potent antitumor activity with the combined ability of both T cells and NK cells and minimal cytotoxicity to normal cells, but tremendous specificity to cancer cells[138]. Multiple clinical trials revealed that CIK cell-based immunotherapy increased RFS in HCC patients who underwent surgical resection[139,140]. The production of an individual autologous CIK cell-based immunotherapeutic agent involves activating peripheral blood mononuclear cells from the relevant patients with IL-2 and anti-CD3 antibodies[141]. According to research by Lee *et al*[141], the average RFS for HCC patients who accepted the CIK cell-based agent after curative therapy was 44.0 mo, as opposed to 30.0 mo for those who did not receive adjuvant immunotherapy. The results of a meta-analysis reported that the results of DC-based immunotherapy increased antitumor immunity, enhanced survival rate, and improved survival times in HCC patients[142]. Another meta-analysis listed 22 distinct studies with 3756 HCC patients that received DC-based vaccine and/or CIK-based adoptive therapy after receiving different HCC interventional therapies. These studies showed a prolonged OS (6 mo, 1, 3, and 5 years) and reduced mortality and recurrence at 1, 2, and 3 years but not 5 years[143]. For HCC patients, a personalized neoantigen vaccine served as a safe, practical, and effective anti-recurrence treatment [144]. After a radical operation on seven postoperative HCC patients who had received all of the planned neoantigen vaccinations, five of them showed neoantigen-activated cell responses and longer RFS than the other five patients, who had only received primary vaccination and had propensity scores that matched with those of control patients[144]. After curative resection or RFA in the first stage, the personalized neoantigen-loaded DC vaccine and neoantigen-activated T-cell therapy were successfully used on ten patients with HCC without unexpected delay or grade 3 therapy-related side effects[145]. New circulating multiclonal neoantigen-specific T-cell responses, activated neoantigen-specific immunity, an upregulated immune stimulatory signature, increased immune-cell infiltration, and elevated T-cell inflammatory gene expression, were produced in 70% of patients who had improved DFS compared to non-responders, and 71.4% of patients were without relapse for 2 years after curative treatment. Neoantigen depletion (immunoediting) also increased in recurrent tumors compared to primary tumors, suggesting that immune evasion developed as a result of immunological therapy[145].

CONCLUSION

With its unique characteristics, recurrent HCC is still a difficult disease to treat. Every stage of the disease calls for a multidisciplinary approach, which is still predominantly evolving. LT and hepatectomy remain successful therapeutic strategies for patients with recurrent HCC. Additionally, neoadjuvant and/or adjuvant therapy techniques may improve the long-term prognosis and increase the chance of cure in refractory patients with recurrent HCC. Relying on the tumor biology and possible hepatic reserve, multimodality therapy should be used in patients with recurrent HCC. By simultaneously optimizing oncologic outcomes and minimal side effects, this therapy helps these patients have better OS and tolerability.

FOOTNOTES

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