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Recent advances in recurrent hepatocellular carcinoma therapy

Hepatocellular carcinoma therapy

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 hepatocellular carcinoma 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 recurrent HCC. For individuals with recurring HCC after curative treatment, no approved therapeutic regimen was used. 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 direct the clinical treatment. The data supporting several neoadjuvant and adjuvant therapies for patients with recurring HCC are outlined in this review. We also discussed the potential for future clinical and translational investigations.

Key Words: Recurrent hepatocellular carcinoma; Liver transplantation; Therapy; Immunotherapy

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Core Tip: Hepatocellular carcinoma (HCC) is the most prevalent form of primary liver cancer 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 direct 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.

INTRODUCTION

With an expected 906,000 new cases and over 800,000 fatalities, primary liver cancer is ranked as the sixth most commonly diagnosed disease and the third most prevalent cause of cancer-related deaths worldwide in 2020 [1]. HCC accounts for 75%-85% of instances 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 the early stage HCC with the intention of curing 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 edge) but is also frequently affiliated 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 poor 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 match 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 four weeks of each other were considered multimodal therapy [9]. Preclinical findings and the predictive mechanism suggest that neoadjuvant and adjuvant dosages should be used in combination instead of using neoadjuvant or adjuvant immunotherapy 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 (TARE), radiofrequency ablation (RFA), LT, tyrosine kinase inhibitors, and immunotherapy. Here, we will discuss the current state of knowledge and recent advances in the therapy of recurrent HCC in this narrative review.

Mechanism 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 interacted spatiotemporally in complex tumor ecosystems [13]. Recent research has found similarities between the genetic variants of primary and early-recurrence 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, higher dendritic cells (DCs), and

CD8+T cells compared to initial HCC, which were associated to 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 the primary HCC, CD8+ T cells in relapsed HCC displayed higher CD161 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. The regulatory T cell (Treg) 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 the rat transplantation model [17].

According to a meta-analysis, HCC patients with high forkhead box protein P3 (Foxp3) + T cells infiltration had worse 1, 3, and 5-year survival rates and had a greater rate of recurrence than patients with low Foxp3+ T cells 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 anticipated minimal relapse, and extended relapse-free survival in both the 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, shorter OS, and DFS, along with worse differentiation [23]. In HCC patients who received LT but not Foxp3+ T-lymphocytes, the 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 cells [26].

In the HCC patients after surgery, higher interleukin (IL-11) levels enhanced tumor expansion, and in the genetic mice 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 manifests a pathological modification; therapy emerges as pathological variation, particularly sarcomatous transformation, which 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 Li *et al* [34]. The incidence of intrahepatic metastasis and multicentric recurrent HCC were 59.4% and 27.5%, respectively, which were accompanied by loss of heterozygosity and microsatellite instability of 63.8% and 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 HCV-related HCC patients following surgical resection, and the impact of DAA on HCC recurrence remain unclear. A low risk of HCC recurrence after DAA 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 by DAAs. With a 5.7-month follow-up in 20 DAA-treated HCV patients, a high rate of early HCV-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-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-HCC complete response and initiation of DAA, and similar recurrences in patients treated with DAA, interferon, or untreated patients [38]. HCV-HCC patients, who had a shorter interval between HCC treatment and DAA therapy (less than 4 mo), appeared to be at greater risk, by 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 accepted an original complete response to local-regional therapy, but rather involves a low risk of waitlist dropout due to cancer aggression or death [41]. Three separate prospective cohorts did not find any increased risk of HCC recurrence following DAA therapy, particularly in patients who received curative treatment, such as liver transplantation [42].

Even though the impact of DAA on HCV-related HCC recurrence remains debatable, the results of anti-HBV treatment following HCC therapy showed that NAs might potentially inhibit HCC recurrence after curative hepatectomy in patients with HBV-related HCC [43]. Administering viral conditions and reactivation of viral replication play a major role in suppressing HCC recurrence, maintaining the liver function, and improving survival for HBV-related HCC post-therapy [44]. After curative therapy, NA significantly improved recurrence-free survival and OS in HBV-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 immune globulins was significantly effective at inhibiting 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 remanent liver volume, which resulted in significantly improved tolerance to follow-up treatment for HCC recurrence [48]. A large cohort of 4,569 patients with HBV-related HCC disease who underwent curative resection revealed that the anti-HBV therapy cohort had a significantly lower 6-year HCC recurrence rate than the Control cohort (anti-HBV therapy, 45.6%; 95%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 DAN 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 has a four-fold higher one-year OS rate and lower HCC recurrence, suggesting that entecavir may be more suitable for HBV-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 patients and 20 extrahepatic patients) received complete hepatectomy and had a longer median

survival of 35 mo than nonresected 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 5-year overall survival rates and better 5-year disease-free survival 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 is associated with shorter hospitalization and prolonged operation time compared to open repeat LR for recurrent HCC but had similar perioperative results for primary HCC except for a longer operation time [56]. Patients who underwent wedge resection during laparoscopic repeat LR showed significantly lower postoperative complication rates 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 a better liver function, long recurrence-free survival (16.5 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 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 with intrahepatic-only recurrences had a better prognosis than those with either extrahepatic-only or with intra and extrahepatic recurrences [60]. Additionally, repeated resection of recurrences with a remediable objective produced better outcomes than other therapy opinions [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 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].

Liver Transplantation

According to reports, the results of salvage liver transplantation 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* made the first suggestion for salvage liver transplantation (SLT), which was used in patients with recurrent HCC or liver dysfunction following primary hepatectomy as initial treatment [69]. Fortunately, liver transplants were an option for 80% of patients with recurrent HCC following curative hepatectomy [70]. A case of salvage living donor liver transplantation in a patient with tumor recurrence following surgical resection of combined hepatocellular carcinoma- and cholangiocarcinoma has multiple tumor recurrences after 21 mo due to 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 who 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 higher 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 vs. 0 days), and hospitalization (19.8 vs. 7.1 days) but significantly decreased recurrence (15.4% vs. 70.3%) and a 5-year cumulative incidence of recurrences (19.4% vs. 68.4%) to improve long-term survival outcomes for recurrent HCC [73]. Salvage liver transplantation was found in a meta-analysis to have higher blood loss, longer hospital stays and surgeries, increased disease-free survival, and elevated risk of postoperative morbidity than repeat LR, while there was no clear difference in postoperative mortality and OS [74] for recurrent HCC. In terms of disease-specific and recurrence-free survival of 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 higher 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 that exceeds Milan criteria 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]. Patients with recurrent HCC after hepatectomy acknowledged that SLT has 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 the 5-year actuarial survival [80]. Salvage LT 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 child-Pugh class A, more than three transplant treatments, and reoperation rates for postsurgical bleeding [81]. Patient background possibly has various effects on therapy, as Hong Kong patients with recurrent HCC following LR and who received SLT showed an increased recurrence rate but not Roman patients [82].

Radiofrequency ablation

Clinical therapy for HCC and frequently involves ablation. Following ablation, the tumor experience 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 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 first, third, and fifth-year OS (90.7%, 69.04%, 55.6% vs. 87.7%, 62.9%, 38.1%) and progression-free survival (PFS) (56.5%, 27.9%, 14.6% vs. 50.2%, 21.9%, 19.2%) were comparable between the RFA and repeat resection groups for locally recurrent HCC following primary resection, the former is 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]. The 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 one, three, five, and ten year OS rates [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 of recurrent HCC following LR has such low morbidity that the OS and DFS rates at one, three, and five years were 94.0%, 70.2%, 53.3%, and 52.6%, 19.7% and 15.8%, respectively [92]. RFA is beneficial and effective for intrahepatic recurrent HCC with 68.5%, 40.3%, and 40.3% at the one, three, and five-year OS rates, 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 lower recurrence-free survival than LT [94].

In patients with recurrent HCC (size <3 cm, number ≤2), a phase III non-inferiority trial found that proton beam radiotherapy at 2, 3, and 4-year local PFS was comparable to those 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.

Transarterial chemoembolization

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. Overall survival 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 disease-free survival 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 experience recurrence after resection, and TACE treatment is more effective than resection and RFA for recurrent HCC [100]. There were no significant differences in Prognostic factors and overall survival 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 one, three, and five-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 overall survival time following the diagnosis of HCC recurrence pos-LT than those who did not receive the treatment [103]. The one, three, and five-year OS rates did not significantly differ between the repeat resection or RFA and the TACE groups, suggesting that TACE likely was likely 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 two-year disease-free survival rates (20% *vs* 14%) and four-year OS rates (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 (VEGFR-2) inhibitor in conjunction with TACE significantly improved the median PFS, short-term objective responses, disease control rate, and a tendency of increasing the one and two 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), far exceeding that of patients with LR/Ablation (27

mo, range 4–75), TACE/XRT (13 mo, range 4–68), and systemic treatments (26 mo, range 3–59) [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 hepatocellular carcinoma [107, 108]. Sorafenib has a few drawbacks, including poor oral bioavailability and drug toxicities, and its overall survival 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 better median survival at 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*, sorafenib for recurrent HCC performs greater prognosis because it involves the smaller intrahepatic HCC combined with favorable liver function in LT recipients, which may explain why the median OS (16.8 vs. 7.1 mo) and time to development were higher in 42 HCC patients in the LT group than in 790 patients with non-LT [113]. Sequential sorafenib treatments are similarly common in recurrence HCC patients following LT. These treatments improve OS compared to non-LT, flow with preferable baseline characteristics, and do not suppress systemic

treatments with concurrent antirejection strategy [35]. Treatment with Sorafenib and TACE had higher 5-year OS and PFS compared to those treated with TACE alone in patients with recurrent intermediate-stage hepatocellular carcinoma and lesions positive for microvascular invasion (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 significantly improved OS than RFA alone treatment (one, three, and five-year OS rates of RFA-sorafenib vs. RFA group; 97.7%, 83.7%, 54.7% vs. 93.1%, 61.3%, 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 a 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* developed HCC-targeted SP94 peptide and cyanine (Cy) 5.5-conjugated Prussian blue nanoparticles loaded with sorafenib for HCC-targeted multimodality imaging and combined photothermal therapy/sorafenib treatment [118]. These nanoparticles accumulated in HCC tumor sites and then controlled the release of sorafenib to eradicate tumor without any local recurrence and with a minimal amount of toxic side effects.

Other TKI

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 liver transplant with a median OS of 12.9 mo and was tolerable to sorafenib [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 matched primary tumors, 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 (ICPI). Only 15–20% of patients benefit from the anti-PD-L1 monoclonal antibody (mAb), which blocks interactions with PD-1 and PD-L1 and restores 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 superior recurrence-free survival compared to RFA monotherapy [130]. By combining anti-PD-L1 mAb with SP94-Prussian blue-sorafenib-Cy5.5 nanoparticles plus near-infrared therapy, Zhou and colleagues also observed the production of extraordinary results, such as suppression of distant metastases and obstruction of cancer relapse [118]. Note that, different from primary hepatocellular carcinoma, the therapeutic strategy of 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 the partial radiological response of metastatic retroperitoneal lymph node 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 low 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-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, CD3-/CD56+ natural killer (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 interleukin 2 (IL2) and anti-CD3 antibodies [141]. According to research by Lee and colleagues, 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 [141]. 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 propensity scores that matched 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 10 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 improved DFS compared to non-responders, and 71.4% patients were without relapse for two 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. Liver transplantation 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 reserves, 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.

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