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Review Article

Non-surgical Treatment Options in Managing Recurrent Hepatocellular Carcinoma

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Abstract

Despite advances in current treatment options, Hepatocellular Carcinoma (HCC) recurrence still presents as a significant clinical challenge. After initial treatment, HCC recurrence occurs in a considerable portion of patients without an available standardized protocol for managing such an incident. Recurrence of advanced liver disease may make surgical treatment options impossible, in which case, locoregional therapy should be considered as an alternative. This review article discusses recurrent HCC after initial treatment and available non-surgical treatment options. Along with systemic therapy, liver-targeted therapies for recurrent HCC including, radiofrequency, microwave ablation, transarterial chemoembolization, and stereotactic body radiation therapy are promising options. Thermal ablation with radiofrequency or microwave ablation is a suitable treatment option for patients who experience smaller tumor recurrences but are not operable because of comorbidities, impaired liver functions, or tumor locality. Transarterial chemoembolization or radioembolization using Yttrium-90 can be used for patients with an incurable disease and have comparatively low adverse effects.

Introduction

Hepatocellular carcinoma (HCC), the third most common cause of cancer-related deaths globally,[1] has shown a 75% increase in frequency in Europe and North America over the past decades.[2] The primary line of treatment for patients with early-stage disease and maintained liver function is liver resection. Nevertheless, the recurrence rate in the liver remnant has been reported to be up to 80%.[3] More than 70% of recurrent HCC occurs early, within the first two years after intervention in about half of patients, even after successful surgical resection.[4] In some reports, the recurrence rate at five years ranges from 50% to 70%.[4,5] Among HCC patients chosen for liver transplantation (LT) based on established criteria, 10% to 60% of them will experience a recurrence of the disease.[6] Some patients will experience post-LT recurrence within two to five years.[6] The main factor contributing to the bad prognosis of HCC is the high prevalence of recurrence.[7] Many treatment options are available for recurrent HCC (RHCC), including surgical resection, LT, and local ablation techniques, albeit LT cannot be done frequently due to the scarcity of donors.[8] To date, there are no specific guidelines discussing the optimal management recommendations for RHCC after curative treatment.[9,10] This review discusses this challenging issue that currently confounds clinicians and patients, and aims to highlight available non-surgical treatment options.

Keywords: Hepatocellular carcinoma; Recurrence; Non-surgical; Transarterial chemoembolization; Systemic therapy.

Abbreviations: AFP, alfa fetoprotein; ANGPT2, angiopoietin-2; DAAs, direct-acting antivirals; HBV, hepatitis B virus; HCC, hepatocellular carcinoma; HCV, hepatitis C virus; HIFU, high-intensity focused ultrasound; ICIs, immune checkpoint inhibitors; lncRNA, long noncoding RNA; IL-6, interleukin-6; LT, liver transplantation; LTP, local tumor progression rate; mTOR, mammalian target of rapamycin; MWA, microwave ablation; OS, overall survival; PEI, percutaneous ethanol injection; PD-L1, programmed death ligand 1; PFS, progression-free survival; RCTs, randomized controlled trials; RFA, radiofrequency ablation; RHCC, recurrent HCC; SBRT, Stereotactic Body Radiation Therapy; TACE, transarterial chemoembolization; TARE, trans-arterial radioembolization; TKIs, tyrosine kinase inhibitors; TNF-α, tumor necrosis factor α; VEGF, vascular endothelial growth factor.

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The pattern of HCC recurrence

HCC recurrence can occur in various scenarios, including local recurrence in the previously treated lesion, de novo recurrence, and the appearance of extrahepatic metastasis that may or may not be associated with liver tumors.[11] De novo recurrence usually has a delayed onset (two years after initial treatment) and is associated with the presence of risk factors like liver cirrhosis. Local recurrence, however, happens more commonly during the first two years after treatment. Both tumor characteristics and biological behaviors can account for the variable timing of tumor recurrence.[12] De novo HCC can also appear after a long period of no recurrence.[13] And predictably, poor prognosis is related to the emer-

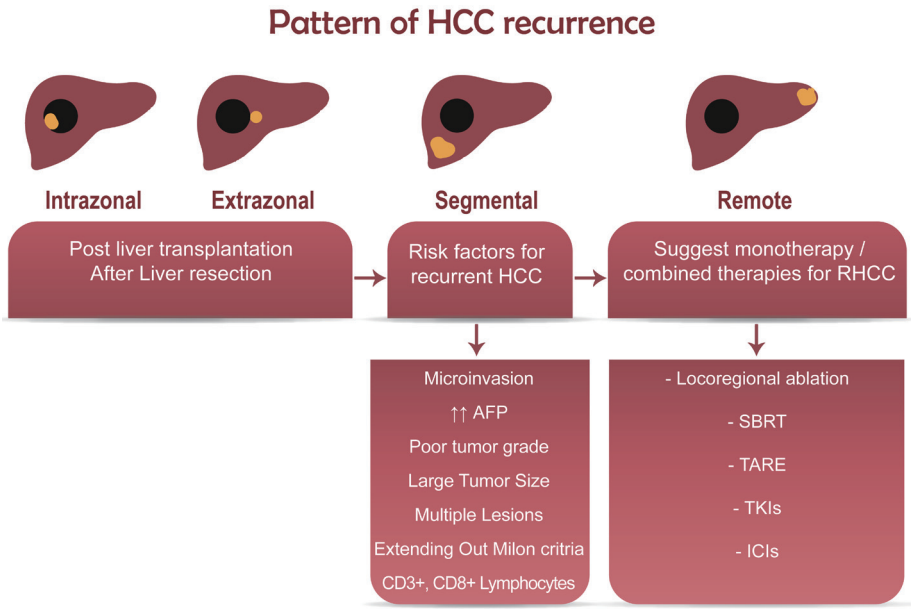

Fig. 1. The patterns of HCC recurrence, risk factors and suggested therapies. AFP, alfa fetoprotein; HCC, hepatocellular carcinoma; ICIs, immune checkpoint inhibitors; RHCC, recurrent HCC; SBRT, Stereotactic Body Radiation Therapy; TARE, trans-arterial radioembolization; TKIs, tyrosine kinase inhibitors.

gence of extrahepatic metastatic lesions.[11] It is believed that tumor cells with mutations in certain genes, such as TP53 and ARID1A, exhibit aggressive behaviors with increased vascular invasion, metastasis, and epithelial-to-mesenchymal transition.[14,15] The graphical abstract shows HCC recurrence patterns, risk factors and suggested therapies (Fig. 1).

Risk factors for HCC recurrence after curative treatment modalities

Several studies have demonstrated that factors such as advanced tumor grading, larger lesions, the presence of microvascular invasion, and elevated tumor markers, are linked to high recurrence rates in post-LT.[16,17] Age, bi-lobar affection, tumor multiplicity, lack of necrosis, lesions outside Milan criteria, high neutrophil-to-lymphocyte ratio, micro satellitosis, and prior surgical resection are additional reported factors.[18,19] Diabetes also seems to negatively affect the natural history and prognosis of HCC patients, regardless of the cirrhosis etiology.[20] The key factors for recurrence in liver resection were microvascular invasion, increased serum alpha-fetoprotein, multinodular tumors, and tumor size.[21] As vital tools for patient selection, genetic markers, and liquid biopsies for circulating microRNA and tumor cells have all been demonstrated to predict the possibility of recurrence.[22,23] Some immunological characteristics may serve as recurrence predictors.[24] For example, the levels of CD3+ and CD8+ T lymphocytes at the margins of the tumor after resection are used as indicators for recurrence.[24] Additionally, tumor aggressiveness and recurrence risk are related to the expression of programmed death ligand 1 (PD-L1) in immune and tumor cells.[24] Table 1 shows different hypotheses of HCC recurrence.[25–32]

Potential therapies for the prevention of recurrent HCC after radical treatment

Numerous studies on recurrence prevention have been conducted to date, but none have been successful.[33,34] The most prominent adjuvant therapy for recurrence prevention conducted are investigated vitamin K,[33] retinoids (the NIK-333 study),[35] and sorafenib.[34]

Everolimus may prevent the recurrence of HCC post-LT and increase overall survival (OS) by inhibiting progression in recurrent HCC.[36] Adding everolimus to calcineurin's inhibitors-based immunosuppressive regimen is a potential treatment for HCC patients despite its multiple adverse effects, including dyslipidemia and proteinuria.[36]

In a study from Hong Kong, hepatitis B virus (HBV) anti-viral therapy (Lamidin or entecavir) given after hepatectomy, enhanced disease-free survival and OS, especially in stage 1 or 2 tumors.[37] This suggests that the anti-tumorous effect of antivirals in HCC recurrence is attributable to the decrease in HBV viral load and consequently chronic inflammation.[37]

Aspirin, statins, and anti-diabetic medications have all been linked in various trials to protect against HCC recurrence.[38] Statins can prevent HCC recurrence through decreasing viremia in patients with viral hepatitis either hepatitis C virus (HCV) or HBV.[38] Possible pathways include lowering blood concentrations of pro-inflammatory cytokines,[38,39] reducing the virulence of viral infections[39,40] or slowing progression to cirrhosis.[39] A recent meta-analysis confirmed the role of statins in chemoprevention of HCC occurrence especially with lipophilic statins.[41]

Treatment modalities for recurrent HCC

Radiofrequency ablation

Due to excellent efficacy and minimum invasiveness, radiofrequency ablation (RFA) has become widely used in treating primary and metastatic liver tumors.[42,43] Albeit, studies using RFA to treat RHCC following curative hepatectomy are scarce.[44] According to a report published by Choi et al, the overall 1, 2 and 3-year survival rates were 82, 72 and 54% respectively.[44] Reported survival rates in early-stage RHCC patients did not differ significantly between repeat hepatectomy and RFA, according to a randomized clinical trial.[45]

Table 1. Summary of the different hypotheses of HCC recurrence

Author	Theory	Sample size	Type of study
Wang *et al.*, 2019[25]	High IL-11 levels	HCC patients undergoing surgery	Prospective study
Wang *et al.*, 2021[26]	9-IR-lncRNA signature	319 HCC samples from HCC radical resection, were randomly divided into a training cohort (161 samples) and a testing cohort (158 samples).	Prospective study
Du *et al.*, 2019[27]	High expression of Sec62	60 HCC samples with Sec62 knockdown (Sec62(KD)) or overexpression (Sec62(OE))	Case-control study
Debes *et al.*, 2018[28]	Increased TNFα Secretion. Change in IL-6 serum level.	13 patients with HCC appeared within 18 months after DAAs therapy	Case-control study
Villani *et al.*, 2016[29]	Rapid reduction of IL-10 & TNFα serum level	103 chronic hepatitis C patients during DAA regimens	Prospective study
Casadei *et al.*, 2018[30]	Modulation of differential white blood cell count: The disproportion between lymphocytes and neutrophils is obvious in HCC patients, which results in an unfavorable microenvironment, and favors the growth of cancer cells.	308 patients with cirrhosis, treated with DAA for HCV	Retrospective study
Francesca *et al.*, 2018[31]	Increase of VEGF serum level. ANGPT2 expression in the primary tumor.	242 HCC patients with advanced fibrosis who received DAA for HCV	prospective study
Rosanna *et al.*, 2018[32]	Immune cell alteration. Imbalance of cytokine network and angiogenesis		

ANGPT2, angiopoietin-2; DAAs, direct-acting antivirals; HCC, hepatocellular carcinoma; HCV, hepatitis C virus; lncRNA, long noncoding RNA; IL, interleukin; TNFα, tumor necrosis factor α; VEGF, vascular endothelial growth factor.

In RHCC after resection, the most frequently used therapeutical approaches are transarterial chemoembolization (TACE) and percutaneous ethanol injection (PEI).[46] However, long-term survival in these situations is not optimal.[46] RFA causes higher instances of necrosis compared to PEI in small lesions and in infiltrating tumors of any size but circumvents the adverse effects that occur when a large dose of ethanol is administered.[47]

RFA can be simply and safely repeated in treating a residual tumor or intrahepatic recurrence.[46] Six patients who experienced three or four sessions of RFA reported a survival of 14 to 54 months without experiencing any major problems.[46] Percutaneous RFA, however, has some limitations and a higher risk of inadequate tumor ablation in tumors close to the major hepatic vessels.[46]

In comparison to repeat hepatectomy, RFA is more tolerable, with patients experiencing fewer adverse events, lessened risk of bleeding risk and shorter times in hospital admission.[48] Tumor location is a significant factor that affects RFA technique, and tumors that are adjacent to the liver capsule or a sizable vessel may be at higher risk for complications.[49]

In general, the tumor locality in low-efficiency areas, such as near the gallbladder, stomach, and diaphragm, should be carefully examined when performing the RFA procedure.[50,51] Subcapsular HCC has a high local tumor progression rate (LTP) because of the small safety margin of ablation around the liver capsule and the small space for placing electrodes.[52] Additionally, the related thermal harm to nearby structures, hemorrhage, or tumor seeding alongside the needle tract during subcapsular tumor ablation raised the likelihood of serious consequences.[53] RFA can also be utilized for HCC lesions near the liver capsule, according to some reports.[49,54] A second recurrence of HCC is nevertheless a common occurrence, even when RHCC is completely eliminated by repeated surgical resection and RFA.[55] In the repeated surgical resection and RFA groups, up to 73.7% and 78.4% of patients experienced another recurrence.[55] Similarly, Chan *et al.* observed that 84.4% of patients who had RFA and 72.4% of patients who had surgical resection experienced another recurrence.[56] It has been claimed that surgical resection better eliminates small, invisible lesions than RFA.[57] Microwave ablation (MWA) and RFA were compared in a meta-analysis including 921 patients from various randomized controlled trials (RCTs), and the results showed that the two procedures had comparable efficacy and safety profiles. However, MWA does appear to lower the frequency of long-term recurrences.[58]

Transarterial chemoembolization

Transarterial chemoembolization (TACE) is the main treatment option as a palliative therapy for HCC. It combines targeted chemotherapy with vascular embolization.[59] Resection or local ablation is the best treatment choice for recurrent HCC, assuming the liver condition is Child-Pugh class A or B, and the tumor is in the proper site.[60] If these requirements are not met, TACE might then be the best option.[61] TACE is a well-tolerated therapy with less liver damage than surgical resection.[62,63] It therefore can be used effectively and widely for individuals with intrahepatic HCC recurrence.[61] Retrospective data analysis from 70 HCC subjects that received conventional cTACE showed that post-treatment transient elevation in liver enzymes was an independent predictor of response in super selective cTACE.[64] Some reports, meanwhile, have examined the effects of TACE in RHCC.[61] According to a recent study, patients with RHCC who received TACE had satisfactory outcomes; however, their progression-free survival (PFS) was not as good as those with treatment-naïve HCC who had never received treatment for their HCC.[65] According to other studies, liver resec-

tion was the preferable option for improving survival compared to TACE patients.[66,67] Additionally, some reports examined the effectiveness of TACE in reducing the recurrence of HCC following orthotopic liver transplantation.[68] After TACE treatment, there is an opportunity for immunotherapy since TACE increases the expression of the programmed death receptor 1 and programmed death ligand 1 (PD-L1) and the tumor-specific CD8 + T cell response.[69] However, there was a comparable efficacy between TACE combined with camrelizumab and TACE alone for RHCC, with no appreciable statistical differences between both comparators as regards PFS, and rates of objective response and disease control.[70] According to data from the STORM study, sorafenib did not significantly benefit HCC patients after resection or ablation.[34] Its usage has been severely constrained by severe side effects and the high resistance rate.[71,72] Apatinib is ten times more effective than sorafenib at blocking the vascular endothelial growth factor receptor 2,[73] and an RCT was carried out to examine the impact of TACE combined with apatinib on RHCC.[74] When compared to TACE therapy alone, apatinib + TACE produced a PFS benefit of 4.7 months, besides greater objective response and disease control rates.[74] Neoadjuvant TACE, when used in conjunction with RFA, could prevent hepatic artery flow and decrease the flow coming from portal circulation, reducing the possible heat-sink effect that may occur during RFA, and increasing the ablation efficiency.[75] Neoadjuvant TACE could help RFA to expand the size of ablated area in lesions where microvascular invasion is MVI-positive, which would subsequently increase the likelihood of clearing micrometastases and aid in lowering the risk of recurrence.[75,76]

Microwave ablation

In past years, microwave ablation (MWA) use as a curative treatment for HCC has increased.[77] MWA offers some benefits over RFA, inclusive of shorter ablation periods, larger ablated areas, more intra-tumoral temperatures, and complete coagulative necrosis.[77] Even though MWA produces a larger ablation zone and a higher disease-free survival rate than RFA, it has comparable two-year OS and complete response rates.[78] Many studies have reported similar efficacy between MWA and RFA regarding the possibility of local recurrence and the survival rates in primary HCC and with reported 5-year OS rates of 43–60%.[79,80–82] However, Liu *et al.* showed that, in cases within the Milan criteria, MWA produced a superior five-year OS when compared to RFA with a longer follow-up.[78] For more than 20 years, surgical MWA, also known as microwave coagulo-necrotic treatment, has been used to treat primary and recurrent HCC with positive long-term oncological outcomes.[83–85] More than 60% of patients with RHCC following the first resection have had surgical MWA.[85] For patients with recurrent small HCC, TACE-MWA may provide superior tumor control than TACE.[86] This was consistent with the findings of the study by Chen *et al.*[87] Following the initial treatment, this study revealed that 82.7% of tumors in the combined TACE-MWA arm had complete tumor ablation, compared to 42.8% of lesions in the TACE alone arm at one month ($p = 0.013$), and that the cumulative OS rates at five years were 61.1% for the combined TACE-MWA group, and 50.3% for TACE alone in patients with recurrent small HCC, which is comparable to other similar reports examining the 5-year cumulative OS rates of combined TACE and RFA treatment (46–60%).[76,88] Total necrosis following TACE has been associated with favorable survival outcomes in RHCC,[63] however, the authors could not find a significant difference in OS between the TACE and combined TACE-MWA arm.

High-intensity focused ultrasound

High-intensity focused ultrasound (HIFU) ablation is one of the recent modalities that could offer a completely non-invasive ablation for HCC, which is also feasible for patients with advanced liver cirrhosis.[89] In order to cause necrosis of the target lesion by raising the tissue temperature to above 60°C, it uses a particular ultrasound wave frequency, 0.8–3.5 MHz, which can be controlled and focused remotely.[90,91]

For HCCs less than 3 cm, HIFU attained a total ablation rate of 82.4% in a single treatment session.[92] It is also well tolerated in elderly patients.[92] Ascitic patients can receive HIFU safely because it acts as a conduit for energy transfer and shields other parts of the body from the effective HIFU waves.[93]

The advantage of HIFU over RFA is that the temperature outside the target point is constant, which makes it less prone to accidental collateral damage.[91] New research has shown that HIFU could successfully treat recurrent HCC.[94] Throughout a median follow-up period of 27.9 months, there were no variations in lesion size, disease-free survival rates, or OS rates between patients with RHCC who received HIFU (n = 27) and those who had RFA (n = 76).[94] Some HIFU-related side effects, including momentary pain and superficial skin injuries (81% and 39%, respectively), have been documented in studies.[95] In one Hong Kong center, HIFU is used with comparable survival results to RFA for lesions less than 3 cm and in patients with RHCC.[92,94,96] Retrospective study data revealed that more HIFU-bridged patients than TACE-treated patients had responded completely to treatment.[89]

Radiotherapy

Stereotactic Body Radiation Therapy

Stereotactic Body Radiation Therapy (SBRT) is included in the practice guidance statement from the American Association for the Study of Liver Diseases, and the 2019 National Comprehensive Cancer Network Guidelines as an effective non-surgical treatment option for localized intrahepatic HCC.[97,98] When compared to TACE or thermal ablation, SBRT exhibits equivalent safety and efficacy, with control rates of 70–80% for intrahepatic tumors, even for large sizes. It is important to keep the radiation dose affecting the surrounding liver tissue to a minimum and consider the liver functions before the intervention.[99,100] For patients with maintained liver function, repeated SBRT for RHCC provided good tumor ablation results with an acceptable safety profile and satisfactory OS similar to other ablative therapies with cure intent.[101] According to Honda *et al.*, the SBRT and TACE combination dramatically decreased local recurrences and improved OS.[102] After surgical resection or RFA, the remaining or RHCC may also be treated with SBRT.[103]

According to several studies, SBRT showed good results in recurrent malignancies as a salvage treatment or as an alternative to TACE/RFA.[104–106] TACE/RFA was not appropriate for the patients in these investigations because they frequently received extensive pretreatment, had large tumors, comorbidities, and advanced liver disease.[106] At two years, the results from recent prospective and retrospective trials ranged from 68 to 95 percent and were comparable with the control.[106] SBRT does not appear in liver cancer treatment guidelines since no completed randomized trials provide level 1 evidence of its effectiveness.[107–109] However, SBRT is an option for HCC management according to the American Society of Radiation Oncology recommendations.[110] SBRT offers acceptable tumor control and survival benefits (3-year disease control: 68–97% and 3-year survival: 39–84%) in cases where RFA is not

feasible or in HCC recurrence following RFA or TACE.[111]

Trans-arterial radioembolization

Trans-arterial radioembolization (TARE) with 90Y-loaded glass or resin microspheres is one of the available treatment modalities for patients with advanced liver disease.[112] However, concerning survival, available studies do not prove the superiority of TARE coupled with chemotherapy as a first-line treatment for colorectal cancer metastases.[113] The same was reported regarding the combined TARE and Sorafenib treatment in HCC with advanced or recurrent disease.[114] TARE showed benefit in colorectal cancer metastases of distinct origin, intrahepatic cholangiocarcinoma, or advanced HCC.[115,116] A decline in liver function or the occurrence of radioembolization-induced liver disease (ascites, liver insufficiency, hyperbilirubinemia), as well as pancytopenia, or post-embolization syndrome (fatigue, hyperthermia, pain, and gastric upset), have all been documented as signs of toxicity.[115,117] Slower disease progression after TARE (mean, 13.3 months) was reported compared to TACE (8.4 months), but without a significant improvement in OS (20.5 months in TARE vs 17.4 months in TACE).[118] The same study reported significant postembolization syndrome after TACE, but with a similar rate of severe adverse events in both TACE and TARE.[118] Another study reported a non-significant difference between TACE and TARE with regard to HCC recurrence rates (p-value = 0.33).[119] Combining an immune-checkpoint inhibitor with vascular endothelial growth factor blockade and 90Y-TARE might help prevent primary resistance encountered with the sole administration of each of these medications.[120]

Systemic therapy

Sorafenib, Lenvatinib, and atezolizumab/bevacizumab are currently the Food and Drug Administration approved first-line systemic treatment options for patients with advanced-stage liver disease.[121] Tyrosine kinase inhibitors and other new drugs are used in clinical trials to increase patients' frontline systemic treatment choices.[122] Failure of sorafenib as the first-line treatment opens the door for using second-line options. The following drugs are licensed for use in the second-line setting: regorafenib, nivolumab/ipilimumab, pembrolizumab, cabozantinib, and ramucirumab (for patients with an alfa fetoprotein >400).[123,124] Lenvatinib and atezolizumab/bevacizumab were approved as a consequence of the recently announced landmark trials REFLECT and IMbrave150.[121,122] RHCC or a progression of recurrence, not eligible for resection or local ablative treatments, have been considered as untreatable presentation/progression.[125] Recent reports proved the benefit of treating post-LT RHCC in the untreatable presentation/progression stage with the multitarget tyrosine kinase inhibitor, sorafenib.[126,127] Furthermore, due to the synergistic interaction between sorafenib and immunosuppressive drugs like the mammalian target of rapamycin (mTOR) inhibitors, the combination of sorafenib with these agents has come under scrutiny.[128–130] Sorafenib has been approved to treat RHCC following LT as an extension of the recommendations of the European Association for Study of the Liver and American Association for the Study of Liver Diseases as the front-line treatment for advanced HCC.[131–133]

The median survival after sorafenib administration, according to case reports and a limited number of case series ranges between 14 and 42 months.[126,131] This is a meaningful improvement in survival compared to other systemic therapies, such as chemotherapy or best supportive care.[125,126,134,135] Evidence of radiologic regression in LT patients with RHCC suggests sorafenib's effectiveness in inhibiting cancer cell proliferation,[136,137] whereas the use of mTOR continues to be controversial.[127,138]

In Asia, several randomized studies have shown that after curative resection or ablation, adoptive immunotherapy decreased the rate of HCC recurrence and increased OS in some reports.[139,140] Tumor-directed vaccinations have decreased recurrence rates in a few small, randomized trials.[141,142] A report revealed a link between high Immunoscore (a composite assay integrating density of CD3+ and CD8+ T cells in the center and periphery of the lesion), a significantly lower rate of HCC recurrence and prolonged recurrence-free survival RFS.[143] According to this, CD3+ and CD8+ positive T-cell populations invading the tumor likely play a crucial part in triggering the immune reaction against cancer which serves as a mediator to prevent the recurrence of HCC.[143] Other cytotoxic T-cell infiltration, including that of CD4+ cells, is also associated with a decreased recurrence likelihood.[144] Despite concerns over the preventive role of sirolimus in patients receiving LT for HCC, only one substantial series has reported sirolimus as a therapy for HCC recurrence.[145] In 2010, a report from the Bilbao group included two patients with RHCC, treated with an everolimus/sorafenib combination, and reported a survival of 18.5 (without recurrence) and 10 months (with recurrence).[146] However, finding consistent predictors of response to immunotherapy in HCC needs further study as about 70% of patients with advanced HCC receiving immune checkpoint inhibitors (ICIs) do not respond to this treatment.[147] The use of immunotherapy in HCC has nominally been associated with several limitations.[148] Early death with first-line ICI is a clinically relevant phenomenon across solid malignancies, which is not predictable by PD-L1 expression but is preventable through the addition of other treatments to ICI.[149] Recently, Zheng *et al.*, observed some dynamic alterations in microbiota of HCC patients during immunotherapy administration.[150] In this intriguing study, stools from patients who responded to ICIs had higher taxonomic richness than stools from patients who did not respond, indicating that the human microbiota may have a significant influence on the effectiveness of the immunotherapy in HCC patients.[150] In addition, long noncoding RNAs represent a new area of investigation in the prediction of immunotherapy response.[151,152] The long noncoding RNA MIR155 host gene is linked to PD-L1 and CTLA-4, and this gene could be a potential biomarker for predicting ICI response.[153] Table 2 shows a summary of some non-surgical treatment options used in patients with RHCC.[44,68,76,78,136,145,154–157]

Combination therapies

Limited retrospective reports have demonstrated that the administration of sorafenib following RFA had a considerably greater ablation area, fewer recurrence incidents, and better OS compared to RFA alone in 0-B stages of HCC by Barcelona clinic liver cancer.[158,159] Meanwhile, there was no significant difference between adjuvant sorafenib and placebo following response to local ablation regarding median recurrence-free survival in the phase III STORM trial.[34] A meta-analysis examined the effect of RFA and MWA as locoregional ablative treatments in combination with sorafenib, reported that this combination had extended OS at one, two, and three years, less two-year HCC recurrences, and higher overall efficacy compared to RFA-alone.[160] Moreover, a Korean phase III RCT showed that curative treatments for HCC (resection, RFA, or ethanol injection) had an extended recurrence-free and OS with adjuvant immunotherapy with activated CIK cells (CD3+/CD56+ and CD3+/CD56- T cells and CD3-/CD56+ natural killer cells) than without it.[140] Another report showed that patients with RHCC who have no more than three lesions, tumors with a di-

Table 2. A summary of the decision-making for patients with RHCC

Study	Primary radical treatment before HCC recurrence	Newley used non-surgical treatment option
Lai *et al.*, 2018[44]	liver resection	RFA
Zhang *et al.*, 2017[154]	liver resection	RFA
Yamagami *et al.*, 2014[68]	LT	TACE
Lee *et al.*, 2022[78]	LT	MWA
Na *et al.*, 2016[155]	LT	Sorafenib+ mTOR inhibitor
Takahara *et al.*, 2011[136]	LT	Sorafenib
Alamo *et al.*, 2009[145]	LT	Sirolimus
Peng *et al.*, 2012[76]	liver resection	TACE-RFA
Invernizzi *et al.*, 2020[156]	LT	Sorafenib+ mTOR inhibitor
Yoon *et al.*, 2010[157]	LT	Sorafenib

HCC, hepatocellular carcinoma; LT, liver transplantation; mTOR, mammalian target of rapamycin; MWA, microwave ablation; RHCC, recurrent HCC; TACE, Transarterial chemoembolization; RFA, radiofrequency ablation.

ameter less than 3 cm, extrahepatic metastases, or portal vein/hepatic vein invasion, responded well to RFA plus anti-programmed death receptor 1 therapy.[161] In general, data regarding the efficacy of combination therapies are scarce. The availability of more evidence in the near future could prioritize this approach in management guidelines.

Future perspectives

There is a pressing need to understand the predictors of ICIs and identifying tissue and molecular markers that respond to ICIs is an important future challenge for its use in several solid tumors, including HCC.[120] Efforts are also aimed at evaluating novel predictors for the response to ICIs, contemplating tumor-intrinsic (*e.g.*, PD-L1 expression, TMB, MSI status, *etc.*), immune-properties, and combinative biomarkers. Combination systemic therapies in RHCC is a facet that is still relatively unexplored, and research based on larger clinical trials is needed to further develop our understanding.

Conclusion

HCC recurrence can occur in 70–80% of cases following potentially curative interventions like resection or ablation. There is no available standardized approach for managing RHCC since HCC has diverse recurrence forms and timing. However, existing data from clinical trials or real-life studies regarding the treatment options and expected outcomes of treating HCC recurrence shows some promise. Optimal selection of candidates for curative interventions like liver resection, local thermal ablation with RFA or MWA, and LT is an obligate demand for the success of the retreatment with such modalities. Strict follow-up protocols after intervention are a must for early detection of any subsequent recurrence.

Less invasive palliative techniques with potential benefits, like TACE and radioembolization, have relatively low risk and can be used for patients with incurable diseases who are not eligible for hepatectomy or LT. Similarly, SBRT is an option that provides reasonable disease control and a modest survival benefit in recurrent small HCC following surgical intervention. Response to systemic therapy offered to patients with advanced RHCC is promising, and more studies are required to better identify target patient populations that may benefit from this line of therapy. Immunotherapy-based therapeutic choices are emerging as an attractive option for RHCC because the immune constituent of the hepatic microenvironment plays a crucial role in disease recurrence. Finally, even though the majority of available evidence regarding RHCC management shows encouraging findings, additional prospective RCTs are required to provide more reliable clinical data that can be used for the development of standardized guidelines for managing RHCC.

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Author contributions

MEK contributed to the conception and design of the work and literature review. WA wrote the first draft of the manuscript. MEK provided critical revision and editing. Both authors revised and approved the final version of the manuscript.

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