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REVIEW

Recurrent Hepatocellular Carcinoma: Patterns, Detection, Staging and Treatment

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Abstract: Hepatocellular carcinoma (HCC) is the third most common cause of cancer-related deaths worldwide with the incidence of recurrence being as high as 88% even among patients who have undergone curative-intent treatment. Despite improvements in overall survival, recurrence remains a challenge necessitating accurate reappraisal of patient and disease status. To that end, accurate staging of recurrent HCC is a necessity to provide better care for these patients. Risk factors for poor survival after HCC recurrence have been identified and include characteristics of the primary disease, such as tumor multifocality, large size (≥5 cm), macroscopic vascular or microscopic lymphovascular invasion, preoperative a-fetoprotein (AFP) levels, R0 resection, and the presence of impaired liver function. Close surveillance with imaging is warranted following curative-intent therapy, with magnetic resonance imaging (MRI) being the preferred approach to identify small, early recurrent HCCs. Treatment decisions at the time of recurrence involve ruling out extrahepatic disease and identifying candidates for potentially curative-intent repeat treatment options. Patients with recurrent disease are, however, very diverse in terms of tumor morphology and biologic behavior, as well as residual hepatic functional reserve. Patients with preserved liver function may benefit from repeat liver resection or ablation. Patients with recurrence within the Milan criteria may even be candidates for salvage liver transplantation, while multimodality treatment with combination of liver-directed therapies appears to enhance oncologic outcomes for individuals with advanced recurrent disease. A "one-size-fits-all" approach in staging recurrent HCC does not exist. Rather, individualized and evidence-based decision-making is necessary in order to optimize outcomes for patients with recurrent HCC.

Keywords: hepatocellular carcinoma, recurrence, staging, treatment, classification

Introduction

Hepatocellular carcinoma (HCC) is the principal histologic type of liver cancer, accounting for the majority of liver malignancies and constituting the third most common cause of cancer-related death worldwide.[1] HCC is a generally aggressive disease, with a 5-year survival less than 20% and an incidence of recurrence as high as 88%.[2–4] Unlike most other common malignancies, HCC is unique as it features two coexisting disease components; the first disease process relates to the primary tumor and its associated characteristics, while the second clinical consideration involves the underlying liver disease (ie, liver cirrhosis/fibrosis and/or hepatitis B/C infection). Consequently, choice of treatment strategies can often be limited due to insufficient liver function reserve. In addition, outcomes related to various treatment options can vary significantly based on different clinicopathologic factors including underlying liver function, tumor size, vascular invasion, as well as genetic variants related to tumor biology.

Irrespective of etiology and treatment strategy, HCC can often recur.[3] As such, close post-operative surveillance is warranted, and, when recurrence is detected, reassessment of disease status and treatment options is necessary. Optimal staging schemas for recurrent HCC have not been well documented in the literature compared with staging systems related to primary HCC.[5] Treatment algorithms, staging systems, and data on management of recurrent HCC are critical to guide clinical decisions. In part due to advances in early diagnosis, as well as optimization of treatment options, patients with recurrent HCC now have better prognosis and tend to live longer.[6,7]

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The optimal staging strategy for recurrent HCC should incorporate as much disease-relevant information as possible. Staging schemes related to recurrent HCC should, in principle, take into account tumor-specific characteristics (ie, size and number of nodules, site of recurrence, as well as other pathologic characteristics indicative of aggressiveness), the extent of underlying liver disease (ie, liver cirrhosis based on imaging and functional studies and hepatitis viral activity), and also details regarding previous treatments. Moreover, the optimal staging system should allow for prognostic stratification of patients, as well as enable treatment allocation. In this context, further investigation of the epidemiologic, biologic, and clinical features of recurrent HCC is essential.

Patterns of HCC Recurrence and Risk Factors

HCC is a disease that exhibits marked geographic variability in terms of incidence, largely due to differences in the prevalence of underlying risk factors. In particular, the disease burden is higher in areas with endemic hepatitis B (HBV) such as East Asia and sub-Saharan Africa,[8,9] while hepatitis C (HCV) and non-alcoholic fatty liver disease (NAFLD) are prominent risk factors for HCC in Europe, North America, and Japan.[10,11] Although such differences in chronic liver disease etiologies would be expected to give rise to diverse disease phenotypes with varying recurrence patterns, no clear association with disease aggressiveness has been established.[2,12] Instead, the presence of cirrhosis and/or fibrosis, which is the ultimate biologic endpoint of all liver disease processes if left untreated, has previously been linked to poor overall and disease-free survival outcomes.[12–14] In particular, the presence of cirrhosis can lead to an increased risk of HCC recurrence.

Globally, there has been a trend towards an increased incidence of HCC, likely due to an increased incidence of HCV infections and NAFLD, which has been slightly offset by the decrease of HBV infection incidence in East Asia, as antiviral treatments become more widely available.[15] Data on temporal trends related to the incidence of HCC recurrence are sparse. A recent meta-analysis by Tan et al, which reported on transplanted patients, reported that the incidence of HCC recurrence following transplantation decreased over time, although this finding was not statistically significant.[16] In the same patient population, recurrence rates seemed to follow a similar incidence pattern to that of primary tumor, with Asian populations who had higher HBV infection rates having an increased incidence of HCC recurrence.

Following initial treatment of HCC, the disease may enter a latent phase. Depending on the primary treatment utilized, patients may experience disease recurrence (ie, after curative-intent liver resection) or disease progression (ie, after ablation or chemoembolization). While different index treatment modalities may be associated with different risk levels of recurrent disease, patterns of HCC recurrence have been most extensively studied after resection. A recent retrospective multicentre study reported a recurrence rate of 45.5% among 756 patients who underwent curative-intent liver resection.[3] The investigators noted that most recurrences were intrahepatic in nature, arising in the liver remnant rather than close to the resection margin; in addition, the vast majority of recurrences occurred within two years of the index operation. In a separate study by Xu et al,[12] late recurrences (ie, >2 years after the index procedure) were also noted to be predominantly intrahepatic (90.1%); of note, the authors reported that up to 54.5% of patients had a recurrence that was potentially amenable to repeat curative-intent treatment. In yet another study, Kim et al estimated that the hazard to develop recurrent disease peaked within the first year following hepatectomy and then gradually decreased until the fifth postoperative year, remaining stable thereafter.[17] Similar recurrence patterns have been described after liver transplantation.[18] Collectively, the data seemed to indicate that primary tumor clinico-morphological parameters, as well as the timing of the recurrence, are the main determinants of long-term outcomes among patients with recurrent HCC disease.

Even after treatment of recurrent disease, a large number of patients will develop a second recurrence with a reported incidence of 50–70%.[19,20] Some patients may even go on to develop a third or fourth recurrence after previous curative-intent treatment. While this is uncommon, the data that are available suggest that each successive curative-intent procedure is associated with diminishing probability of long-term survival.[21] Risk factors associated with HCC recurrence have largely been related to patient and tumor-specific parameters. For example, factors indicative of HCC aggressiveness and increased risk of recurrence have included tumor multi-nodularity, large size (≥5 cm), macroscopic vascular or microscopic lympho-vascular invasion, high preoperative a-fetoprotein (AFP) levels, as well as the presence of cirrhosis and advanced initial BCLC stage.[3,12,22] While recurrence has largely been examined post-liver resection[14,23] or liver transplantation,[24–26] other authors have sought to develop composite recurrence risk scores after ablation,[27] with some investigators employing artificial intelligence.[28] Previous studies have largely focused on risk assessment related to survival following primary treatment; however, prognostic indicators associated with factors related to the primary HCC

tumor are unlikely to be as relevant in the setting of recurrent disease. Instead, other factors such as time to recurrence, extrahepatic spread, and size and number of recurrent nodules are likely to be more useful to estimate the overall survival (OS) and disease-free survival (DFS) after the recurrence has occurred.[29–32]

Detection of Recurrent Disease

Appropriately timed follow-up is key to detect HCC recurrence. Since many patients develop a recurrence early following treatment of the primary tumor,[2] close surveillance is mandatory. While surveillance guidelines can vary, patients should generally be followed every 3–4 months for the first 1–3 years, every 6 months for years 3–5, and then annually to at least 10 years.[3] The timing of surveillance should be informed both by primary tumor characteristics (ie, risk of recurrence), as well as the underlying liver quality itself (ie, risk of de novo disease). Surveillance generally involves contrast-enhanced multidetector computed tomography (MDCT) or magnetic resonance imaging (MRI) scanning combined with AFP level measurement.[33]

Detection of early recurrent disease is of paramount importance, especially given that prior treatments may have reduced the remaining liver volume and/or impaired functionality, which could limit treatment options for advanced recurrences. To this point, in a head-to-head comparison of gadoxetic-enhanced MRI versus MDCT, MRI was noted to be more sensitive to detect HCC recurrences smaller than 2 cm (96% versus 65%, respectively) and had a higher overall accuracy (97% versus 85%, respectively).[34] Of note, gadoxetic acid-based MRI techniques also conferred a significant advantage in the ability to recognize early recurrence; in contrast, non-contrast enhanced MRI had comparable performance to MDCT in detecting recurrences 1 year post-hepatectomy.[35]

In addition to cross-sectional imaging, biomarkers also have a role in detecting recurrence following the index treatment of HCC. For example, AFP has traditionally been used as a marker of HCC recurrence, despite its relatively low sensitivity. Instead, des-γ-carboxy-prothrombin (DCP) has been reported to be superior to AFP measurements to detect HCC recurrence.[36–38] To this point, DCP has been implemented into the Kyoto criteria to select transplantation candidates; however, DCP has yet to be incorporated into routine surveillance for HCC recurrence.[39] Inflammatory and angiogenic markers have also been evaluated among transplanted patients.[40] Furthermore, detection of circulating tumor DNA, otherwise called liquid biopsy, has also been postulated to increase the predictive performance of AFP.[41] Currently, there is no "best" biomarker combination to detect early HCC recurrence with high accuracy. Novel biomarkers are, however, critically important in specific patient subgroups, such as those individuals who are AFP-negative.[42]

Staging and Treatment of Recurrent HCC

After establishing the diagnosis of HCC recurrence,[43] staging should begin with searching for evidence of extrahepatic disease (present in 12% to 27% of patients)[3,4,44] since this is largely considered a contraindication to surgical treatment. Some investigators have, however, suggested that even patients with isolated extrahepatic recurrence may still benefit from resection.[45] Intrahepatic recurrences are present in the majority of patients irrespective of the primary treatment modality employed (ie, resection, transplantation, or ablation). In turn, patients with intrahepatic recurrence represent the most diverse group in terms of recurrent tumor morphology, amenability to curative-intent treatments, and biologic behavior. Although no staging schema has been established to date relative to recurrent HCC, primary HCC staging schemas, such as the BCLC classification, are often extrapolated and used to help predict outcomes and guide decision-making in the setting of recurrent HCC. Indeed, Yao et al recently investigated the applicability of BCLC staging for recurrent HCC and demonstrated distinct prognosis in terms of OS among individuals with variable recurrent HCC BCLC staging, thus validating the prognostic ability of BCLC staging in the setting of recurrent disease.[46] Nevertheless, the majority of patients who recurred did not receive the treatment suggested by the BCLC algorithm in the setting of primary HCC.[46] Existing staging schemas such as the BCLC and the Hong Kong Liver Cancer (HKLC) classifications were not developed to assist with prognostication or decision-making in the setting of recurrent HCC.[47] In turn, these staging systems and treatment algorithms should not be applied indiscriminately to patients with recurrent disease.

In general, the presence of extrahepatic disease or portal vein thrombus, lesion size, recurrence within or beyond the Milan criteria, disease resectability, and eligibility for transplantation should all be taken into account when assessing patients with recurrent HCC. In addition, AFP levels at the time of recurrence can also predict post-recurrence survival independent of the secondary treatment modality; as such, AFP levels should routinely be evaluated when recurrence is suspected.[48] Perhaps not

surprisingly, the most important determinant of long-term survival after recurrence is whether the recurrent disease is amenable to curative-intent therapy (Table 1).[49] In a retrospective multi-center study from Italy that included 1560 patients, Famularo et al reported an increase in OS and DFS among patients who were treated with curative-intent repeat liver resection and/or ablation versus palliative TACE with or without sorafenib.[50] Ablation has previously been demonstrated to be more effective than systemic sorafenib therapy.[51] While TACE has also been associated with better survival outcomes than sorafenib, these data suffer from significant selection bias.[52] While possibly providing better long-term control than TACE, ablation has limited applicability in the setting of recurrent multinodular disease.[53,54] Similarly, repeat resection is also limited to patients with solitary or oligo-recurrent disease, as well as individuals with preserved liver volume and function. The treatment of recurrent HCC should be individualized and needs to take into account the location and extent of recurrent disease, as well as the volume and function of the remnant liver. A suggested flowchart to guide treatment decision-making in the setting of recurrent disease is presented in Figure 1.

Table 1 Recent Studies Comparing Treatment Modalities in Patients with Recurrent Hepatocellular Carcinoma

Author	Year	Type of Study	Selection Criteria	Overall Survival	Disease-Free Survival	Mortality	Major Complications
Repeat liver resection versus RFA							
Xia et al[19]	2020	RCT	Early disease (BCLC 0/A)	Comparable 5-year OS (43.6% vs 38.5%, p=0.15)	Comparable 5-year DFS (52.4% vs 41.7%, p=0.09)	None	Increased (22.4% vs 7.3%, p=0.001)
Zhong et al[20]	2021	Retrospective -PSM	N/a	Comparable 5-year OS (56.4% vs 53.1%, p=0.6)	Increased 5-year DFS (25.5% vs 16%, p<0.001)	Comparable (0.9% vs 0.4%, p=1)	Increased (19 vs 5.3, p<0.001)
Wei et al[31]	2021	Retrospective -PSM	Early disease (BCLC 0/A	Comparable 5-year OS (59% vs 71.4%, p=0.36)	Comparable 5-year DFS (32.4% vs 34%, p=0.78)	N/a	Comparable (p=0.62)
Feng et al[57]	2020	Retrospective -PSM	Up to three nodules, ≤5 cm	Comparable 5-year OS (38.1% vs 55.6%, p=0.11)	Comparable 5-year DFS (14.6% vs 19.2%, p=0.78)	None	Increased (9.1% vs 0.5%, p<0.001)
Lu et al[61]	2020	Retrospective -PSM	None	Increased 5-year PRS (71.8% vs 41.7%, p=0.002)	N/a	None	N/a
Salvage liver resection after previous radiofrequency ablation vs repeat hepatectomy after previous liver resection							
Yamashita et al[62]	2015	Retrospective	N/a	Decreased 5-year OS (52%, p=0.02)	Decreased 3-year DFS (p=0.02)	None	Increased (26% vs 4%, p<0.1)

(*Continued*)

Table 1 (Continued).

Author	Year	Type of Study	Selection Criteria	Overall Survival	Disease-Free Survival	Mortality	Major Complications
Yamagishi et al[63]	2019	Retrospective	N/a	Decreased 5-year OS (41.8% vs 63.2%, p=0.02)	Comparable 5-year DFS rate (10.3% vs 15.9%, p=0.4)	Comparable (1.8% vs 0, p=1)	Comparable (27.7% vs 31.4%, p=0.83)
Salvage liver transplantation versus repeat resection							
Ma et al[69]	2018	Retrospective -PSM	UCSF	Increased 5-year OS (71.6% vs 32.8%, p<0.001)	Increased 5-year DFS (72.8% versus 48.3%, p=0.007)	Comparable (0 vs 1.9%, p>0.99)	Comparable (16% vs 8.3%, p=0.21)
Chan et al[68]	2013	Retrospective	Within Milan criteria	Increased 5-year OS (60% vs 48%, p=0.004)	Increased 5-year DFS (57.9% versus 49.3%, p<0.001)	N/a	N/a
RFA vs TACE							
Wang et al[54]	2020	Retrospective	Tumor size ≤3 cm, ≤3 tumors	Comparable 3-year OS (68.8% vs 45%, p=0.49)	Increased 3-year PFS (p=0.004)	None	None
Gou et al[53]	2022	Meta-analysis	N/a	Increased odds for 5-year OS (OR=3.22, 95% CI=1.34–7.72, p=0.009)	N/a	N/a	Comparable (OR=1.78, 95% CI=0.55–5.78, p=0.33)

Abbreviations: RFA, radiofrequency ablation; TACE, transarterial chemoembolization; OS, overall survival; DFS, disease-free survival; OR, odds ratio; CI, confidence interval; RCT, randomized controlled trial; PSM, propensity-score matching; BCLC, Barcelona Clinic Liver Cancer staging system.

Repeat Resection versus Other Treatments

Liver resection is often the index operation for primary HCC, and similarly should be considered for recurrent disease in the proper clinical setting. Repeat resection is generally preferable – when feasible – to ablation or TACE for recurrent HCC. Decisions about resection versus ablation/TACE need, however, to consider multiple factors; clinical decisions about treatment should involve size and location of the lesion, as well as the underlying liver function. Ablation has the advantage of being percutaneous and potentially less morbid. Whether repeat resection or ablation confers equivalent long-term survival has been debated. In a propensity-score matched analysis, Chua et al noted that ablation and repeat resection were equivalent with respect to short-term survival (p=0.84); however, repeat hepatectomy was associated with superior 3-, 5-, and 10-year survival compared with ablation.[55] Patients who underwent repeat hepatectomy also experienced improved DFS (p=0.02), yet had higher 30-day morbidity and mortality compared with patients who underwent ablation. Therefore, the authors concluded repeat resection was associated with a higher peri-operative risk of complications and death, yet a higher chance at long-term survival compared with ablation. Other studies have failed, however, to confirm a long-term survival benefit of repeat resection over ablation.[20,56,57] The comparability of repeat

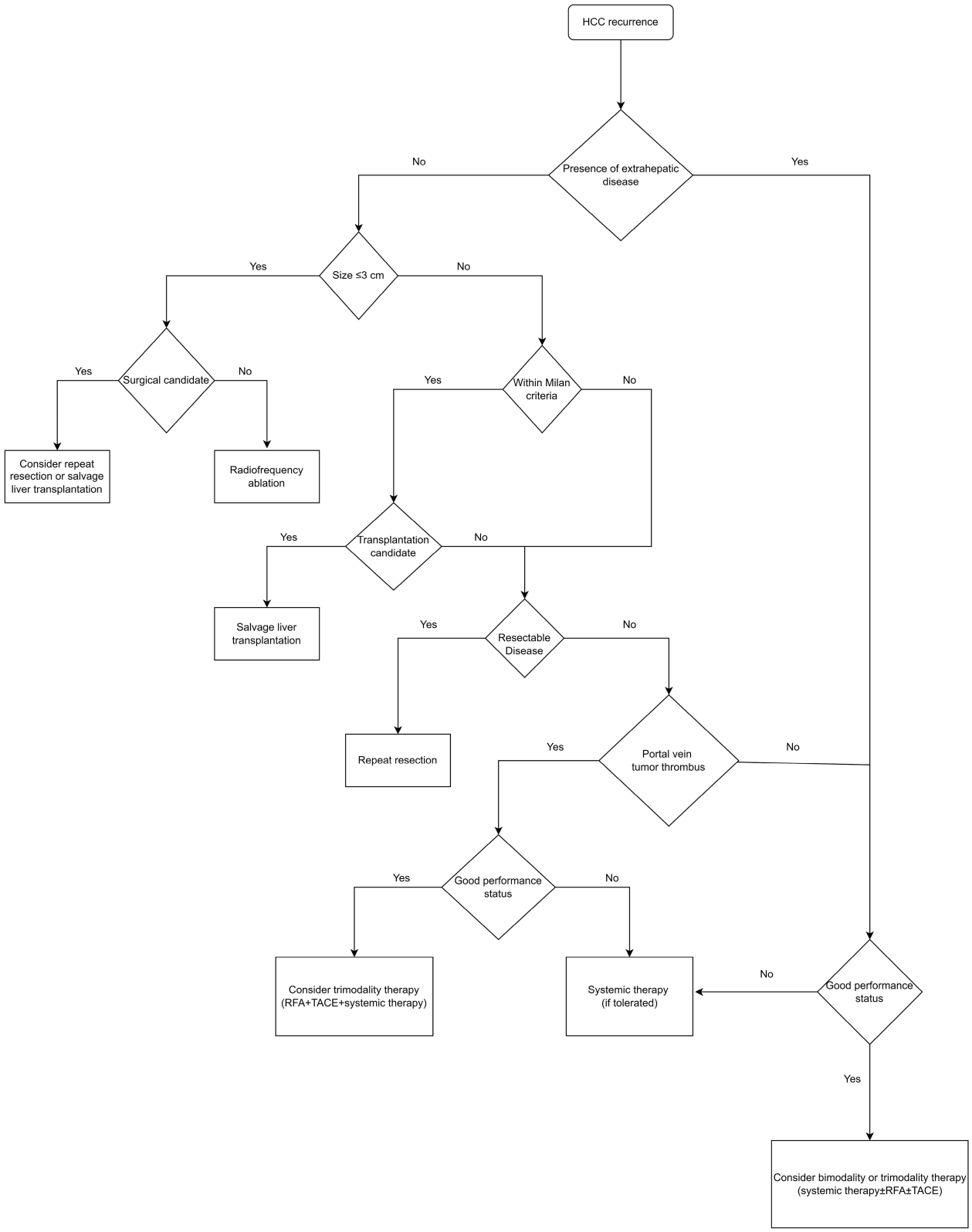

Figure 1 Suggested flowchart of recurrent HCC management.

resection and ablation relative to long-term outcomes following treatment of recurrent HCC was particularly pronounced among patients with early recurrence. In particular, several studies have noted no difference in outcomes following repeat resection versus ablation among patients with recurrent HCC who met Milan criteria or had early-stage disease according

to the Barcelona Clinic Liver Cancer (BCLC) classification.[19,56,58,59] In particular, patients with recurrent tumors less than 3 cm had no difference in post-treatment outcomes following resection versus ablation, yet ablation was associated with a lower incidence of complications.[60] In contrast, patients with recurrences outside the Milan criteria did better in terms of post-recurrence survival after repeat hepatic resection.[61] Collectively, these data strongly suggest that resection should be preferred in eligible patients with recurrent disease larger than 3–5 cm, while ablation may be considered for smaller-sized recurrent disease.

A subset of patients with primary HCC is sometimes initially managed by ablation. When recurrence occurs post-ablation, "salvage" liver surgery can sometimes be considered. In fact, this approach (ie, ablation followed by salvage resection) may be preferable in some patients as it may allow for better selection of candidates for resection (ie, a "step-up" approach from less invasive to more invasive treatments). Yamashita et al evaluated 46 patients who underwent salvage liver resection for HCC recurrence following ablation.[62] In this study, the authors compared outcomes of patients who underwent ablation followed by salvage resection with patients who underwent a second liver resection following an index hepatectomy for HCC.[62] Of note, patients who underwent the "step-up" approach had worse DFS and OS than patients who had an initial resection followed by a second liver resection. These data are hard to interpret, however, due to the lack of propensity-score matching and the considerable imbalances in patient baseline and tumor variables, which precluded any robust conclusions. In a separate study, Yamagishi et al examined the efficacy of salvage liver resection using propensity score matching (n=54, ablation followed by salvage resection vs n=54 resection followed by second hepatectomy).[63] While median OS was worse in the salvage liver resection group (4.4 years versus 5.6 years, respectively; p<0.02), median DFS was comparable. In addition, the incidence of complications and mortality were equivalent between the two different treatment modality groups. Despite data suggesting worse survival among patients who underwent salvage hepatectomy, no previous study adequately controlled for all confounders. In turn, further investigation and careful case-control matching is required to elucidate better the role of salvage resection following ablation in the management of recurrent HCC.

Salvage Liver Transplantation

The presence of cirrhosis is a major limiting factor in considering repeat hepatectomy for recurrent HCC. For patients with poor underlying liver reserve, orthotopic liver transplantation (OLT) may be an option to treat recurrent HCC. OLT yields excellent oncologic outcomes in the treatment of primary HCC.[64] However, the scarcity of available organs and the increased logistic requirements limit its applicability in the setting of recurrent HCC. Salvage liver transplantation (SLT) after HCC recurrence following hepatectomy has been demonstrated to provide acceptable outcomes. While no randomized trials exist to compare SLT with repeat resection, a number of observational studies and meta-analyses have demonstrated superior DFS with SLT rather than repeat resection for recurrent HCC.[65] For example, in one meta-analysis, Wang et al analyzed 840 patients across 7 retrospective studies and concluded that SLT was associated with improved 3-year (OR 3.23, 95% CI 1.45–7.20) and 5-year (OR 4.79, 95% CI 1.88–12.2) DFS compared with repeat hepatectomy for recurrent HCC.[66] Nevertheless, no difference in OS was observed between the two groups.[66] In a different meta-analysis, Zheng et al ranked all treatment modalities for recurrent HCC with respect to OS and DFS. Of note, SLT was associated with significantly better DFS compared with all other treatment modalities including repeat hepatectomy, stereotactic beam radio-therapy (SBRT), ablation, and TACE; yet, no significant differences in OS were noted between SLT and repeat hepatectomy for recurrent HCC.[67] In contrast, other studies have noted better OS following SLT versus resection for recurrent HCC, especially among patients matched with respect to MELD score.[68,69] While no official guidelines currently exist to recommend SLT in the setting of recurrent HCC, a number of institutions currently apply the Milan or UCSF criteria to identify candidates for SLT. Given the scarcity of available organs, repeat resection remains the mainstay of treatment for patients with resectable HCC recurrence and adequate liver function, while SLT is largely reserved for individuals who develop cirrhosis following hepatectomy for primary HCC or have unresectable disease but meet transplantation criteria.

Systemic and Combination Therapies

Advanced recurrent HCC usually refers to lesions that are not amenable to curative-intent treatments either due to tumor multicentricity, tumor size, presence of extrahepatic disease, vascular invasion, or poor performance status. When recurrent disease is not amenable to locoregional treatments, systemic therapy should be considered.[70] Although there are increasing

data on the effectiveness of various systemic therapies in primary advanced HCC, data focusing on advanced recurrent HCC are limited. Based on the recent data from the IMbrave150 clinical trial, the combination of atezolizumab with bevacizumab was demonstrated to be superior to sorafenib among patients with advanced HCC and, thus, is currently considered first-line treatment for this patient group based on the latest Barcelona Clinic Liver Cancer (BCLC) guidelines.[71] Given the recent update in the BCLC guidelines, there are currently no official recommendations as to what should represent the second-line treatment following atezolizumab-bevacizumab. Second-line treatment for individuals with advanced-stage HCC who failed to respond and/or progressed on sorafenib include regorafenib (for individuals tolerant to sorafenib), cabozantinib (irrespective of tolerance to sorafenib), or ramucirumab (if AFP levels are >400 ng/dL, irrespective of tolerance to sorafenib).[72] Although these recommendations largely apply to patients with primary HCC, the BCLC guidelines can be extrapolated and utilized as treatment guide for individuals with recurrent HCC. In addition, several new-generation molecular inhibitors that target MET, VEGFR, FGF, and AXL tyrosine kinases are now being tested, yet have not proved better than best supportive care.[73–75] Despite the ongoing research in the field of targeted therapies, none of the newer agents has been officially recommended in the setting of recurrent HCC either as stand-alone or as adjunct treatment modality.

Other investigators have examined the combination of systemic therapies with ablation and/or TACE in the setting of advanced recurrent HCC. In one study, Peng et al retrospectively evaluated the efficacy of combined ablation, TACE, and sorafenib therapy versus sorafenib alone among 207 patients with advanced recurrent HCC.[76] Patients with extrahepatic recurrence and right or left portal vein invasion were mainly included in the analysis, which demonstrated a prolonged median OS (14 vs 9 months, $p<0.001$) and time to disease progression (7.0 vs 4.0 months, $p<0.001$) with trimodality treatment compared with sorafenib monotherapy. In addition, Jiang et al performed a meta-analysis of 21 studies.[77] This report demonstrated that bimodality with ablation and TACE treatment was associated with better survival outcomes than any either modality alone. Of note, however, the addition of TACE to RFA for lesions less than 3 cm did not seem to provide any additive benefit.

Conclusion

HCC is an aggressive disease with more than one-half of patients developing recurrence despite stage-appropriate treatment. A multitude of risk factors for recurrence following curative-intent treatment of primary HCC have been identified in the literature, most of which relate to the size, number of primary lesions, presence of lymphovascular invasion, as well as the presence of underlying liver cirrhosis. Irrespective of adverse characteristics of disease and type of primary treatment employed, close surveillance in the postoperative period is of paramount importance especially during the first two years following curative-intent treatment. More than half of patients will develop a recurrence and will require re-evaluation of disease status given that a second curative-intent treatment holds the best chance for disease control and long-term survival. Careful staging of recurrent HCC patients is important and should take into account the characteristics of the tumor itself (ie, number of lesions and size), as well as patient performance status and underlying liver function at the time of recurrence. Current data suggest that a size cut-off of 3 cm could be applied to characterize very early recurrent HCC that could potentially be managed by less invasive modalities such as ablation, while the Milan criteria remain relevant in the recurrent setting pertaining to the selection of candidates for SLT. Multimodal treatment for recurrent HCC appears to provide a benefit to assess oncologic outcomes. As researchers continue to share their experiences regarding the treatment and outcomes of patients with recurrent HCC, well-designed prospective studies with appropriate patient matching will undoubtedly bring more insight regarding which criteria can be used to further optimize treatment decision-making at the time of HCC recurrence.

Disclosure

The authors report no conflicts of interest in this work.

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