



Management of recurrent hepatocellular carcinoma after resection

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Introduction

Hepatocellular carcinoma (HCC) is currently the fifth most common cancer globally, accounting for the third highest cancer-related deaths (1). Liver resection is the treatment modality of choice for resectable HCCs with adequate liver function in the absence of portal hypertension (1), but actuarial recurrence rates remain as high as 70% at 5 years post-resection (2). The recurrence of HCC post-resection portends poorer prognosis, with a 24% reduction in 5-year survival (2). While there have been a multitude of guidelines for the management of primary HCC across the world (3), the international expert consensus recently published by Wen *et al.* represents the first systematic, evidence-based consensus guidelines for the management of recurrent HCC (RHCC) following liver resection (4).

Unique considerations in RHCC

There are a few key considerations in the management of RHCC which sets it apart from managing primary HCC. Firstly, the disease biology of RHCC usually represents a subset of HCC with a higher proportion of aggressive behavior, evidenced by the poorer prognosis which RHCC carries (2). Amongst RHCC, there are two described mechanisms of recurrence with distinct clinicopathologic characteristics—intrahepatic metastasis (IM) and multicentric occurrence (MO) (5,6). Recurrences due to IM are thought to originate from the primary HCC, tend to be similarly or less differentiated than the primary HCC, and usually recur earlier (within one year) following resection. Recurrences due to MO occur *de novo*, tend to

be better differentiated, and usually recur later (more than one year) following resection. A meta-analysis of seven studies comprising 704 patients examining the comparative prognosis of IM and MO RHCC concluded that MO was associated with significantly better overall (HR =0.495, 95% CI: 0.378 to 0.648, P<0.001) and disease-free survival (HR =0.774, 95% CI: 0.663 to 0.903, P=0.001) (6). Additionally, following repeat liver resection for RHCC, further recurrences are significantly lower for MO (7).

Secondly, the future liver remnant (FLR) is invariably smaller when contemplating resection as a treatment modality for RHCC as compared to the primary HCC. While several retrospective cohort studies have demonstrated the safety and efficacy of repeat hepatectomies for RHCC (8,9), there remains inherent selection bias in examining these outcomes in patients who have been pre-selected to undergo repeat liver resection. The comparative proportion of patients with primary HCC and RHCC who have tumours amenable to liver resection remains unclear.

Thirdly, the underlying liver function is likely to be poorer in RHCC as compared to primary HCC. This is because liver cirrhosis is a major risk factor for MO of RHCC. This could also in part be due to the natural progression of the underlying chronic liver disease, as RHCC tend to occur later in terms of temporality. Additionally, a proportion of patients with RHCC may have experienced post-hepatectomy liver failure following previous liver resection, which can result in enduring impairments to underlying liver function, and has been associated with poorer long-term overall and disease-free survival (10,11).

Implications of RHCC on Management

The general management principles of RHCC as proposed by Wen *et al.* in their consensus guidelines largely mirror that of primary HCC, taking into account the baseline functional status, underlying liver function (Child-Pugh class), tumour characteristics (presence of extrahepatic disease, tumour number and tumour size) and treatment-specific considerations (e.g., FLR for liver resection, proximity to major biliovascular structures for locoregional interventions) (1,4).

The various treatment modalities for HCC including liver resection, liver transplantation and locoregional interventions [e.g., transarterial chemoembolization (TACE), radiofrequency ablation (RFA)] apply similarly to RHCC. Repeat liver resection for RHCC remains a widely adopted treatment option especially in the East for resectable lesions with adequate underlying liver function, and has been reported to achieve long-term survival benefit (8,9), superior to TACE (12). Salvage liver transplantation is the treatment of choice when treating RHCC especially following prior liver resection. It offers long-term survival benefit comparable to primary liver transplantation (13,14). Additionally, when compared to repeated liver resection and locoregional treatments for RHCC, it offers superior long-term outcomes (15,16). The main limitation to the wider use of liver transplant for recurrent HCC is organ scarcity. This is reflected in its role as an alternative treatment option for Child-Pugh class A and B patients, and as the only curative option for Child-Pugh class C patients in the consensus guidelines by Wen *et al.* (4). However, it is important to emphasize that in most instances, salvage liver transplant would likely provide the best long-term prognosis for patients with early-stage RHCC. Hence, this option should always be made known to the patient including the possibility of living donor transplantation.

In terms of locoregional interventions, RFA has been well-established as a curative option for individual early HCC lesions less than 2–3 cm in size, in both the primary and RHCC settings, while TACE is primarily used as bridging and/or palliative treatment of larger lesions not amenable to curative options (1,4). Additionally, combination therapy of RFA and TACE has been shown to be superior to either modality used in isolation when treating RHCC (17).

In recognition of the important role disease biology plays in treatment outcomes, Wen *et al.* highlighted the

presence of ‘recurrent high risks’ as a dichotomizing tool to recommend upfront liver resection as opposed to locoregional interventions for RHCC (4). In the presence of high-risk features, which includes a short interval (less than 1 year) between primary resection and RHCC, the guidelines recommend upfront locoregional interventions as a therapeutic trial, with patients who respond favorably then considered for repeat liver resection. This approach helps patients with poor disease biology who progress on locoregional interventions avoid the morbidity of a repeat resection which may not have yielded them significant long-term survival benefit (5–7,18). It is also important to emphasize that although consideration for the use of adjuvant treatment to reduce recurrence in high risk patients after liver resection was proposed in the guidelines, there is lack of robust evidence in the literature supporting this recommendation and it is not known to date if the use of adjuvant treatment would improve patient survival.

Future directions

While the treatment principles of RHCC largely mirrors that of primary HCC, the poorer disease biology and morbidity associated with repeated interventions necessitate a prudent approach towards managing RHCC. More data is needed to establish robust prediction models for outcomes following various treatment options for RHCC, so as to improve patient selection when contemplating surgical options, and to improve organ allocation when contemplating salvage liver transplantation.

Additionally, anatomical alterations in RHCC as a result of post-operative adhesions and post-resection liver hypertrophy can potentially complicate repeat liver resection, especially when minimally invasive approaches are adopted. Existing literature on the comparative outcomes of open versus laparoscopic repeat liver resection for RHCC suggest comparable perioperative outcomes, with mixed data on differences in operative time and long-term survival outcomes (19,20). Extrapolating from the findings of the first randomized controlled trial comparing laparoscopic and open liver resection, the laparoscopic approach potentially offers a lower postoperative morbidity profile (21). Whether this applies to in the treatment of RHCC remains to be confirmed by a prospective trial.

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