

Review

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Treatment options for recurrence of hepatocellular carcinoma after surgical resection: review of the literature and current recommendations for management

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Abstract

The recurrence rate after primary resection for hepatocellular carcinoma (HCC) has been reported to be up to 80%. There is no consensus or guideline about the best treatment option for such recurrent HCC (rHCC). It is therefore of paramount importance to select patients for suitable treatment due to the high risk of associated morbidity and mortality. In this paper, we review the literature on treatment for rHCC and propose a strategy based on the best evidence available. Even in rHCC, it is still possible to achieve cure and good survival rates through careful patient selection. Repeat hepatectomy is recognized as a feasible and safe procedure even in cirrhotic patients and should be considered as the best option with curative intent when the patient is fit enough. Greater adoption of minimally-invasive liver surgery could have the potential to increase the number of candidate patients with rHCC for repeat resection in the next few years. Liver transplantation offers longer disease-free survival compared to repeat resection, curing the underlying cirrhosis, but is not widely available due to organ shortage. When surgery is not feasible, locoregional treatments such as radiofrequency ablation and transarterial chemoembolization have an important role for patients who cannot tolerate repeat hepatectomy and are not suitable for transplantation. For advanced cases, systemic therapy could be considered.

Keywords: Recurrence, hepatocellular carcinoma, hepatic resection, second resection



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INTRODUCTION

Hepatocellular carcinoma (HCC) is the third most common cause of cancer related death worldwide^[1] and its incidence in Western countries has increased by 75% in the last three decades^[2]. Liver resection represents first-line treatment in patients with early tumors and preserved liver function, with a 5-year overall survival ranging from 60% to 80%. Nonetheless, HCC frequently arises from chronic liver disease and the recurrence rate in the remnant liver, even after R0 resection, has been reported to be up to 80%^[3]. Although guidelines from European, American and Eastern societies recommend hepatic resection as first-line treatment with curative intent for primary HCC^[3-5], none exist for recurrent liver cancers. Liver transplantation, in the case of recurrent HCC (rHCC), would offer the best chance at disease-free survival, by treating both the cancer and the underlying cirrhosis at the same time, but the scarcity of deceased organs limits its application. Furthermore, surgical treatment may not always be feasible and non-surgical options should then be considered.

To date, many papers have been published on the treatment algorithm for rHCC but evidence and consensus are still lacking. These studies are mainly from Eastern centers and almost all are retrospective data.

In this paper, we reviewed the literature on treatment for rHCC and propose our personal strategy based on the available evidence.

TREATMENT OPTIONS FOR RECURRENT HCC

Repeat hepatectomy

Liver resection is recognized as the mainstay of treatment in patients with HCC. In both Eastern and Western countries^[6], it is the first choice option in non-cirrhotic patients who can tolerate resections with low morbidity and mortality^[7,8]. On the other hand, HCC resection in cirrhotic livers requires careful patient selection and adequate surgical skills. Patient selection relies mainly on the preoperative assessment of reserve liver function and portal hypertension. Traditionally, liver function is evaluated through standard liver biochemical tests integrated into several scores such as the Child-Pugh or MELD score^[9], but nowadays, more sophisticated quantitative liver function tests such as indocyanine green retention (ICG) test^[10,11] or hepatobiliary scintigraphy^[12,13], are used in predicting post-hepatectomy liver failure. The presence of clinically relevant portal hypertension can be ruled out by measuring the hepatic vein pressure gradient, or indirectly by liver stiffness, to decrease the risk of postoperative decompensation^[14-16].

According to the BCLC algorithm, patients with a single, very early- or early-stage HCC and preserved liver function should be offered liver resection^[4]. While international guidelines tend to reserve resection for patients harboring early stage HCC, expert institutions have shown good outcomes even in patients with multinodular, large, and macrovascular, invasive HCC^[17], thus justifying expansion of HCC resectability criteria. However, even after potentially curative resections with negative margins, early recurrence accounts for more than 70% of rHCC and occurs within 2 years in 30%-50% of patients. The recurrence rate at 5 years has been reported to range from 50% to 70%^[18-20]. The key parameters related to recurrence include tumour size, multinodular tumours, serum alpha-fetoprotein and microvascular invasion^[21].

Currently, there are no guidelines or clinical algorithms for the best treatment option in rHCC^[22,23] except for expert opinion and local policies. Many authors agree with re-resection as the best therapeutic option for rHCC, when feasible. Improvement in surgical technique and implementation of the use of energy devices have led to a lower incidence of complications. Liver resections are therefore safer in patients with previous resection. Concern still exists however and is mainly related to poor remnant liver function and adhesions caused by previous surgery that could lead to iatrogenic injuries. Many studies have addressed

this topic, showing that repeat hepatectomy (RH) can be performed safely with complication rates comparable to the first resection^[24]. Another issue is the risk of further recurrence, which is dependent on the presence of multinodular cirrhosis in the remnant liver^[25,26].

Most case series of rHCC treated with RH are from Eastern Asia. Since none were randomized trials and patients were selected for resection according to different clinical criteria and hospital policies, comparison is difficult. Nagasue *et al.*^[27] first reported a small series of RH carried out in 9 of 31 patients who experienced tumor recurrence after initial resection of primary HCC. They reported that the survival rate of resected patients was significantly better than that of patients treated with palliative methods. Hu *et al.*^[28] described a retrospective analysis of 59 patients who were treated with RH. 43 had a second recurrence (median follow up 19 months) and survival at three years was 44%. Another paper from the same institution^[29] compared RH to TACE for rHCC and advocated for aggressive surgical treatment after recurrence in selected patients.

Larger series have since been published in the last 20 years, again mainly from Eastern institutions, with 5-year overall survival (OS) ranging from 30% to 60%^[30-33]. In 2011, Roayaie *et al.*^[34] presented the first and largest Western series of RH ($n = 35$), showing an overall 5-year survival rate of 67%. Only patients with a single recurrent tumor on imaging, Child's A liver disease and a platelet count $> 100,000/\text{L}$ underwent RH.

Several studies have been published in recent years and have established RH as safe in referral centers [Table 1]. The largest Eastern series by Zou *et al.*^[35] reported 635 consecutive patients who received a second resection for rHCC. The median OS was 54.8 months and the 1-, 3-, and 5-year OS rates were 96.9%, 74.8%, and 47.8%, respectively. Post-recurrence survival (i.e., calculated from the date of reoperation) rates were 75.8%, 45.7% and 37.6%, respectively. In this large, single institution series, a perioperative complication rate of 22.8% was reported with a median blood loss of 303 mL (range 100-5300). With regard to postoperative complications, a systematic review by Chan *et al.*^[36] reported a median mortality rate of 0% (ranging from 0% to 6%) and a postoperative bleeding rate (with need for transfusions) of 1%. Other postoperative complications (ascites, bile leak, liver failure) were in line with those reported in the literature for patients without preoperative liver surgery.

ROLE OF MINIMALLY-INVASIVE SURGERY

The adoption of laparoscopic liver resection (LLR) has increased over the past decade. Laparoscopy for HCC has been shown in studies to produce superior short-term and equivalent long-term outcomes compared to the open approach. However, due to the formation of intra-abdominal adhesions, LLR for rHCC after previous hepatic resection may represent a challenge. For this reason, there are only a few studies reporting a laparoscopic approach to treat liver recurrence. However, this number is believed to rise in the next few years since liver resection will increasingly be approached laparoscopically. A recent meta-analysis showed that LLR for rHCC offered a benefit in terms of lower in-hospital complication rates, blood loss and a shorter hospital stay compared to open resection, although similar 90-day mortality was observed between the two groups^[45]. This could be partially explained by the fact that, unlike conventional laparotomy, the laparoscopic approach does not require a wide surgical field, thus minimizing the freeing of adhesions and consequently, bleeding as well as other intraoperative complications. Even the scoring system for predicting complications in LLR proposed by Halls *et al.*^[46] showed that a previous open liver resection was the strongest among all independent risk factors (β coefficient = 1.401) of having high blood loss or conversion to an open approach during surgery. This finding should prompt us to at least consider more patients for minimally-invasive surgery at the time of primary resection so as to increase the number of eligible patients who may benefit from a RH in the event of rHCC. LLR has been also demonstrated to facilitate liver transplantation (LT) in terms of decreasing blood loss and transfusion requirements.

Table 1. Review of the literature on the surgical treatment of recurrent hepatocellular carcinoma

Ref.	Year	No of pts	Mortality (%)	5-year OS (%)
Zou <i>et al.</i> ^[35]	2016	635	7	47
Huang <i>et al.</i> ^[37]	2012	85	1	22
Faber <i>et al.</i> ^[38]	2011	27	0	42
Roayaie <i>et al.</i> ^[34]	2011	35	0	67
Kubo <i>et al.</i> ^[39]	2008	51	0	48
Itamoto <i>et al.</i> ^[40]	2007	84	0	50
Tralhão <i>et al.</i> ^[41]	2007	16	1	31
Kobayashi <i>et al.</i> ^[42]	2006	80	0	53
Sun <i>et al.</i> ^[31]	2005	57	0	31
Minagawa <i>et al.</i> ^[33]	2003	67	0	56
Sugimachi <i>et al.</i> ^[43]	2001	78	0	48
Shimada <i>et al.</i> ^[30]	1998	41	NR	45 (3-y)
Hu <i>et al.</i> ^[44]	1996	59	0	44 (3-y)

OS: overall survival

Nevertheless, we acknowledge that this important aspect surely requires further dedicated study and every effort should be made to minimize blood loss and the associated transfusion requirements to improve outcomes in both liver surgery and LT.

Liver transplantation (salvage)

Many transplant centres recommend LT as salvage for rHCC. Salvage LT (SLT) was proposed as an ideal treatment for patients fulfilling the Milan criteria, treating both the cancer and the underlying cirrhosis at the same time^[47]. However, many authors have questioned whether RH could be performed instead of LT. A recent meta-analysis^[48] comparing SLT with RH showed that SLT was inferior to RH with regard to operative and postoperative short-term results, but had better results in terms of overall- and disease-free survival. In fact, in SLT, a more complex operation has to be accounted for, especially in patients who are thought to have more advanced liver cirrhosis. A recent study by Lim *et al.*^[49] showed, in particular, that 90-day mortality was significantly higher in the SLT group compared to the RH group. The negative impact of resection on subsequent LT was also demonstrated in other studies comparing SLT and primary liver transplantation (PLT). Adam *et al.*^[50] first showed that LT after prior liver resection was associated with higher operative mortality and risk of intraoperative bleeding than PLT. Similarly, a recent meta-analysis has demonstrated a significantly higher rate of postoperative bleeding and operative mortality in the SLT group. However, despite the higher perioperative risk, SLT may still achieve better disease-free survival (DFS) rates compared to RH. This has to be expected, given that resection of existing distant micrometastases and removal of the underlying liver disease may prevent de novo HCC development in the remnant liver. A recent meta-analysis^[51] comparing SLT to curative locoregional treatments among seven retrospective studies showed better outcomes with SLT. In particular, SLT was associated with higher 5-year OS and DFS; when compared to RH alone, subgroup analysis still indicated a significantly higher 3- and 5-year DFS for the SLT group. Nevertheless, the authors stated that the feasibility of SLT is impaired due to donor organ shortage.

The decision to proceed with either strategy is clearly biased by institutional practices and for this reason, any comparison between SLT and RH may not be completely reliable. However, it is our opinion that patients should be listed for LT in case of worsening liver function, or any other case such that a second liver resection will not be tolerated. When feasible, any attempt to rescue these patients without affecting the donor pool should be made^[52].

Locoregional treatments

Radiofrequency ablation (RFA), applicable both via the percutaneous or open approach, is considered a safe procedure and as effective in achieving long-term survival as surgical resection, in selected patients^[53].

In particular, RFA is proposed for small primary HCC up to 3 cm in diameter^[54,55]. However, some authors have also proposed RFA for rHCC because of its low morbidity compared to surgical treatments, negligible blood loss and sparing of adjacent normal liver parenchyma^[56]. Furthermore, in patients not amenable to surgical resection due to liver dysfunction, multifocal nodules, tumour location or postsurgical adhesions, RFA represents a potentially curative alternative. In a recent meta-analysis, Gavriilidis *et al.*^[57] demonstrated similar 5-year OS and DFS between RFA and RH in treating rHCC although a significant difference in morbidity was reported (2% for RFA vs. 17% for RH). However, a systematic review of 18 previous studies published by Thomasset *et al.*^[58] concluded that RFA for rHCC had a very low rate of complications but was still less efficacious than RH and thus, should be offered only to patients who cannot tolerate surgical resection.

A further treatment option for rHCC is trans-arterial chemoembolization (TACE), although it is not applied with curative intent^[26,59]. A median survival of 30 months and a 3-year survival of 29% has been reported in the treatment of primary HCC with TACE^[60,61]; outcomes reported for rHCC are arguably poorer^[26]. This interventional radiology procedure should be offered to patients who are not candidates for surgical resection, SLT or RFA. Although a recent study reported TACE to be superior to RH and RFA in cases of microvascular involvement^[62], the majority of the literature consider TACE to be palliative^[63] so it is widely used as a treatment for tumours with greater sizes or number of nodules which cannot be treated with RH or RFA. A review from Erridge *et al.*^[64] reported a 5 year survival of 15.5% in patients with rHCC treated with TACE.

Systemic therapies

When recurrence presents beyond the limits of transplantation criteria and is not amenable to locoregional treatment, survival rates are dismal but systemic therapies can still be considered in selected cases. Effective systemic treatment for HCC have been available only in recent years - since sorafenib was introduced, it has become the standard of treatment for advanced HCC^[4,65]. Several compounds have since been tested in this setting but few have proven to be effective: regorafenib was approved as a second-line treatment for patients with HCC disease progression on sorafenib^[66] and levatinib recently showed non-inferiority as first-line therapy^[67]. Since good cardiovascular status and preserved liver function are both necessary for chemotherapy to be tolerated, most reports are on the use of sorafenib in patients with rHCC after LT^[67], given the poor results obtained in the adjuvant setting after resection^[68]. On the contrary, when no clinical benefit is expected from chemotherapy, the management of end-stage rHCC is symptomatic and only supportive care should be offered^[68].

SUMMARY

Herein, we propose our recommendations for selecting the best candidate, and limiting the risk of recurrence in cases of rHCC, based on the above literature review, available guidelines on primary HCC and our personal experiences.

RH

Patients presenting with a single rHCC should undergo repeat resection whenever possible. Candidates for RH are required to have preserved liver function and no or limited signs of portal hypertension. The laparoscopic approach should be considered for RH in rHCC when the requisite expertise is available.

RFA

Patients with preserved liver function and a single rHCC ≤ 3 cm can be considered for RFA. RFA should be preferred over RH, especially in cases of patients with high surgical risk.

TACE

Patients with deteriorated liver function can be treated with TACE. Patients planned for LT should also be considered for TACE as bridging.

SLT

Patients with decompensated liver function, severe portal hypertension and single or even multiple liver recurrences, but still fulfilling LT criteria, may be referred for SLT.

Systemic therapies

In the setting of rHCC not amenable to other treatments due to disease that is far too advanced, systemic therapies can be employed in selected cases.

CONCLUSION

Recurrent HCC may occur after liver resection in up to 80% of cases. A standardized treatment algorithm for rHCC does not exist but surgical resection should be attempted whenever possible, since it may provide favourable long-term outcomes with acceptable perioperative risk comparable to primary resection. In experienced hands, laparoscopic liver resection for both primary and recurrent HCC should be considered. LT should be considered in all cases where surgical resection cannot be performed, especially in the context of underlying cirrhosis, if conventional transplantation criteria are met. The use of RFA or TACE as a bridge to LT, or for palliation represent alternatives for these patients.

DECLARATIONS

Authors' contributions

Made substantial contributions to conception of the paper, reviewed the literature and drafted the manuscript; equally contributed to the work: Pasini F, Serenari M
Supervised the work, reviewed the manuscript, provided technical support and expert guidance: Cucchetti A, Ercolani G

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All authors declared that there are no conflicts of interest.

Ethical approval and consent to participate

Not applicable.

Consent for publication

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