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MINIREVIEWS

Management of recurrent hepatocellular carcinoma after liver transplant

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Abstract

Hepatocellular carcinoma (HCC) is the leading cause of deaths in patients with hepatitis B or C, and its incidence has increased considerably over the past decade and is still on the rise. Liver transplantation (LT) provides the best chance of cure for patients with HCC and liver cirrhosis. With the implementation of the MELD exception system for patients with HCC waitlisted for LT, the number of recipients of LT is increasing, so is the number of patients who have recurrence of HCC after LT. Treatments for intrahepatic recurrence after transplantation and after other kinds of surgery are more or less the same, but long-term cure of posttransplant recurrence is rarely seen as it is a "systemic" disease. Nonetheless, surgical resection has been shown to be effective in prolonging patient survival despite the technical difficulty in resecting graft livers. Besides surgical resection, different kinds of treatment are also in use, including transarterial chemoembolization, radiofrequency ablation, high-intensity focused ultrasound ablation, and stereotactic body radiation therapy. Targeted therapy and modulation of immunosuppressants are also adopted to treat the deadly disease.

Key words: Hepatocellular carcinoma; Recurrence; Transarterial chemoembolization; Liver transplantation; Targeted therapy; Resection; Radiofrequency ablation; Transarterial radioembolization; Immunosuppression; Stereotactic body radiation therapy

Core tip: The management of recurrent hepatocellular carcinoma (HCC) after liver transplantation (LT) seems to be a losing battle. Nonetheless, tremendous efforts have been made to combat this deadly disease. Intrahepatic recurrence may be treated by resection, which has some survival benefits as shown by small clinical trials. Other kinds of therapy including high-intensity focused ultrasound (HIFU) ablation, radiofrequency ablation (RFA) and transarterial chemoembolization (TACE) are also in use. HIFU ablation has been shown to produce better results when compared with RFA and TACE. The efficacy of systemic and targeted therapies for multiple recurrences is under investigation. Early results have suggested that the combination of sorafenib with mammalian target of rapamycin inhibitors may be useful for treating recurrent HCC after LT.

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INTRODUCTION

Hepatocellular carcinoma (HCC) is the fifth most common malignant tumor, the third leading cause of cancer-related deaths, and the first leading cause of deaths in patients with hepatitis B or C, and its incidence has increased considerably over the past decade and is still on the rise[1-3]. There are different modalities for treating HCC and underlying liver cirrhosis, but liver transplantation (LT) is the ultimate solution[4]. Various patient selection criteria for LT have been introduced with the hope that as many patients as possible can benefit from the treatment while patient survival is not compromised. Mazzaferro *et al*[5] introduced the Milan criteria (solitary tumor ⩽ 5 cm, or ⩽ 3 tumors with each measuring < 3 cm) on the basis of a retrospective study of 48 patients who received LT for HCC. In the study, a 75% overall survival and an 83% recurrence-free survival were achieved in LT recipients chosen according to the Milan criteria at 4 years after transplantation. A set of modestly expanded criteria was developed by the University of California, San Francisco (UCSF). Yao *et al*[6] showed that HCC patients selected for LT according to the UCSF criteria (solitary tumor ⩽ 6.5 cm, or ⩽ 3 nodules with the largest lesion ⩽ 4.5 cm and a total tumor diameter ⩽ 8 cm) had survival rates of 90% and 75.2% at 1 year and 5 years respectively. However, discrepancy between radiological results and pathological results of tumor characteristics is not uncommon. A 30%-50% discrepancy rate has been reported[6,7].

In Hong Kong, about 8% of the population are carriers of hepatitis B virus (HBV) and most of the cases of HCC are caused by HBV. A survey found that about 10.4% of male adults and 7.7% of female adults were positive of hepatitis B surface antigen (surveillance of viral hepatitis in Hong Kong - 2010 update report. Hong Kong SAR: Department of Health, 2011). On the other hand, the numbers of carriers of hepatitis C virus (HCV) are rising in Japan and the United States. In these places where hepatitis C is epidemic, there is a surge of HCV-related liver cirrhosis and HCC[8,9].

Even though HCC patients are selected for LT according to standard criteria, 10%-60% of them will have disease recurrence. Some of them will develop recurrence 2 years or even 5 years after transplantation[10]. With the adoption of the MELD exception system for HCC patients waitlisted for LT, more LTs are performed for HCC. Hong Kong adopted the system in 2009[11], and nowadays HCC accounts for one third of LTs in Hong Kong. As a corollary, the incidence of HCC recurrence after LT is on the increase in places where the system is adopted. Recurrence of HCC after LT is notoriously difficult to manage. Here is a review of the treatment options available for this challenging situation, trying to shed some light on its management.

RISK FACTORS FOR HCC RECURRENCE

Post-LT HCC recurrence occurs at a rate of 13%-27%[10,12]. It was reported that 5% of patients developed late (after 5 years) recurrence[10]. Most patient selection criteria for LT, including the Milan and the UCSF criteria, use tumor size and tumor number as surrogate markers. A meta-analysis by Sotiropoulos *et al*[13] identified a number of risk factors for poorer patient survival after LT, which were venous invasion, poor tumor cell differentiation, tumor size and stage beyond the Milan criteria, and a high pretransplant serum α-fetoprotein level. Since radiological results and pathological results of tumor characteristics may differ, some centers use pretransplant serum α-fetoprotein level and biopsy to determine tumor cell differentiation and use it as a biological surrogate marker in patient selection criteria[14,15]. However, preoperative biopsy may cause tumor seeding and bleeding. Saborido *et al*[16] reported that a significantly higher chance of HCC recurrence came with fine-needle aspiration biopsy before LT (31.8% *vs* 5.9%, $P = 0.003$). In Hong Kong, contrast computed tomography (CT)[17] is used for tumor staging. Sometimes positron emission tomography (PET) using both radiotracers of ^{11}C-acetate and ^{18}F-FDG is also employed. In a report, dual-tracer PET had an overall sensitivity of 96.8% and an overall specificity of 91.7%, which are significantly higher than those of contrast CT (41.9% and 33.0% respectively; $P < 0.05$ in both cases)[18]. It was found that sources of error for contrast CT were related to liver cirrhosis or previous treatment, and there was difficulty in differentiating cirrhotic nodules from HCCs (39%) and in the estimation of tumor size (14%). There was infrequent overstaging of vascular invasion (4.6%) or extrahepatic metastasis (4.6%). Dual-tracer PET and contrast CT had a 4.7% rate of false-negative results. PET using the radiotracer ^{18}F-FDG seems effective in detecting ^{18}F-FDG-avid lesions and thus can be used as an adjunct to detect microvascular invasion[19]. Nonetheless, such use is still at its infancy and more large-scale trials are needed for its validation.

Deceased-donor LT vs living-donor LT

Living-donor LT (LDLT) has the most significant impact in Asia, where the issue of organ shortage is most extreme. The availability of LDLT has provided the driving force for a drastic increase in cases of LT in recent years. The number of LDLTs performed in Asia each year has increased tremendously. In 2005, LDLT accounted for 90% of the 1497 LTs performed in Asia (excluding mainland China)[20]. In Hong Kong, about half of the LTs are LDLTs, and more than half are for HCC.

To justify LDLT for HCC, it should have a survival outcome comparable to that of deceased-donor LT (DDLT). Roayaie *et al*[21] reported a tendency for early tumor recurrence after LDLT (mean: 8.7 mo) when compared with DDLT (mean: 19.6 mo) in a cohort of 311 patients with histologically confirmed HCC after LT. Another multicenter LDLT cohort study (A2ALL) of 106 HCC patients reported a significantly higher 3-year tumor recurrence rate after LDLT (29%) compared with that after DDLT (0%)[22]. In Hong Kong, a retrospective study

has been conducted to compare LDLT and DDLT in terms of treatment outcomes in 60 HCC patients[23]. Given the standard patient selection criteria based on radiological tumor size and number according to the UCSF criteria, there was an obvious selection bias for some important clinical characteristics in the LDLT group. Patients having LDLT for HCC had fewer incidental tumors, a lower rate of preoperative transarterial chemoembolization (TACE), a lower rate of salvage transplantation (with pretransplant resection or ablation), shorter waiting time on list, and a lower graft-weight-to-standard-liver-weight ratio. The inferior oncological outcomes in the LDLT group were possibly caused by more aggressive tumor behavior and small-for-size graft injury and regeneration[24]. Although the overall survival rates were comparable between the LDLT and DDLT groups, the cumulative 5-year HCC recurrence rate was significantly higher in LDLT group (29% *vs* 0%). Thus, selection of patients with early HCC based on standard tumor size and number for LDLT and DDLT may eventually result in different clinical outcomes. When considering a patient for an LDLT, besides a certain set of patient selection criteria, there are more factors to be taken into account, which include the unique nature of a living-donor graft as a dedicated gift to the recipient and potential donor risks, and additional clinical characteristics should also be considered and good preoperative counseling should be given to the donor and patient. In Hong Kong, the policy of "6-mo-wait" before salvage transplantation does not apply to LDLT, since both donors and recipients willingly accept the relatively higher recurrence rate with the realization that LDLT is their only option.

TREATMENTS FOR HCC RECURRENCE

Theoretically, all modalities for treating HCC can be used to treat its recurrence. Aggressive treatments can usually be given to patients who have satisfactory liver function and no widespread tumor cell dissemination. However, HCC recurrence after LT is considered a "systemic disease", and the efficacy of locoregional treatment for a systemic disease is doubtful. For LT recipients, the use of immunosuppressants may hinder wound healing and thus lead to a higher chance of infective complications. Variable vascular anatomy in a graft liver or dense adhesion at the hilum may cause damage to important structures during dissection. Difficulties may be encountered in interventional radiological procedures like TACE when the catheter is negotiating through the arterial anastomosis. The use of targeted agents for post-LT HCC recurrence has not been validated by any large randomized trials and it may have adverse effects on immunocompromised patients. A multidisciplinary approach with the involvement of hepatologists, surgeons, radiologists, oncologists and radiation oncologists is definitely for the best interest of this group of patients.

Liver resection and local ablative therapy for intrahepatic recurrence

Catalano *et al*[25] reported the initial results of graft liver resection for graft ischemic damage in 12 patients. The perioperative mortality rate was high at 66.6%, manifesting the difficulty of graft liver resection in the presence of sepsis. On the other hand, Sommacale *et al*[26] reported that graft liver resection for intrahepatic recurrence achieved a low mortality rate and satisfactory long-term survival with a median follow-up of 92 mo. Nonetheless, there were only 3 patients in the series. According to unpublished data from the only LT center in Hong Kong, in 252 patients who underwent LT for HCC, 35 had disease recurrence. Three patients had only intrahepatic recurrence and underwent aggressive resection. This very small series had a 66.7% 3-year survival and 0% mortality. Actually, all reported series were small and the studies had a retrospective nature with significant selection biases. Hence, more evidence is needed to support graft liver resection as a good treatment for HCC recurrence.

Radiofrequency ablation (RFA), a local ablative treatment, is the established treatment option for resectable and unresectable HCCs. Its efficacy has been shown to be comparable to that of partial liver resection in treating small HCCs[27]. It would be reasonable to extrapolate that RFA can be an option for treating post-LT intrahepatic recurrence of HCC too. A case report showed that percutaneous RFA achieved 2-year disease-free survival in a 65-year-old patient who had a solitary recurrent HCC inside the graft liver[28].

Stereotactic body radiation therapy and intra-arterial infusion of yttrium-90 microspheres for intrahepatic recurrence

Numerous advances in external-beam radiation therapy have allowed more accurate targeting and made aggressive dose-fractionation strategies possible with techniques such as stereotactic body radiation therapy (SBRT). As a kind of radiosurgery, SBRT was originally developed to treat intracranial malignancies. It has since been adopted to treat extracranial diseases. The use of SBRT as treatment of HCC has yet to be established, but it is tested by a number of clinical trials for its efficacy in treating unresectable and unablatable HCCs. Initial results showed that it achieved a local control rate of 87%-100%[17,29-31].

Intra-arterial infusion of yttrium-90 microspheres (Y-90 SIR) is an established treatment for unresectable HCCs[32] and has gained popularity in recent years. It is often used to treat advanced HCC, especially in patients with a large tumor burden, suboptimal performance status, or lobar portal vein thrombosis[33]. Chan *et al*[34] reported that in the treatment of primary HCC, it achieved a 38%-65% partial response rate and a median survival duration of 23 mo, which is 2.6-4.7 times the duration seen in historic controls. In a recent study of 20 patients with unresectable HCCs, it achieved

an overall survival rate of 90% at a median follow-up period of 275 d (range: 32-677 d)[33]. However, the data on the use of SBRT and intra-arterial infusion of Y-90 SIR for recurrent HCC after LT are extremely scarce. In the only two case reports, complete tumor necrosis was observed in a 52-year-old and a 42-year-old patient with solitary intrahepatic recurrence of HCC after a course of SBRT and intra-arterial infusion of Y-90 SIR respectively[35,36].

TACE for intrahepatic recurrence

TACE is often used as a bridging therapy for waitlisted patients and its results are satisfactory. Lo *et al*[37] reported that it resulted in marked tumor response, and the actuarial survival was significantly better in the TACE group (1 year: 57%, 2 years: 31%, 3 years: 26%) compared with the control group (1 year: 32%, 2 years: 11%, 3 years: 3%, $P = 0.002$). When adjustments for baseline variables that were prognostic on univariate analysis were made with a multivariate Cox model, the survival benefit of TACE remained significant (relative risk of death: 0.49; 95%CI: 0.29-0.81; $P = 0.006$).

Chok *et al*[38] compared TACE and RFA for unresectable HCCs and found that they were comparable in terms of time to disease progression ($P = 0.95$) and overall survival ($P = 0.02$).

Successful outcomes of TACE therapy (with and without the use of iodized oil) for the treatment of recurrent intrahepatic HCC after LT have been reported[39,40] although the studies were small and retrospective in nature. As said before, the transcatheter procedure can be technically demanding in the presence of distorted vasculature in a post-LT setting.

New therapy for intrahepatic recurrence

High-intensity focused ultrasound (HIFU) ablation is a relatively new totally extracorporeal treatment for unresectable HCCs. Ng *et al*[41] in their initial research reported that it achieved a primary effective treatment rate of 79.5% and 1-year and 3-year overall survival rates of 87.7% and 62.4% respectively.

Cheung *et al*[42] compared HIFU ablation with TACE and reported that HIFU ablation achieved rates of complete tumor response, partial tumor response, stable disease and progressive disease (in accordance with the modified Response Evaluation Criteria in Solid Tumors) of 50%, 7.7%, 25.6% and 7.7% respectively. As with TACE, the corresponding rates were 0%, 21.2%, 63.5% and 15.4% respectively ($P < 0.0001$). The 1-year, 3-year and 5-year survival rates achieved by HIFU ablation were 84.6%, 49.2% and 32.3% respectively, and those by TACE were 69.2%, 29.8% and 2.3% respectively ($P = 0.001$).

Chan *et al*[43] compared HIFU ablation with RFA in terms of survival. The two kinds of ablative treatment produced similar results. The 1-year, 2-year, and 3-year disease-free survival rates were 37.0%, 25.9% and 18.5% respectively in the HIFU group, and 48.6%, 32.1% and 26.5% respectively in the RFA group ($P = 0.61$). The 1-year, 2-year, and 3-year overall survival rates were 96.3%, 81.5% and 69.8% respectively in the former, and 92.1%, 76.1% and 64.2% respectively in the latter ($P = 0.19$).

In the pilot study on HIFU ablation as a bridging therapy for HCC patients waitlisted for LT conducted at the only LT center in Hong Kong, it was found that with the availability of HIFU ablation, the rate of receiving bridging therapy increased dramatically from 39.2% to 80.4%. HIFU ablation and TACE achieved similar percentages of tumor necrosis as seen in excised livers ($P = 0.353$), and both treatments resulted in significantly higher necrosis rates than that in the best medical treatment group ($P = 0.010$ and 0.020)[44]. As HIFU ablation has been shown to be a useful bridging therapy, it should have great potential in the management of recurrent HCC after LT.

Treatment for multiple recurrence

Mammalian target of rapamycin (mTOR) inhibitors have been shown to have a direct antitumorigenic effect and to be able to inhibit cell growth[45-47]. In experimental models of HCC, the mTOR pathway was aberrantly activated in up to half of the cases. Although the currently available data came from retrospective studies and are premature, there is the hope that mTOR-based immunosuppressive therapy after LT will one day come into use[48]. The use of sorafenib, an inhibitor of multiple tyrosine kinases (including c-Raf and b-Raf), has been approved as a first-line treatment for advanced HCC[49]. Activation of the Ras/mitogen-activated protein kinase pathway is a common finding in neoplastic processes (including in HCC) and is a determinant for promoting cell proliferation and the survival of tumor cells. This makes sorafenib an interesting drug; its use as a treatment for unresectable HCCs and as an adjuvant treatment before and after HCC recurrence is being investigated[50]. A study from Spain demonstrated that combination therapy resulted in an overall response (in accordance with the Response Evaluation Criteria in Solid Tumors) rate of 3.8% (1/26), and there was sustained stabilization of disease in 13 additional cases (50.0%)[42]. The median overall survival was 19.3 mo (95%CI: 13.4-25.1 mo), and the median time to progression was 6.77 mo (95%CI: 2.3-11.1 mo). Although a few studies have shown that there is some evidence of synergistic anticancer activity, early-phase clinical studies of mTOR inhibitors plus sorafenib for advanced HCC reported ambivalent findings, which were the results of increased toxicity (*e.g.,* hand-foot syndrome) in combination therapy[51,52]. In a recent study from Italy, the outcomes of sorafenib treatment for post-LT HCC recurrence were significantly better than those of best medical care [median patient survival from recurrence: 21.3 mo *vs* 11.8 mo, hazard ratio (HR) = 5.2, $P = 0.0009$; median patient survival from untreatable presentation or progression: 10.6 mo *vs* 2.2 mo, HR = 21.1, $P <$

0.0001]. The only factor associated with survival found by multivariate analysis was treatment with sorafenib (HR = 4.0, P = 0.0325). No severe adverse event was registered[53]. Individualized treatment should be tailor-made for individual recipients, and input from oncologists would be of great value. However, drug toxicity is a major concern as shown in many studies, and their recommendations should not be overlooked.

Use of different immunosuppressants

It has been suggested that immunosuppressive therapy should switch from using non-mTOR inhibitors to using mTOR inhibitors. Another suggestion is that mTOR inhibitors can be used as an add-on. Monaco[54] found that the use of mTOR inhibitors might decrease the incidence of new malignancy after transplantation, mainly skin cancer.

A clinical trial by Alamo *et al*[55] comparing calcineurin inhibitors with everolimus and sirolimus for patients who received LT for oncological disease reported that the HCC recurrence rate was significantly lower and survival significantly prolonged in patients receiving either everolimus or sirolimus. A meta-analysis by Liang *et al*[56] endorsed the safety and efficacy of sirolimus-based immunosuppression for patients who received LT for HCC. Pooled results of the five studies eligible for evaluation showed that sirolimus-based regimens prolonged overall survival (OR = 2.47; 95%CI: 1.72-3.55) and decreased tumor recurrence (OR = 0.42; 95%CI: 0.21-0.83), with no significant differences in acute rejection and hepatic artery thrombosis.

A United States study compared sirolimus-based maintenance therapy with calcineurin inhibitor treatment for recipients of LT for HCC and found that overall survival was better in the sirolimus arm[57]. Clinical trials examining the anticancer effects of mTOR inhibitors in recipients of LT for HCC have shown encouraging results[58]. On multivariate analysis in a large Canadian trial, sirolimus-based maintenance therapy was one of the factors associated with improved survival after LT for HCC (HR = 0.53, 95%CI: 0.31-0.92, $P \leqslant 0.05$)[59].

The reported results of using these relatively new agents has suggested that they may prevent or reduce the incidence of HCC recurrence after LT, but a definite answer from large randomized controlled trials is still lacking.

CONCLUSION

Recurrence of HCC after LT is a deadly disease. Although there are a variety of treatment approaches, long-term cure is rarely seen. One of the reasons is that the disease is "systemic" in most of the cases, even if the recurrence is intrahepatic only. Effective adjuvant or systemic therapy has yet to be identified. A multidisciplinary approach with fine-tuning of treatment goals and objectives will definitely be beneficial, and development of new drugs or modification of current systemic agents is urgently needed.

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