TOPIC HIGHLIGHT

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Hepatectomy for hepatocellular carcinoma in the era of liver transplantation

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Abstract

The aim of management of hepatocellular carcinoma (HCC) is to improve the prognosis of the patients by radical resection and preserve remnant liver function. Although liver transplantation is associated with a lower tumor recurrence rate, this benefit is counteracted by long-term complications. Therefore, hepatectomy could be the first choice of treatment in selected patients with HCC. However, the higher frequency of tumor recurrence and the lower rate of resectability after hepatectomy for HCC led to an unsatisfactory prognosis. New strategies are required to improve the long-term outcome of HCC after hepatectomy. In this paper, we introduce some strategies to increase the low rate of resectability and reduce the high rate of tumor recurrence. Some aggressive treatments for tumor recurrence to extend long-term survival are also involved. We believe that hepatectomy combined with other therapies, such as portal vein embolization, transarterial chemoembolization, radioembolization, antiviral treatment, radiofrequency ablation and salvage transplantation, is a promising treatment modality for HCC and may improve survival greatly.

Key words: Hepatocellular carcinoma; Hepatectomy; Prognosis

Core tip: We discuss the new strategies to improve the long-term outcome of hepatocellular carcinoma after hepatectomy.

INTRODUCTION

Liver cancer is the fifth most frequently diagnosed cancer in men worldwide but the second most frequent cause of cancer death. In women, it is the seventh most commonly diagnosed cancer and the sixth leading cause of cancer death. An estimated 748300 new liver cancer cases and 695900 cancer deaths occurred worldwide in 2008, and half of these cases and deaths were estimated to occur in China[1]. After Starzl *et al*[2] performed the first case of human liver transplantation (LT), a new avenue was opened for treatment of HCC. In recent years, some authors have advocated LT even for resectable early HCC associated with cirrhosis because LT was believed to cure the tumor and the underlying cirrhosis at the same time in well-selected patients who met the Milan or UCSF criteria[3]. Although LT is associated with a lower tumor recurrence rate, this benefit is counteracted by long-term complications such as immunosuppression-related complications and a significant risk of tumor progression, or the severe shortage of grafts for patients on transplantation waiting lists leading to dropout[4]. Therefore, hepatectomy became the first-line treatment of HCC.

The 5-year survival rate and tumor recurrence rate

were 30%-50% and 70%-85% after hepatectomy, respectively[3]. Consequently, new strategies are required to improve the long-term outcome of HCC after hepatectomy. In this paper we propose three strategies to optimize long-term survival: (1) increasing resectability rate; (2) improving disease-free survival by preventing recurrence; and (3) prolonging survival after recurrence.

STRATEGIES TO INCREASE RESECTABILITY

Various factors may limit the application of surgical resection in patient cases, such as tumor spread, severe underlying cirrhosis, having too small of a residual liver to provide adequate functional hepatic reserve (< 25% of a normal liver or < 40% of a cirrhosis-afflicted liver), and involvement of the inferior vena cava (IVC) or the three main hepatic veins[5]. Only 10%-37% of patients with HCC could be offered the curative hepatic resection at the time of diagnosis[6]. The prognosis of the patients with unresectable HCC and without specific anti-HCC treatment is very poor. The median survival for patients with unresectable HCC is eight to nine months, but only one to two months for those patients with advanced stage HCC[7,8].

Four strategies can be used to increase the clinical resectability rate in patients with HCC, which mainly include (1) downstaging treatment; (2) portal vein embolization (PVE); (3) hepatectomy with vascular reconstructions (*e.g.,* the IVC and/or hepatic vein); and (4) *ex situ* liver resection.

Downstaging treatment

Tumor downstaging is a new concept in the management of unresectable malignancy[7,8]. Some regional therapies can downstage tumors from unresectable to resectable lesions because tumors shrink in size, satellite lesions disappear, main portal vein tumor thrombi regress and disappear, and future remnant part of the liver undergoes hypertrophy[7,8]. Several requirements are needed for successful tumor downstaging and salvage surgical resection for unresectable HCC[7,8]: (1) an approach which can shrink the tumor effectively; (2) radiological monitoring of the tumor response to the treatment closely; (3) assessment by a surgeon with a view to perform hepatic resection at the proper time repeatedly; and (4) a curative hepatic resection. Downstaging therapies in patients with unresectable HCC for a salvage hepatic resection include: transarterial chemoembolization (TACE), transarterial 90Y microspheres, hepatic artery infusion, or a combination of hepatic artery ligation with HAI[8].

Clinical studies suggested that 10.9%-57.1% of unresectable HCC cases were successfully downstaged from unresectable to resectable lesions[9]. The initial reason for the tumor being unresectable does not affect the prognosis after liver resection[10].

PVE

The cutoff points for potential liver remnant volume in patients with normal liver parenchyma and those with cirrhosis are 25% and 40%, respectively, in order to provide adequate functional hepatic reserve. However, some patients are not appropriate for resection as their tumor is too extensive and/or the residual liver is too small. Techniques have been used preoperatively to increase the volume of residual functional liver, thereby increasing the proportion of candidates for resection. PVE was first proposed almost a decade ago[11]. In PVE, the portal vein supplying the resected hemi-liver was embolized in order to induce hypertrophy of the other hemi-liver. This has been demonstrated to result in an increase in functional residual liver hypertrophy of 70%-80% in the future liver remnant[12]. However, it has been reported that live metastases present in the regenerating lobe grow at a faster rate than in the normal parenchyma[13].

Hepatectomy with vascular reconstructions

Traditionally, involvement of the IVC or/and hepatic vein was considered a contraindication for hepatectomy because of a higher surgical risk. Recent advances of in liver surgical techniques have improved the resectability rate in patients with HCC. In Hemming *et al*[14]'s report, 16 patients' hepatic veins were reconstructed to provide venous outflow to the affected hepatic segments, with 1- and 3-year survival rates of 88% and 50%, respectively, and a perioperative death rate of 12%. In another Hemming *et al*[15]'s report, the IVC was reconstructed in 22 patients with hepatic malignancies, with a mortality rate of 9%, and 1-, 3- and 5-year global survival rates of 85%, 60% and 33%, respectively.

Hepatectomy with vascular reconstructions may be undergone for the patients with involvement of IVC or/and hepatic vein by HCC in selected cases, which must be addressed at highly skilled centers in the hepato-biliary-pancreatic surgery where surgeons are familiar with techniques of both complex liver surgery and LT. The higher surgical risk with the procedure could be balanced by the possible good benefits, particularly when the cases were considered as the lack of alternative curative treatments[14,15].

Ex vivo liver resection

Because of the limited warm ischemia tolerance of the liver or poor accessibility of the tumor region, some HCCs cannot be resected using a conventional approach. In such situations, the techniques of *ex vivo* liver surgery, pioneered by Rudolf Pichlmayr in 1988, offer new chances for R0 hepatic resection[16]. *Ex vivo* liver surgical techniques require the use of measures originally developed for transplantation and liver resection. This approach allows better access to difficult tumor locations and extended resection procedures with complicated vascular reconstructions[17].

Ex vivo liver surgery is an important extension of surgical treatment possibilities, and the procedure is suitable only for a small number of carefully selected patients and

should be reserved for use in specialized centers. However, the early postoperative mortality rate is high, especially when the liver parenchyma has a pre-existing injury like cholestasis. In these patients, *ex situ* liver surgery should be avoided[17].

IMPROVEMENT OF DISEASE-FREE SURVIVAL BY PREVENTING RECURRENCE

The frequency of tumor recurrence is still very high after liver resection for HCC. In different series between 43%-65% of the patients had recurrences within 2 years after removal of the first tumor and up to 70%-85% of the patients had recurrence within 5 years[3,18]. The recurrence rate may be reduced by careful attention to some of the following technical aspects: wider resection margin, anatomical resection encompassing portal area of tumor, using an anterior approach to minimize the risk of tumor cell dissemination, minimizing intraoperative blood loss so as to avoid blood transfusion, and effective adjuvant treatment.

Reducing blood loss and transfusion
Reduced blood transfusion is a significant factor in multivariate analysis for improving survival after resection of HCC. The association of transfusion with decreased survival may be partly due to unmeasured effects of intraoperative hemorrhage[19,20]. Blood loss may be an important prognostic factor for HCC after resection and it was firstly reported by our group[19]. In our report, multivariate regression analysis revealed that intraoperative blood loss independently influenced the HCC prognosis[19]. Katz *et al*[20] also found increased intraoperative blood loss during HCC resection was an independent prognostic factor for tumor recurrence and overall survival time. Factors associated with increased intraoperative blood loss on multivariate analysis were male gender, vascular invasion, extent of hepatectomy, and operative time[20]. Intraoperative blood loss may increase the risk of spillage of cancer cells and spread during hepatectomy, which could stimulate HCC recurrence[21,22]. Some of techniques during hepatic resection may reduce intraoperative blood loss, such as low CVP anesthesia and portal triad clamping, which could minimize intraoperative blood loss during hepatic parenchymal transection[23,24].

Wide resection margin
As a general principle of surgical oncology, wide resection margin to ensure histologic clearance is a very important factor for reducing local cancer recurrence[25]. A wider margin may reduce local recurrence, but it has to be balanced with the need to preserve liver remnant volume in cirrhotic patients. A reduced postoperative recurrence rate and better prognosis were found to be associated with a macroscopic margin of 1 cm or more[25,26]. Shi *et al*[27] compared the efficacy and safety of partial hepatectomy aiming grossly at a narrow (1 cm) and a wide (2 cm) resection margin in patients with macroscopically solitary HCC. They found the survival time of the patients after HCC recurrence was significantly worse in the narrow margin group than in the wide margin group (5-year overall survival rate: 49.1% *vs* 74.1%), therefore, a resection margin more than 2 cm could decrease postoperative recurrence rate and improve survival outcomes for patients with macroscopically solitary HCC[27].

Anatomical hepatic resection
In hepatic anatomic resection, the hepatic parenchyma is dissected based on the portal venous anatomy to remove the parenchyma of one or more Couinaud's segments fed by portal branches bearing the HCC. The concept was first reported by Makuuchi *et al*[28] in 1985. Anatomical hepatic resection of the hepatic parenchyma encompassing the portal area of the tumor may reduce recurrence compared with wedge resection because the intrahepatic metastases of HCC spread *via* the portal vein as an efferent vessel, and may be more reasonable because the maximal extent of possible functional liver parenchyma was preserved and the intrahepatic metastasis was eradicated[29]. Hasegawa *et al*[29] found that in the anatomic resection group both the 5-year overall survival and disease-free survival rates were significantly better than those in the nonanatomic resection group.

Anterior approach for difficult major right hepatectomy
Traditionally, it is a standard approach to mobilize the right liver before parenchymal transection for a major right hepatectomy. However, there are several disadvantages during the rough mobilization of the right liver: (1) excessive bleeding caused by avulsion of the hepatic veins; (2) prolonged hepatic ischemia of the future remnant liver part from rotation of the hepatoduodenal ligament; (3) iatrogenic tumor rupture; and (4) spillage of cancer cells into the systemic circulation[30]. To avoid the above disadvantages, the anterior approach first reported by Lai *et al*[31] can be adopted, which is considered as one of the "no touch techniques "to advanced HCC. Using this nonconventional approach, hepatic parenchymal was transected from the anterior surface down to the IVC before mobilization of the right hemi-liver.

A prospective randomized controlled study was performed in 120 patients who had large (≥ 5 cm) right liver HCC and underwent curative major right hepatic resection. Overall survival time in the anterior approach technique group was better than the conventional technique group (median > 68.1 mo *vs* median = 22.6 mo), while major operative blood loss ≥ 2 L also occurred less frequently in the anterior approach group (8.3% *vs* 28.3%)[30].

Belghiti *et al*[32] propose a new technique of hanging the liver after lifting it with a tape passed between the anterior surface of the IVC and the hepatic parenchyma, which has three advantages: (1) it gives the shorter distance of the transection between the anterior surface of

the liver and the anterior surface of the IVC; (2) it facilitates the hepatic parenchymal transection for a easier hemostasis of the transection surface and the IVC protection; and (3) it permits the surgeon to follow the middle hepatic vein trunk safely. With Belghiti's modification of the anterior approach to right hepatectomy, the risk of massive bleeding is reduced[32].

Postoperative adjuvant therapy

The aim of postoperative adjuvant therapy is to eliminate micrometastases and hence reduce the risk of intrahepatic metastatic recurrence, thereby improving the prognosis of hepatectomy for HCC[33]. TACE, radioembolization, immunotherapy, and antiviral therapy may be promising adjuvant therapies after hepatectomy for patients with HCC, which may be beneficial to get prolonged disease-free survival time[34].

TACE

Postoperative TACE is regional chemotherapy to treat the intrahepatic micrometastases after hepatectomy. The procedure uses a catheter which was inserted percutaneously through the femoral artery to deliver both chemotherapy medication and embolization materials into the hepatic artery under X-ray image guidance. According to their meta-analysis, Mathurin *et al*[35] reported that postoperative transarterial chemotherapy improved survival and decreased the cumulative probability of recurrence. They found that postoperative transarterial chemotherapy improved survival significantly at 2 (difference, 22.8%; 95%CI: 8.6%-36.9%; $P = 0.002$) and 3 years (difference, 27.6%; 95%CI: 8.2%-47.1%; $P = 0.005$).

Radioembolization

In a prospective randomized trial from Hong Kong[36], adjuvant treatment with radioembolization (1 dose of postoperative adjuvant intra-arterial iodine-131-labeled lipiodol, 1850 MBq) for patients with HCC after curative resection and recovered within 6 wk could significantly increase the long-term disease-free survival and overall survival time up to 7 years after randomization. However, there was no significant difference between the adjuvant radioembolization treatment group and the control group in disease-free and overall survival at 8 years after randomization. The possible reason for the insignificant difference is that the adjuvant ^{131}I-lipiodol cannot prevent new lesions developing from the cirrhotic liver in the long term. However, in Partensky *et al*[37]'s plot study from France, patients undergoing adjuvant therapy with intra-arterial ^{131}I-lipiodol after curative liver resection for HCC failed to demonstrate any clinically significant adverse effect.

Adjuvant immunotherapy

Some of small trials suggested that immunomodulation may reduce the risk of HCC recurrence after hepatic resection. A randomized controlled trial from Japan assessed whether postoperative immunotherapy could reduce the recurrence rate after hepatectomy for HCC

by the examination of autologous lymphocytes activated *in vitro* with recombinant interleukin-2 and antibody to CD3[38]. They found that adoptive immunotherapy decreased the frequency of HCC recurrence by 18% compared with control patients after hepatectomy and had significantly longer recurrence-free survival and disease-specific survival, but not overall survival time[38]. In a prospective randomized trial from Japan, Kubo *et al*[39] reported that the cumulative survival rate was higher in the interferon group (interferon-alpha 6 MIU intramuscularly every day for 2 wk, then three times a week for 14 wk and finally twice a week for 88 wk) than that in the control group. According to another prospective randomized clinical trial of postoperative interferon therapy, there was a significant benefit on reduction of late recurrences in hepatitis C virus (HCV)-pure patients adherent to treatment. Interferon does not appear to affect overall prevention of HCC recurrence after resection, but it may reduce late recurrence in HCV-pure patients receiving effective treatment[40].

Antiviral therapy

In hepatitis B virus-related HCC patients, preoperative high viral load can lead to poorer overall and recurrence-free survival than those with low viral load after curative resection. To prevent postoperative recurrence, antiviral therapy should be initiated in those patients with hepatitis B virus infection in whom the level of viral DNA is ≥ 10000 copies/mL[41]. According to a cohort study involving 4569 hepatitis B virus (HBV)-related HCC patients, Wu *et al*[42] reported that the nucleoside analogue-treated cohort had a lower risk of HCC recurrence [$n = 106$ (20.5%) *vs* $n = 1765$ (43.6%)] and lower overall death as well [$n = 55$ (10.6%) *vs* $n = 1145$ (28.3%)]. On their modified Cox regression analysis, nucleoside analogue use was independently associated with a reduced risk of HCC recurrence as well as a lower risk of HCC recurrence among patients with HBV-related HCC after liver resection.

AGGRESSIVE TREATMENT OF RECURRENCE IMPROVES SURVIVAL

The early discovery of HCC recurrence depends on the frequency and duration of follow-up examinations. About 30%-91% of cases of recurrence is confined to the liver and in multiple or diffuse patterns of HCC the rate is up to 50%[18].

Treatment modalities, including repeat resection, TACE, and percutaneous ablation (*e.g.* radiofrequency ablation) have been used in postoperative recurrent HCC and may improve survival rates.

Repeat hepatic resection

Survival rates after repeat resection for the recurrent intrahepatic HCC ranged from 37% to 86% after 5 years and were better than those treated by other palliative methods[25].

The extent of the primary hepatic resection and status of liver parenchyma decided the resectability rates ranging from 10% to 77% with mortality ranging from 0% in most series to 8%[25].

In a study analyzing the poor prognostic factors after repeat resection, Tsujita found that (1) portal vein invasion at primary hepatectomy; (2) recurrence interval; (3) tumor size; (4) gender; and (5) estimated blood loss were the independent adverse prognostic factors[43]. In another study, Arii showed that survival in patients with multicentric carcinogenesis was better than that in intrahepatic metastasis group after repeat resection (3-year survival rate: 80.0% *vs* 38.1%), which suggested that patients with multicentric HCC may be more favorable candidates for repeat hepatic resection[44].

Salvage transplantation

Salvage transplantation is defined as management for patients with recurrence or hepatic decompensation after liver resection, which should be considered when repeat resection is not feasible. It has been shown to be the optimal strategy with the best use of organs. Salvage transplantation may not be an appropriate option when: (1) the recurrence is extrahepatic; or (2) the patient has contraindications to liver resection. In addition to these factors, previous hepatic resection due to scarring and vascularized adhesions would pose increased challenges, particularly when the hepatic hilum and the peri-caval area were dissected extensively during liver resection[45].

In a report from France, Fuks *et al*[46] showed that salvage transplantation is an effective approach for the patients who developed recurrence within the Milan criteria after initial hepatectomy. After salvage transplantation, overall survival at 5 years was 71% and mortality rate was 5%[44]. Predictive factors for nontransplantability due to recurrence beyond the Milan criteria included microscopic vascular invasion, satellite nodules, tumor size > 3 cm, poorly differentiated tumor and liver cirrhosis[46]. Therefore, it may be a feasible and rational strategy to use primary resection for HCC with preserved liver function and salvage transplantation for the patients who developed recurrence within the Milan criteria.

TACE

TACE is considered the most widely used locoregional treatment for patients with intrahepatic recurrent HCC that is unresectable for multifocal pattern or inadequate functional reserve of the remaining liver. It also is considered the first-line approach of palliative therapies for recurrent HCC. After TACE for the intrahepatic recurrent HCC after resection, the 1-year survival rate ranged from 64% to 88%, but the 5-year survival rate was only in the range from 0% to 27%[25]. Although the survival results of TACE for recurrent HCC were still modest compared with repeat resection, it does play an important role in the overall treatment strategy, because it is applicable to most intrahepatic recurrent patients with unresectable disease for multifocal pattern or inadequate liver function

reserve.

Radiofrequency ablation therapy

Percutaneous radiofrequency ablation can be used for patients with recurrent HCC after hepatectomy who are not eligible for repeat hepatic resection, which should be limited to the patients with a solitary tumor smaller than 5 cm or less than 3 small lesions. For patients with recurrent HCC treated by radiofrequency ablation (RFA), the complete ablation rates were 93.3%-96.0% and 5-year overall survival rates were 18.0%-51.6%[47,48]. Pre-RFA serum AFP level[47,48] and resected tumor size[47] were significant prognostic factors. The effectiveness rate of sequential combined TACE and RFA is better than that of RFA alone for patients with intrahepatic recurrence[49]. Performing TACE before RF ablation can achieve better ablation than RFA alone in selected candidates with recurrent HCC smaller than 5 cm[49]. The results could be explained as follows[50]: (1) occlusion of hepatic arterial flow by means of TACE before RFA reduces the cooling effect of hepatic blood flow on thermal coagulation; and (2) filling the peripheral portal vein around the tumor by lipiodol sponge particles used in TACE *via* multiple arterio-portal communications may reduce the portal flow around the recurrent tumor. However, the long-term survival of patients with intrahepatic recurrence treated by repeat hepatectomy or salvage transplantation may be better than that of patients treated by RFA.

Extrahepatic recurrence

The extrahepatic HCC recurrence rate was associated with early recurrence (within 6 mo after hepatic resection) and poor survival time after hepatectomy (5-year survival rate: 24.0%)[51]. Taketomi *et al*[51] also showed that the presence of microscopic hepatic vein invasion and the amount of blood loss during operation were independent risk factors for extrahepatic HCC recurrence. There are three patterns of extrahepatic HCC recurrence after hepatectomy[52]: (1) pattern I (first recurrence in the liver and then spread outside the liver after repetitive intrahepatic recurrences and repetitive locoregional treatments); (2) pattern II (simultaneous recognition of intrahepatic and extrahepatic recurrences); and (3) pattern III (extrahepatic, but no intrahepatic, lesions at first recurrence). Although pattern I has a better long-term overall survival in the three patterns, prognosis was poor in all three patterns once extrahepatic HCC recurrence developed[52].

Some selected patients with solitary extrahepatic recurrent HCC may benefit from aggressive surgical resection, which can be indicated not only for patients with localized intrahepatic recurrence but also for those who developed extrahepatic metastasis. A report from Hong Kong showed that the aggressive resection of a solitary lung metastasis in 9 patients resulted in a good long-term prognosis after recurrence (5-year survival rate: 67%)[53]. Other reports have also found that long-term survival time was prolonged after the aggressive resection in selected patients with solitary extrahepatic recurrent

HCC in the adrenal gland or abdomen[54-56]. Therefore, it appeared that aggressive resection may be a beneficial treatment for the patients with isolated extrahepatic HCC recurrence.

CONCLUSION

The aim of management of HCC is to improve the prognosis of the patients by radical resection and preserve remnant liver function. The first choice of treatment is hepatectomy of the tumor-bearing part of the liver. Meanwhile, there are some strategies to increase the low resectability rate in the clinic, such as downstaging treatment, PVE, *ex situ* liver resection, and hepatectomy with vascular reconstructions. The surgeon can improve disease-free survival by preventing recurrence with various techniques including wider resection margin, anatomical resection encompassing portal area of tumor, using an anterior approach to minimize the risk of tumor cell dissemination, minimizing intraoperative blood loss so as to avoid blood transfusion, and effective adjuvant treatment. Repeat resection, TACE and RFA used in postoperative intrahepatic recurrent HCC and surgical resection are effective options for patients with isolated extrahepatic recurrence. Overall, we believe that hepatectomy combined with other therapies, such as PVE, TACE, radioembolization, antiviral treatment, RFA and salvage transplantation, is a promising treatment modality for HCC and may improve survival rates greatly. Future clinical research should reveal the optimal combination of therapies in properly selected patients.

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