

Salvage liver transplant for hepatocellular carcinoma: rescues and benefits

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Abstract: Hepatocellular carcinoma (HCC) is one of the most common malignant tumors in China, primary liver transplantation (PLT) and hepatic resection are thought to be the prime and more reasonable treatment. But due to the situation of donor shortage and a higher risk of tumor recurrence, salvage liver transplantation (SLT) is gradually being applied to the patients with HCC, and is confirmed as an effective and feasible treatment for patients. However, the indications and transplantation criteria for SLT still remain controversial. This article reviews the benefits and controversies of SLT and provides an effective reference for the clinical practice.

Keywords: Hepatocellular carcinoma (HCC); primary liver transplantation (PLT); salvage liver transplantation (SLT); transplantation criteria

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Introduction

Hepatocellular carcinoma (HCC) is one of the most common malignant tumors in China, and it is the third cause leading to cancer mortality (1). Primary liver transplantation (PLT) was known as the most effective treatment for patients with HCC, which not only achieves radical tumor resection, but also cures the concurrent end-stage liver diseases, such as severe cirrhosis (2,3). However, the long waiting time for transplant, severe organ shortage, high medical cost and high perioperative risk are important difficulties confronted for PLT. Patients often fail to get a liver transplant in time, and will face tumor progression and loss of the chance for transplantation or even death (4,5).

Primary hepatic resection can achieve a 5-year overall survival rate of approximately 55–71%, remains to be a prime and more reasonable treatment with long-term

survival outcomes for patients with resectable early HCC (6,7). Studies have shown that there is no obvious difference in the total survival rate after hepatic resection compared with that of liver transplantation (8,9). But due to the invasive and metastatic nature of HCC, it might face a higher risk of tumor recurrence or liver function deterioration after hepatic resection. Studies showed that almost 70% of patients would develop intrahepatic recurrence after hepatic resection within 5 years (10,11). Gratifyingly, 80% of patients with recurrent HCC after curative resection had a chance to receive liver transplant (12,13).

Advent of salvage liver transplantation (SLT)

SLT was first proposed in 2000 by Majno *et al.* (5), and has been performed for those patients with recurrent HCC or liver function deterioration following initial treatment with

Table 1 Details of several studies and long-term survival outcomes after SLT

First author	Year	Country	SLT (n)	Median follow-up (months)	Overall survival (%)			Disease-free survival (%)		
					1-year	3-year	5-year	1-year	3-year	5-year
Wu <i>et al.</i> (14)	2012	China	36	61	91	87	70	97	88	74
Adam <i>et al.</i> (15)	2003	France	17	49	71	53	41	47	29	29
Kim <i>et al.</i> (16)	2008	Korea	15	20	90	86	–	–	–	–
Chan <i>et al.</i> (17)	2013	Australia	319	29	89	80	62	86	68	67
Qu <i>et al.</i> (18)	2015	China	111	29	76	56	49	–	–	–
Liu <i>et al.</i> (19)	2012	China	39	30	88	78	61	86	76	67
Hu <i>et al.</i> (20)	2013	China	53	16	72	39	39	63	51	43
Hwang <i>et al.</i> (21)	2007	Korea	17	27	88	65	54	–	–	–
De Carlis <i>et al.</i> (22)	2013	Italy	26	–	–	–	82	–	–	81
Cherqui <i>et al.</i> (23)	2009	France	18	58	85	80	70	82	52	44
Fuks <i>et al.</i> (24)	2012	France	39	–	94	81	71	–	–	–
Kaido <i>et al.</i> (25)	2012	Japan	19	77	90	77	77	92	88	78
Moon <i>et al.</i> (26)	2012	Korea	17	11	83	80	61	67	67	67
Sapisochin <i>et al.</i> (27)	2010	Spain	17	21	59	52	52	86	68	58

SLT, salvage liver transplantation.

primary hepatic resection. Primary resection and SLT may be a rational way to cope with lengthening waiting lists in the current situation of donor shortage (5).

However, the indications for SLT are still controversial, and there is no sufficient research to confirm its safety and postoperative survival rate. SLT has been thought to increase the difficulty and risk of surgery due to the history of previous hepatic resection, severe adhesion in the abdominal operation area, abnormal anatomical structures and more intraoperative blood loss (14). In the early stage of development, it is reported that the mortality rate of patients with SLT was as high as 28.6%, which was much higher than that of patients with PLT (2.1%) (15). Compared with SLT, PLT has less blood loss and risks, is considered to be an ideal choice for the treatment of HCC with liver cirrhosis. Multiple surgical procedures, accompanied by adjuvant therapies such as radiotherapy will increase the difficulty of operation during SLT. Due to previous hepatectomy and severe adhesion during SLT, we suggest directly dissecting the porta-hepatitis, clamping the inferior vena cava first, then mobilizing and rapidly removing the diseased liver, so as to reduce the hemorrhage and the risk of tumor metastasis during operation.

Benefits of SLT

With the advancement of surgical techniques and the continuous accumulation of surgical experience, however, more and more studies have shown that the perioperative risk of SLT gradually decreases (Table 1). Kim *et al.* (16) compared 15 patients who underwent SLT after prior partial hepatectomy with 31 patients following PLT, and found that there was no difference in the incidence of surgical complications and overall survival rates between the two groups, and concluded that SLT is a feasible procedure for recurrent HCC, the operative risk of the SLT is also acceptable. A meta-analysis has shown that SLT for recurrent HCC can achieve the same short- and long-term outcomes as PLT. Therefore, SLT may be accepted as a valid treatment for patients with recurrent HCC (28). A meta-analysis of 7 studies (29) have shown that there were no significant differences in the overall survival rates of SLT and PLT, and in the incidence of sepsis and biliary complications as for postoperative complications, but there was a significantly higher incidence of bleeding with SLT (P=0.001). A synthesis of 16 studies comprising 319 patients suggests that SLT following primary hepatic resection is a highly applicable strategy with long-term survival outcomes that are comparable to upfront liver transplantation (17). A similar

paper analyzed 111 patients who received SLT, including operative characteristics, survival rate, and prognostic factors, and put forward that primary liver resection can not only completely remove the tumor lesions, but also provide detailed information on the tumor before SLT, such as tumor size, tumor number, degree of differentiation, pathological type, with or without vascular invasion, and other important pathological data (18). SLT is an effective and feasible treatment for patients with HCC recurrence after primary hepatic resection.

Opportunity of SLT

Furthermore, it is very important to select the opportunity of SLT. From the domestic and foreign research, patients with HCC who have severe preoperative cirrhosis, poor liver function, and younger age should choose PLT as much as possible. For those with better liver function, older age may choose to undergo primary hepatic resection, and later may receive comprehensive treatment such as transcatheter arterial chemoembolization (TACE), radiofrequency ablation (RFA), percutaneous ethanol injection, and immunotherapy to delay the progression of the tumor and make preparation for SLT in the future (30). Sala *et al.* (31) also recommended that patients with high risk of recurrence, such as pathological microvascular infiltration and tumor microsatellite lesions, could undergo liver transplantation prior to tumor recurrence, making SLT more targeted.

Transplantation criteria for SLT

So far, there is still a lack of transplantation criteria for SLT in patients with recurrent HCC. In recent years, different transplantation centers have begun to apply indications of liver transplantation for HCC to SLT, in an attempt to continuously expand the surgical indications of SLT. Wu *et al.* (14) compared patients with SLT and PLT performed from 2004 to 2008, and concluded that the Milan criteria are still eligible for the 36 patients at the time of recurrence. And the 5-year overall survival rate and disease-free survival rate are not lower than those undergoing PLT. Liu *et al.* (19) observed the efficacy of SLT for patients with recurrent HCC who met the University of California San Francisco (UCSF) criteria, although SLT group has more intraoperative blood loss, the perioperative mortality and postoperative complications were similar in SLT and PLT groups. There was no significant difference in overall

survival and recurrence rates between the two groups. Moreover, they observed that SLT for recurrent HCC beyond Milan but within UCSF criteria could achieve the same efficacy as patients who met Milan criteria. Therefore, SLT for recurrent HCC within UCSF criteria was feasible and it could achieve the same outcome as PLT. Hu *et al.* (20) retrospectively analyzed 53 cases of SLT patients performed from 2004 to 2012. Among them, 16 cases met the Milan criteria, 14 cases met the Hangzhou criteria. The overall survival rate of the Hangzhou criteria in the first and third year were both 70.1%, which was close to the Milan criteria group of 93.8% and 62.1% ($P=0.586$). Similarly, no statistical difference in the tumor-free survival rates between the two groups, which concluded that the Hangzhou criteria can safely expand the transplantable candidates of SLT.

At present, the medical community has not reached an agreement on the transplantation criteria of SLT, and more and more studies showed that even though the Milan criteria was first proposed and can effectively improve the disease-free survival rate of patients with HCC, the inclusion criteria are too strict, so that many patients who could have received liver transplantation lost surgery opportunity (32-34). And for a country with a large amount of patients with HCC like China, the Milan criteria does not seem to be suitable either. It still depends on a more rigorous design and a larger sample size of prospective, randomized, controlled clinical trials to further verify. In our center, we perform LT for HCC patients based on Hangzhou criteria, the percentage of SLT is about 22% of LT for HCC patients.

The feasibility of salvage living donor liver transplantation (LDLT)

As we know, the initial studies on SLT were almost based on deceased donor liver transplantation (DDLT). However, LDLT, as a choice of liver transplantation, can offer a great opportunity to the supply of transplantable organs, thereby reducing the patients' waiting time and reducing the risk of being removed from the waiting group for liver transplantation due to tumor progression. If appropriate living donor liver resources are available, a significant proportion of patients with HCC tend to adopt LDLT as an initial treatment or as a treatment option when non-surgical treatment fails. So, salvage LDLT will gradually increase with the development of LDLT.

However, the feasibility of salvage LDLT for patients after hepatectomy has been controversial (21,35). Hu

et al. (20) reported in a study that the 1-year, 3-year, and 5-year overall and disease-free survival rates were similar between the LDLT and DDLT in the SLT group, which indicates that salvage LDLT is a safe and good alternative treatment option because of the shortage of cadaveric donor livers. Abe *et al.* (36) researched 45 patients who underwent primary LDLT and 15 patients followed salvage LDLT after initial hepatic resection to investigate the efficacy of salvage LDLT after initial hepatic resection in HCC patients. The salvage LDLT group had significantly more reoperations for postoperative bleeding, nevertheless overall and recurrence-free survival rates were comparable, reported that salvage LDLT for HCC offered long-term outcomes at least as good as those of primary LDLT.

In short, salvage LDLT not only alleviates the situation of the deficiency of donor liver, but also achieves an ideal therapeutic effect, which can be regarded as an effective treatment.

Summary

From the above review, we believe that as long as a reasonable choice of indications, adequate preoperative assessment and precise surgical operation, SLT after hepatic resection can achieve the same satisfactory clinical efficacy as PLT. In particular, under the conditions of many patients with liver cancer in China but few liver resources, SLT has unique advantages and wider prospects. As for the specific treatment to be adopted, a comprehensive assessment should be conducted based on the patient's age, liver function, and patient's willingness. The difficulty of SLT should also be evaluated due to complicated previous treatment. In addition, the transplantation criteria for SLT has not yet reached a consensus and still needs to be confirmed by a large number of multi-center studies.

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Footnote

Conflicts of Interest: The authors have no conflicts of interest to declare.

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