Salvage liver transplantation in the treatment of hepatocellular carcinoma: A Meta-analysis

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Abstract

AIM: To evaluate survival and recurrence after salvage liver transplantation (SLT) for the treatment of hepatocellular carcinoma (HCC) compared with primary liver transplantation (PLT) using a meta-analysis.

METHODS: Literature on SLT versus PLT for the treatment of HCC published between 1966 and July 2011 was retrieved. A meta-analysis was conducted to estimate pooled survival and disease-free rates. A fixed or random-effect model was established to collect the data.

RESULTS: The differences in overall survival and disease-free survival rates at 1-year, 3-year and 5-year survival rates were not statistically significant between SLT group and PLT group (P > 0.05). After stratifying the various studies by donor source and Milan criteria, we found that: (1) Living donor liver transplantation recipients had significantly higher 1-year survival rate, lower 3-year and 5-year survival rates compared with deceased-donor liver transplantation (DDLT) recipients. And in DDLT recipients they had better 1-year and 5-year disease-free survival rate in SLT group; and (2) No difference was seen in 1-year, 3-year and 5-year survival rates between two groups who beyond Milan criteria at the time of liver transplantation.

CONCLUSION: SLT can be effectively performed for patients with recurrence or deterioration of liver function after hepatectomy for HCC. It does not increase the perioperative mortality and has a similar long-term survival rates compared to PLT.

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Key words: Salvage liver transplantation; Primary liver transplantation; Hepatocellular carcinoma; Meta-analysis; Survival rate

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INTRODUCTION

In a normal liver, liver resection for hepatocellular carcinoma (HCC) is the primary treatment of choice. But in cirrhotic livers, the presence of HCC and the limited liver capacity are the two intertwined issues rendering the HCC unresectable. Primary liver transplantation (PLT) is the most effective treatment for such HCC patients, especially for those who meet Milan criteria (solitary liver nodule not exceeding 5 cm in maximum diameter, or 2 or 3 tumors not exceeding 3 cm in diameter)\(^{[1]}\). It has been manifested to provide a considerable disease-free
survival and to be the first choice for these patients. Due to shortage of available donors, long waiting times may harm the benefit that might be acquired from PLT. Salvage liver transplantation (SLT) has been proposed and performed for those who undergo primary liver resection for HCC or HCC recurrence or deterioration of liver function[2]. SLT proposes liver resection as a bridge to prevent tumor progression in the waiting list. Although SLT might be an alternate choice for HCC patients as the preferred treatment, long-term results are difficult to ascertain. Moreover, few data are available on the overall and disease-free survival of patients. A few researches concern on the comparison between the result of SLT and PLT. In order to reduce research bias and difference, we did a meta-analysis to compare survival and recurrences for SLT strategy versus PLT in the treatment of HCC patients, in order to provide a reference for clinical practice.

MATERIALS AND METHODS

Literature search strategy
Search was applied to the following electronic databases: PubMed (1966 to July 2011), Embase (January 1996 to July 2011), CNKI (January 1996 to July 2011) and Cochrane database. The following key words were used: “liver resection” or “hepatectomy”; “liver transplantation” or “transplantation” or “salvage liver transplantation”; “salvage transplantation”; “hepatocellular carcinoma” or “HCC”. The search was limited to the English language and humans. The relevant reference lists of reviews were also searched at the same time. Abstracts or unpublished studies were not considered. If more than 1 study was published by the same author using the same case series, only the most detailed study was included. And if necessary, authors were contacted to obtain more data on their study.

Definitions
SLT was defined as a liver transplantation performed for recurrent HCC or deterioration of liver function after primary liver resection.

Inclusion, exclusion criteria and quality of the studies
Inclusion criteria were as follows: (1) having definition of SLT; (2) follow-up 12 mo at least; (3) case-control or cohort design; and (4) sufficient data were obtained to calculate odds ratio (OR) with confidence interval (CI). Reasons for exclusion were: (1) no-control; (2) duplicate; and (3) no useable data reported. We also excluded articles published before 1996 because there was no definition for “SLT”.

The scoring system was adapted from Stahl, the Cochrane Collaboration and others[3-5]. This system suits not only randomized control trial (RCT) but controlled trial or other studies well. Questions were placed on a 3 point scale: unclear/inadequate (0), adequate (1), good (2). Articles were considered for inclusion if their summary score exceeded 30.

| Author          | Year | Country | Study design | SLT (cases) | PLT (cases) | Score |
|-----------------|------|---------|--------------|-------------|-------------|-------|
| Adam et al[6]   | 2003 | France  | Case-control | 17          | 200         | 32    |
| Belghiti et al[7] | 2003 | France  | Case-control | 18          | 70          | 33    |
| Concejoero et al[8] | 2008 | China   | Case-control | 7           | 28          | 31    |
| Del Gaudio et al[9] | 2008 | Italy   | Case-control | 16          | 147         | 32    |
| Facciotto et al[10] | 2008 | USA     | Case-control | 5           | 32          | 30    |
| Hwang et al[11] | 2007 | Korea   | Case-control | 17          | 200         | 31    |
| Kim et al[12]   | 2008 | Korea   | Case-control | 15          | 31          | 30    |
| Margarit et al[13] | 2005 | Spain   | Case-control | 5           | 36          | 31    |
| Sapisochin et al[14] | 2010 | Spain   | Case-control | 17          | 34          | 33    |
| Shao et al[15]  | 2008 | China   | Case-control | 15          | 62          | 30    |
| Venomacci et al[16] | 2007 | Italy   | Case-control | 9           | 37          | 30    |

SLT: Salvage liver transplantation; PLT: Primary liver transplantation.

Data extraction
All data were extracted independently by 2 reviewers according to the selection criteria. We resolved disagreement through discussion. The following data were extracted: the last name of the first author, study design, publication year, definition of SLT, the type of population described [adults or children (< 18 years)], country of transplant center, number of SLT cases and control (PLT) studies, overall survival, overall recurrence and assessment of risk factors.

Statistical analysis
Meta-analysis was performed using fixed-effect or random-effect methods, depending on the absence or presence of significant heterogeneity. Statistical heterogeneity between trials was evaluated by the Cochran χ² test and was considered significant when P < 0.10. In the absence of statistically significant heterogeneity, the Mantel-Haenszel method in the fixed-effect model was used for the meta-analysis. Otherwise, the DerSimonian and Laird method in the random-effect model was selected.

The OR with 95% CI was used to assess treatment efficacy. The combined result was an average OR and 95% CI weighted according to the standard error of the OR of the trial. P < 0.05 was considered statistically significant. We used funnel plots to assess the publication bias, and tested for funnel plot asymmetry using Egger’s test and Begg’s test. All analyses were performed with Review Manager version 5.0.23 (RevMan, Cochrane Collaboration, Oxford, England).

RESULTS

Studies included in the meta-analysis
There were 410 papers relevant to the search words. Via steps of screening the title, abstract reviewing and article reviewing, 11 studies which included 141 SLT cases and 872 PLT cases were identified to match our inclusion criteria[6-16]. Studies had been carried out in France, Italy, USA, China, Spain, Korea and Chinese Taiwan. Details of studies and the methodological quality of the studies assessed according to a score system described above are described in Table 1.
### Review: SLT vs PLT; Comparison: SLT vs PLT; Outcome: 1-year survival rates

| Study or subgroup | SLT | PLT | Odds ratio M-H, fixed, 95% CI | Total (95% CI) |
|------------------|-----|-----|------------------------------|---------------|
| Adam et al[8]    | 12  | 17  | 0.60 (0.20, 1.80)           | 115.00        |
| Belghiti et al[9]| 15  | 18  | 0.47 (0.11, 2.09)           | 33.00         |
| Concejo et al[10]| 7   | 7   | 0.82 (0.03, 22.20)          | 24.72         |
| Del Gaudio et al[8]| 15  | 16  | 2.06 (0.26, 16.81)          | 41.00         |
| Facchetti et al[11]| 5   | 5   | 1.74 (0.08, 37.08)          | 10.00         |
| Hwang et al[12]  | 15  | 17  | 1.07 (0.23, 4.97)           | 32.00         |
| Kim et al[13]    | 13  | 15  | 1.25 (0.21, 7.34)           | 28.00         |
| Margarit et al[14]| 4   | 5   | 1.14 (0.11, 11.72)          | 9.00          |
| Sapisochin et al[15]| 10 | 17  | 0.25 (0.06, 0.95)           | 27.00         |
| Shao et al[16]   | 12  | 15  | 0.43 (0.09, 1.96)           | 27.00         |
| Vennarecci et al[17]| 8   | 9   | 2.21 (0.24, 20.35)          | 17.00         |
| Total (95% CI)   | 141 | 141 | 0.74 (0.46, 1.21)           | 282.00        |

Total events: 282.00

Heterogeneity: $\chi^2 = 6.42$, df = 10 ($P = 0.78$), $I^2 = 0$

Test for overall effect: $Z = 1.20$ ($P = 0.23$)

![Figure 1](image-url) Fixed-effect model of odds ratio for 1-year survival rates (A), 3-year survival rates (B) and 5-year survival rates (C) after salvage liver transplantation and primary liver transplantation (Experimental: Salvage liver transplantation; Control: Primary liver transplantation). SLT: Salvage liver transplantation; PLT: Primary liver transplantation.

### Meta-analysis

**1-year survival after SLT and PLT:** A total of 1013 patients were included in 11 articles. According to $\chi^2$ test of heterogeneity ($P = 0.78$), a fixed-effect model was used. No difference between SLT group (82.3%) and PLT group (85.7%) were seen in the 1-year survival rate (OR: 0.74, 95% CI: 0.46-1.21, $P = 0.23$, Figure 1A).

**3-year survival after SLT and PLT:** A total of 967 patients were included in 10 articles. According to $\chi^2$ test of heterogeneity ($P = 0.40$), a fixed-effect model was used. No difference between SLT group (72.2%) and PLT...
group (74.1%) were seen in the 3-year survival rate (OR: 0.89, 95% CI: 0.58-1.37, \( P = 0.61 \), Figure 1B).

5-year survival after SLT and PLT: A total of 853 patients were included in 8 articles. According to \( \chi^2 \) test of heterogeneity (\( P = 0.53 \)), a fixed-effect model was used. No difference between SLT group (57.5%) and PLT group (65.3%) were seen in the 5-year survival rate (OR: 0.72, 95% CI: 0.46-1.11, \( P = 0.13 \), Figure 1C).

1-year disease-free survival after SLT and PLT: A total of 620 patients were included in 8 articles. According to \( \chi^2 \) test of heterogeneity (\( P = 0.60 \)), a fixed-effect model was used. No difference between SLT group (80.0%) and PLT group (83.4%) were seen in the 1-year disease-free survival rate (OR: 0.56, 95% CI: 0.31-1.00, \( P = 0.05 \), Figure 2A).

3-year disease-free survival after SLT and PLT: A total of 620 patients were included in 8 articles. According to \( \chi^2 \) test of heterogeneity (\( P = 0.0001 \)), a random-effect model was used. No difference between SLT group (67.8%) and PLT group (67.6%) were seen in the 3-year disease-free survival rate (OR: 0.98, 95% CI: 0.27-3.47, \( P = 0.97 \), Figure 2B).

5-year disease-free survival after SLT and PLT: A total of 506 patients were included in 6 articles. According to \( \chi^2 \) test of heterogeneity (\( P = 0.06 \)), a random-effect model was used. No difference between SLT group (74.1%) and PLT group (76.0%) were seen in the 5-year disease-free survival rate (OR: 0.98, 95% CI: 0.47-2.13, \( P = 0.97 \), Figure 2C).
to χ² test of heterogeneity (P = 0.08), a random-effect model was used. No difference between SLT group (65.7%) and PLT group (65.0%) were seen in the 5-year disease-free survival rate (OR: 0.95, 95% CI: 0.62-1.59, P = 0.97) and 5-year survival rate (OR: 0.99, 95% CI: 0.62-1.59, P = 0.97) between SLT group and PLT group who beyond Milan criteria at the time of liver transplantation (LT). No usable data for patients who met Milan criteria at the time of LT.

**Publication bias**

Publication bias may exist when no significant findings remain unpublished, thus artificially inflating the apparent magnitude of an effect. Funnel plots of our study results are shown in Figure 4. The funnel plots on survival and disease-free survival following SLT or PLT for the treatment of HCC showed basic symmetry, which suggested no publication bias.

**DISCUSSION**

As one of the radical treatments for HCC, LT is nowadays limited by organ shortage. Due to the prolonged waiting times before transplantation, tumor progression and deterioration of liver function may counteract its benefit. The outcome of liver resection is mainly influenced by a high rate of recurrence that limits long-term survival rates. But previous research noted that most of patients with recurrence after primary liver resection were still eligible for LT. Hence, hepatectomy and LT should be considered as complementary, not competitive, treatments for HCC in cirrhotic patients with well-preserved liver function. Therefore, the results of our meta-analysis emphasized the importance of LT.
liver function. Resection of the liver tumor is an optional bridge treatment\textsuperscript{[17-19]}. SLT was proposed in order to reduce the impact of a long waiting time, donor shortage and tumor recurrence after resection in HCC patients.

The increased technical difficulty during SLT and the risk for impaired posttransplant survival worried most of surgeons. Heavy adhesions and portal hypertension are often encountered after prior liver resection. Inattentive dissection of perihepatic adhesions could result in uncontrollable bleeding at the dissection surface. Also due to heavy adhesions, the relationship between hepatic vein and inferior vena cava are hard to identify. Hwang et al\textsuperscript{[11]} found that SLT did not increase the operative risks or postoperative complications. The two major technical concerns—bleeding and reconstruction of the hepatic vein outflow—can be solved successfully by steady and meticulous sharp dissection and sufficient dissection of the recipient inferior vena cava. Kim et al\textsuperscript{[12]} showed that end-to-end anastomosis for bile ducts and hepatic artery was feasible, too. Our study showed that SLT had no bad effect on overall survival and disease-free survival in comparison with PLT.

Considering different surgical methods may have an effect on survival rates, the whole patients were stratified to LDLT recipients and DDLT recipients. In each subgroup, no difference between SLT group and PLT group were seen in 1-year survival rates, 3-year survival rates and 5-year survival rates. But LDLT recipients might have

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**Figure 4** Funnel plot. A: 11 articles in the meta-analysis of 1-year survival after treatment; B: 10 articles in the meta-analysis of 3-year survival after treatment; C: 8 articles in the meta-analysis of 5-year survival after treatment; D: 8 articles in the meta-analysis of 1-year disease-free survival after treatment; E: 8 articles in the meta-analysis of 3-year disease-free survival after treatment; F: 6 articles in the meta-analysis of 5-year disease-free survival after treatment. SE: Standard error; OR: Odds ratio.
a significant higher 1-year survival rates than DDLT recipients, while a significant lower 3-year survival rates and 5-year survival rates. This may be a result of improvement of surgical technique and perioperative management. However, because of a relatively higher incidence (up to 30%) of biliary complication after LDLT, LDLT recipients may have a lower long-term survival rates than DDLLT recipients. Different results in DDLLT recipients’ disease-free survival rates seem hard to explain. We consider a better tumor stage at the time of transplantation (meet Milan criteria) may contribute to better 1-year disease-free survival rates and 5-year disease-free survival rates. A larger sample and more randomized controlled studies may resolve this conflict and draw a right conclusion.

The tumors’ stage at the time of resection and LT is another risk factor for postoperative overall survival and disease-free survival. Some studies were theoretical and assessed the salvage transplantability according to the pattern of recurrence after resection for HCC within Milan criteria and found that 76% to 87% of recurrences were considered eligible for SLT on imaging grounds. For HCC patients not meeting Milan criteria, SLT could be applied for those cases with less aggressiveness, namely tumor size less than 6 cm and pathological well differentiation. For those cases meeting Milan criteria, PLT seems to be the first option. SLT could be performed for those patients with recurrence within Milan criteria after primary resection and without delay before recurrence with advanced disease manifestations. But there is no consensus about the survival rates for patients with recurrence beyond Milan criteria. Our result reveals that SLT group has similar survival rates compared with PLT group beyond Milan criteria at the time of LT. Unfortunately, data extracted from our including studies are not enough to do further meta-analysis on patients’ survival rates meeting Milan criteria at the time of LT and the corresponding disease-free survival rates.

Moreover, in countries with a higher incidence of HCC, a higher proportion of HCC patients on the waiting list and/or a longer median time-to-transplant, SLT could offer a gain in life-expectancy to the remaining waiting-list patients.

This review has some limitations. Although funnel plots may be suggestive of publication bias with lack of negative small RCTs, a firm conclusion about bias is difficult to make as the asymmetry of the funnel plots is minimal. And funnel plots can show asymmetry for other reasons. Therefore, our pooled OR might be an overestimate of the true effect. Due to data constraints, this meta-analysis could not analyze the quality of life score and was unable to carry out stratified analyses of other possible confounding factors. The method need to be more effective. Larger samples and randomized controlled studies with longer follow-up are required. Our conclusions also need more detailed data to confirm the results. The search language was limited. The integrity of the data was affected to a certain extent.

In conclusion, this new strategy SLT can be effectively performed for patients with recurrence or deterioration of liver function after hepatectomy for HCC. It does not increase the perioperative mortality and has a similar long-term survival rates compared to PLT. When surgical technique is no longer a problem for SLT, more patients will benefit from it.

COMMENTS

Background
Due to shortage of available donors, salvage liver transplantation (SLT) has been proposed and performed for the patients who undergo primary liver resection for hepatocellular carcinoma (HCC) or HCC recurrence or deterioration of liver function. This meta-analysis was designed to evaluated survival and recurrence after SLT for the treatment of HCC compared with primary liver transplantation (PLT).

Research frontiers
The study evaluated survival and recurrence after SLT for the treatment of HCC compared with PLT using a meta-analysis of all relevant controlled studies.

Innovations and breakthroughs
This is the first systematic review and meta-analysis on the survival and recurrence after SLT for the treatment of HCC compared with PLT. The author made a comprehensive search of studies. Several important conclusions might be used for future selection in SLT or PLT for HCC patients’ treatments.

Applications
This meta-analysis shows that SLT has a similar survival rates in comparison with PLT. SLT offers an alternative treatment method for HCC patients in facing a shortage of available donors.

Terminology
SLT was defined as a liver transplantation performed for recurrent HCC or deterioration of liver function after primary liver resection.

Peer review
The article should be published as it is a nice overview on the topic after some revisions are performed.

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