Salvage Liver Transplant versus Primary Liver Transplant for Patients with Hepatocellular Carcinoma

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Background:
The strategy of salvage liver transplantation (SLT) originated for initially resectable and transplantable hepatocellular carcinoma (HCC) to preclude upfront transplantation, with SLT in the case of recurrence. However, SLT remains a controversial approach in comparison to primary liver transplant (PLT). The aim of our study was to conduct a systemic review and meta-analysis to assess the short-term outcomes, overall survival (OS), and disease-free survival (DFS) between SLT and PLT for patients with HCC, stratifying results according to the Milan criteria and donor types.

Material/Methods:
A search of PubMed, EMBASE, and the Cochrane Library was conducted to identify studies comparing SLT and PLT. A fixed effects model and a random effects model meta-analysis were conducted to assess the short-term outcomes, OS, and DFS based on the evaluation of heterogeneity.

Results:
SLT had superior 1-year, 3-year, and 5-year OS and DFS compared with that of PLT. After classifying data according to donor type and Milan criteria, our meta-analysis revealed: that for deceased-donor liver transplantation (DDLT) recipients, there were no significant differences in 1-year and 3-year OS rate between the SLT group and the PLT group. However, the 5-year OS rate was superior in the SLT group compared to the PLT group. Similarly, SLT had superior 1-year, 3-year, and 5-year OS rate compared to PLT in living-donor liver transplantation (LDLT) recipients. Moreover, 1-year, 3-year, and 5-year DFS were also superior in SLT compared to PLT in both the DDLT and LDLT recipients. In patients within Milan criteria there were no statistically significant differences in 1-year, 3-year, and 5-year OS and DFS between the SLT group and the PLT group. Similarly, in patients beyond Milan criteria, both SLT and PLT showed no significant difference for 1-year, 3-year, and 5-year OS rate.

Conclusions:
Our meta-analysis included the largest number of studies comparing SLT and PLT, and SLT was found to have significantly better OS and DFS. Moreover, this meta-analysis suggests that SLT has comparable postoperative complications to that of PLT, and thus, SLT may be a better treatment strategy for recurrent HCC patients and patients with compensated liver, whenever feasible, considering the severe organ limitation and the safety of SLT. However, PLT can be referred as a treatment strategy for HCC patients with cirrhotic and decompensated liver.

MeSH Keywords:
Carcinoma, Hepatocellular • Hepatectomy • Liver Transplantation

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Background

Hepatocellular carcinoma (HCC) is the most common liver cancer [1,2], and it is the third highest cause of cancer-associated deaths worldwide [3]. HCC has become a considerable global health issue. Currently, liver transplantation (LT) is an ideal treatment for early stage HCC patients [4,5]. LT treats both the tumor and concealed liver disease, and it has the highest cure rate among treatments [5,6]. In recent years, transplant centers have experienced a consistent growth in the number of patients with HCC who are contenders for LT. LT for HCC constitutes 15–50% of all LTs performed in most transplant centers [7,8]. Even though LT is an exceptional treatment option for HCC patients, the number of patients waiting for an LT surpasses the number of available donors [9,10]. Thus, not all patients with HCC are considered for primary liver transplantation (PLT).

The shortage of donors compared with the number of patients in need of a transplant is a serious and a persisting problem worldwide. To overcome long waiting lists, disease progression, and the dropout rate for LT, different “bridging” therapies, such as liver resection (LR) [11], radioembolization [12], radiofrequency ablation [13], and transarterial chemoembolization [14], have been used if waiting time for LT is more than 6 months. Majno et al. was the first to suggest salvage liver transplantation (SLT), which refers to an LT done after LR for HCC or crumbling of liver function after LR [15]. Since then, several studies have shown SLT is an effective approach for patients with recurrent HCC or crumbling of liver function after LR [11,16]. However, some studies have shown negative results for SLT compared to PLT [17,18], mainly related to surgical difficulties due to adhesions, increased rate of post-transplant complications, and poor long-term outcomes. Thus, SLT remains a controversial approach for many surgeons.

To our knowledge, only a few systematic evaluations of the short-term and long-term outcomes between SLT and PLT have been performed, and these evaluations have included only a few studies and a small total number of patients. Therefore, the main aim of this meta-analysis was to include more studies and a larger sample size in the comparison of SLT and PLT for short-term and long-term outcomes. Our study results may help physicians select which approach would likely have a major survival benefit for HCC patients and allow physicians to efficiently utilize a limited source of liver donors.

Material and Methods

Search strategy

Eligible studies for this systematic review and meta-analyses were identified by 2 authors (DY and WC) independently, following an a priori established protocol using the PubMed/MEDLINE, Embase, and Cochrane Library databases, and combining Medical Subject Headings (MeSH) and non-MeSH terms: liver transplantation, salvage liver transplantation, salvage transplantation, liver resection, PLT, SLT, hepatic resection, hepatocytomy, hepatocellular carcinoma, tumor recurrence, primary liver carcinoma, and HCC. In addition, relevant bibliographical lists of reviews were searched to identify other relevant studies. After an initial screening, abstracts, duplicate articles, or unpublished studies were excluded. The meta-analysis was performed according to the Preferred Reporting Items for Systematic Reviews and Meta-Analysis (PRISMA) guidelines [19].

Study selection

Considering that this systematic review investigated data with respect to outcomes, both retrospective and prospective studies were considered eligible. The goal was to guarantee the quality of the systematic review by only considering complete articles and not abstracts. We established a priori defined eligibility criteria for selection of studies. The inclusion criteria included: 1) study had a definition of SLT and PLT with SLT regarding the first author, study characteristics (publication year, country, and study design), participant characteristics (average age of the recipients, sample size of SLT and PLT within and beyond Milan criteria, and sample size of SLT and PLT according to donor types), pre-transplant Model for End-Stage Liver Disease (MELD) score, pre-transplant alpha-fetoprotein (AFP) level,
pre-transplant tumor status, pre-transplant “bridging” therapies, the duration of follow-up, and outcomes (biliary complications, sepsis, postoperative bleeding, vascular complications, perioperative mortality, OS, and DFS). Moreover, in case of insufficient data, investigators were approached to collect more relevant results. Conflicts in data extraction were resolved by discussion or consensus with a third reviewer.

Quality assessment

The quality of included studies was evaluated with the Newcastle-Ottawa scale (NOS) [20]. The scale is comprised of 3 assessment factors: 1) assessment of a selection of the study groups; 2) comparability of 2 groups; and 3) outcome assessment. The NOS ranges from 0 to 9. Studies with scores 7 were thought to be high quality, 4-6 moderate quality, and less than 4 low quality (Table 1).

Statistical analysis

All results are accounted for as in the original articles and were double-checked. A meta-analysis was carried out with RevMan Version 5.3 (Review Manager, Copenhagen: The Nordic Cochrane Centre, The Cochrane Collaboration, 2014). Outcomes are calculated as pooled odds ratios (ORs) and standard mean difference (SMD) with corresponding 95% confidence intervals (CIs). Fixed-effect or random-effect models were utilized to compute summary estimates based on the evaluation of heterogeneity. Overall effects were evaluated using the Z-test; heterogeneity was tested using Cochran’s $\chi^2$ test. The $I^2$ statistic was used to evaluate heterogeneity, which was characterized as low, moderate, or high (>25%, >50%, and >75% respectively) [21]. Two-sided $P$-values less than 0.05 were considered significant.

Outcome measures

Pre-transplant parameters examined were: MELD score, AFP level, bridging therapies, and tumor status. Postoperative outcome parameters examined were: biliary complications (includes biliary strictures or fistulas), sepsis, postoperative bleeding, vascular complications, and operative mortality. Long-term outcomes were: 1-year, 3-year, and 5-year OS and DFS rates for patients within and beyond Milan criteria, and donor types along with follow-up period.

Results

Study search and included studies

The database search identified 3714 references for assessment (Figure 1) of which 154 full-text articles were assessed for eligibility; of these, 134 articles were excluded (121 did not meet inclusion criteria and 13 had insufficient data). The remaining 20 retrospective studies between 2003 and 2017 were eligible according to our inclusion criteria and were included in this meta-analysis [11,16–18,22–37], with a total of 9879 patients included (SLT=1306 patients and PLT=8573 patients) (Table 2).

Meta-analysis

Pre-transplant MELD score between SLT and PLT

To assess the outcome measurement of MELD scores, a total of 1308 patients were included from 7 studies [16,23,26–28,31,32]. The $\chi^2$ test revealed $P=0.07$ and $I^2=48%$; meta-analysis using a fixed effect model revealed that SLT had a significantly lower MELD score than that of PLT (SMD: –0.22, 95% CI: –0.37 to –0.07, $P=0.004$) (Figure 2A).

Pre-transplant AFP level between SLT and PLT

To assess the outcome measurement of AFP level, a total of 8382 patients were included from 7 studies [17,18,26,27,30,32,37]. The $\chi^2$ test revealed $P=0.002$ and $I^2=71%$; meta-analysis using a random effect model revealed that SLT had a significantly lower AFP level than that of PLT (SMD: –0.27, 95% CI: –0.51 to –0.04, $P=0.02$) (Figure 2B).

Pre-transplant tumor status between SLT and PLT

Our meta-analysis found that the maximum tumor diameter and the number of tumors >3 cm was significantly higher in PLT patients than in SLT patients: (SMD: –0.51, 95% CI: –0.95 to –0.08, $P=0.02$, Figure 3A) [17,22,26,30,32,35,37], and (OR: 0.59, 95% CI: 0.41 to 0.86, $P=0.006$, Figure 3B) [17,26,27,33,34] respectively. However, SLT patients had significantly higher numbers of nodules than PLT patients (SMD: 0.57, 95% CI: 0.17 to 0.97, $P=0.005$, Figure 3C) [17,22,26,30,32,35,37]. But, the meta-analysis of >3 nodules was not significantly different between the 2 groups (OR: 2.36, 95% CI: 0.86 to 6.46, $P=0.09$, Figure 3D) [16,17,33,34].

Follow-up period between SLT patients and PLT patients

While looking at pre-transplant therapy between SLT patients and PLT patients in the included studies, we found no significant difference between the 2 groups (OR: 1.78, 95% CI: 0.87 to 3.62, $P=0.11$, Figure 4A) [16,17,26,28,30,33,34].
OS outcomes between SLT and PLT

To assess the outcome measurement of 1-year OS, a total of 9725 patients were included from 19 studies [16–18,22–37]. The \( \chi^2 \) test revealed \( P=0.48 \) and \( I^2=0\% \); meta-analysis using a fixed effect model revealed that the SLT group (74.30%) had superior 1-year OS rate compared to the PLT group (77.01%), which was statistically significant (OR: 0.86, 95% CI: 0.75 to 0.98, \( P=0.03 \)) Figure 5A.

To assess the outcome measurement of the 3-year OS rate, a total of 9649 patients were included from 18 studies [16–18, 22–30,32–37]. The \( \chi^2 \) test revealed \( P=0.48 \) and \( I^2=0\% \); meta-analysis using a fixed effect model revealed that the SLT group...
(55.69%) had a superior 3-year OS rate compared to the PLT group (59.07%), which was statistically significant (OR: 0.85, 95% CI: 0.76 to 0.96, \( P = 0.01 \)) Figure 5B.

To assess the outcome measurement of the 5-year OS rate, a total of 9756 patients were included from 18 studies \([11,16–18,22–30,32–36]\). The \( I^2 \) test revealed \( P = 0.37 \) and \( I^2 = 7\% \); meta-analysis using a fixed effect model revealed that the SLT group (48.67%) had a superior 5-year OS rate compared to the PLT group (52.32%), which was statistically significant (OR: 0.85, 95% CI: 0.76 to 0.96, \( P = 0.009 \)) Figure 5C.

Data was classified according to donor type: DDLT and LDLT. In DDLT recipients, there was no significant difference in 1-year OS rate (OR: 0.93, 95% CI: 0.80 to 1.09, \( P = 0.40 \), Figure 6A) \([16,17,22–24,27,29,30,33–37]\) and 3-year OS rate (OR: 0.89, 95% CI: 0.78 to 1.02, \( P = 0.08 \), Figure 6B) \([16–18,22–24,27,29,30,33–37]\) between the SLT group and the PLT group. However, 5-year OS rate was superior in the SLT group compared to the PLT group (OR: 0.89, 95% CI: 0.78 to 1.02, \( P = 0.08 \), Figure 6B) \([16–18,22–24,27,29,30,33–37]\), and (OR: 0.89, 95% CI: 0.78 to 1.02, \( P = 0.08 \), Figure 6B) \([16–18,22–24,27,29,30,33–37]\) respectively. In LDLT recipients, SLT had superior 1-year, 3-year, and 5-year OS rates compared to PLT: (OR: 0.49, 95% CI: 0.26 to 0.95, \( P = 0.03 \), Figure 7A) \([23,30,32,34]\), (OR: 0.47, 95% CI: 0.28 to 0.79, \( P = 0.004 \), Figure 7B) \([23,30,32,34]\), and (OR: 0.43, 95% CI: 0.26 to 0.71, \( P = 0.0009 \), Figure 7C) \([23,30,32,34]\) respectively.

Additionally, data were classified according to Milan criteria: within Milan criteria and beyond Milan criteria. In patients within Milan criteria, the meta-analysis revealed no statistically significant difference for 1-year, 3-year, and 5-year OS rates between the SLT group and the PLT group: (OR: 0.68, 95% CI: 0.44 to 1.04, \( P = 0.08 \), Figure 8A) \([16,18,22–23,25–27,31,33,33,36]\), (OR: 0.78, 95% CI: 0.55 to 1.11, \( P = 0.17 \), Figure 8B) \([16,18,22,23,25–27,33,35,36]\), and (OR: 0.75, 95% CI: 0.40 to 1.42, \( P = 0.38 \), Figure 8C) \([11,16,18,22,23,25–27,33,35,36]\) respectively. Similarly, in patients beyond the Milan criteria, both SLT and PLT showed no significant difference for 1-year, 3-year, and 5-year OS rates: (OR: 0.68, 95% CI: 0.19 to 2.48, \( P = 0.56 \), Figure 9A) \([18,29,31,37]\), (OR: 2.07, 95% CI: 0.92 to 4.66, \( P = 0.08 \), Figure 9B) \([18,29,37]\), and (OR: 2.01, 95% CI: 0.75 to 5.40, \( P = 0.17 \), Figure 9C) \([18,29]\), respectively.

**DFS outcomes between SLT patients and PLT patients**

To assess the outcome measurement of 1-year DFS a total of 8868 patients were included from 13 studies \([16–18,26,28–30,32–37]\). The \( I^2 \) test revealed \( P = 0.08 \) and \( I^2 = 38\% \); meta-analysis using a fixed effect model revealed that the SLT group (67.69%) had superior 1-year DFS rate compared to the PLT group (70.03%), which was statistically significant (OR: 0.86, 95% CI: 0.75 to 0.99, \( P = 0.03 \)) Figure 10A.

To assess the outcome measurement of 3-year DFS, a total of 6910 patients were included from 14 studies \([16–18,22,26,28–30,32–37]\). The \( I^2 \) test revealed \( P = 0.02 \) and \( I^2 = 50\% \); meta-analysis using a random-effect model revealed that the SLT group (67.69%) had superior 1-year DFS rate compared to the PLT group (70.03%), which was statistically significant (OR: 0.86, 95% CI: 0.75 to 0.99, \( P = 0.03 \)) Figure 10A.
Table 2. Study characteristics included in meta-analysis.

| Study code | Study | Year | Country | Study type         | Total N | Follow-up (mo) | Arms | n | Age (yrs) |
|------------|-------|------|---------|--------------------|---------|----------------|------|---|-----------|
| 1          | Adam et al. [17] | 2003 | France  | Case-control       | 212     | 16±50          | SLT  | 17 | 55±10     |
|            |       |      |         |                    |         | 18±6          | PLT  | 195|           |
| 2          | Belghiti et al. [22] | 2003 | France  | Case-control       | 88      | 50±53±33       | SLT  | 18 | 55±10     |
|            |       |      |         |                    |         | 50±53±33      | PLT  | 70 | 53±7      |
| 3          | Hwang et al. [23]  | 2007 | Korea   | Case-control       | 217     | 30±72±68.8     | SLT  | 17 | 49.3±8.6  |
|            |       |      |         |                    |         | 40±1±22.4     | PLT  | 200| 51.2±7.0  |
| 4          | Scatton et al. [24] | 2008 | France  | Retrospective cohort | 93     | 32±4±54        | PLT  | 73 | <70       |
|            |       |      |         |                    |         | 50±6          | SLT  | 6  | 62±6      |
| 5          | Margarit et al. [25] | 2005 | Spain   | Retrospective cohort | 42     | 45.6±1±28.8    | SLT  | 16 | 54±8      |
|            |       |      |         |                    |         | 44±6          | PLT  | 160| 51±7.6    |
| 6          | Del Gaudio et al. [26] | 2008 | Italy   | Retrospective cohort | 163     | 26±2±26.3     | SLT  | 147| 55±7      |
|            |       |      |         |                    |         | 36±32         | PLT  | 180| 47        |
| 7          | Wang et al. [27]   | 2016 | China   | Retrospective cohort | 371    | 30±10±25      | SLT  | 44 | <70       |
|            |       |      |         |                    |         | 33±22         | PLT  | 150|           |
| 8          | Liu et al. [28]    | 2012 | China   | Retrospective cohort | 219    | 27.7±18.77    | SLT  | 5  | <70       |
|            |       |      |         |                    |         | 35±33         | PLT  | 32 | <70       |
| 9          | Facciuto et al. [29] | 2008 | USA     | Retrospective cohort | 37     | 12.2±4.4      | SLT  | 888| 50.0±9.28 |
|            |       |      |         |                    |         | 12±4±42       | PLT  | 6087| 49.7±9.67 |
| 10         | Hu et al. [30]     | 2012 | China   | Retrospective cohort | 6975   | 45.6±1±28.8  | SLT  | 188| <70       |
|            |       |      |         |                    |         | 44±6          | PLT  | 200| 53±8      |
| 11         | Cherqui et al. [11] | 2009 | France  | Retrospective cohort | 154    | 19.5±24.4     | SLT  | 76 | 48.3±8.6  |
|            |       |      |         |                    |         | 19.5±24.4     | PLT  | 295| 48.3±8.5  |
| 12         | Kim et al. [31]    | 2008 | South Korea | Retrospective cohort | 46     | 30±10±25      | SLT  | 44 | <70       |
|            |       |      |         |                    |         | 33±22         | PLT  | 150|           |
| 13         | Vasavada et al. [32] | 2015 | India   | Retrospective cohort | 109    | 35±33         | SLT  | 31 | 56±5      |
|            |       |      |         |                    |         | 31±31         | PLT  | 91 |           |
| 14         | Wu et al. [16]     | 2012 | China   | Retrospective cohort | 183    | 58±7±20.7    | SLT  | 36 | 49.46±7.1 |
|            |       |      |         |                    |         | 64±2±18.1     | PLT  | 147| 47.66±5.8 |
| 15         | Bhangui et al. [33] | 2016 | France  | Retrospective cohort | 371    | 30±10±25      | SLT  | 31 | <65       |
|            |       |      |         |                    |         | 31±31         | PLT  | 340| <65       |
| 16         | Moon et al. [34]   | 2012 | Korea   | Retrospective cohort | 186    | 27.2±21.7     | SLT  | 17 | <70       |
|            |       |      |         |                    |         | 39±18.8       | PLT  | 169| 52        |
| 17         | Sapisochin et al. [35] | 2010 | Spain   | Case-control       | 51     | 88±4±7.5     | SLT  | 17 | 59        |
|            |       |      |         |                    |         | 88±4±7.5     | PLT  | 15 |           |
| 18         | Shan et al. [18]   | 2017 | China   | Retrospective cohort | 239    | 35±10.2       | SLT  | 28 | 47.79±6.4 |
|            |       |      |         |                    |         | 35±6.8       | PLT  | 211| 50.45±9.24 |
| 19         | Vennarecci et al. [36] | 2007 | Italy   | Retrospective cohort | 46     | 28±5±17.1     | SLT  | 9  | <70       |
|            |       |      |         |                    |         | 26±3±14.8    | PLT  | 37 | <70       |
| 20         | Shao et al. [37]   | 2008 | China   | Retrospective cohort | 77     | 18±3±4       | SLT  | 15 | <60       |
|            |       |      |         |                    |         | 21±4±5       | PLT  | 62 | <60       |
To assess the outcome measurement of 5-year DFS, a total of 8842 patients were included from 12 studies [16–18,22,26,29,30,33,35–37], and (OR: 0.61, 95% CI: 0.32 to 1.19, P=0.15, Figure 13C) [16,18,22,26,27,33,35,36], respectively. There was not enough data to do meta-analysis of DFS for patients beyond the Milan criteria.

**Postoperative outcomes**

**Biliary complication between SLT and PLT**

To assess the outcome measurement of biliary complication, a total of 8172 patients were included from 9 studies [16,17,22,23,28,30,31,34,36]. The χ² test revealed P=0.62 and I²=0%; meta-analysis using a fixed effect model revealed no statistically significant difference between SLT and PLT (OR: 1.14, 95% CI: 0.94 to 1.40, P=0.19) Figure 14A.

**Sepsis between SLT and PLT**

To assess the outcome measurement of sepsis, a total of 782 patients were included from 5 studies [17,22,23,28,36]. The χ² test revealed P=0.99 and I²=0%; meta-analysis using a fixed effect model revealed no statistically significant difference between SLT and PLT (OR: 1.14, 95% CI: 0.63 to 2.06, P=0.68) Figure 14B.
Figure 3. Pre-transplant tumor status between SLT and PLT: (A) maximum tumor diameter, (B) number of tumors >3 cm, (C) number of nodules, (D) >3 nodules.
META-ANALYSIS

Study or subgroup  
Adam 2003  
Bhangui 2016  
Del Gaudio 2008  
Faciutto 2008  
Hu 2012  
Liu 2012  
Moon 2012  
Wu 2012  
Total (95% CI)  

Heterogeneity:  
Chi²: 19.35, df=15 (P=0.20); I² = 22%  
Test for overall effect: Z=1.62 (P=0.10)

Figure 4. (A) Pre-transplant therapy between SLT and PLT; (B) follow-up period.
### A

| Study or subgroup | SLT Events | Total | PLT Events | Total | Weight | Odds ratio M-H, fixed, 95% CI | Odds ratio M-H, fixed, 95% CI |
|------------------|------------|-------|------------|-------|--------|-------------------------------|-------------------------------|
| Adam 2003        | 12         | 17    | 156        | 195   | 1.7%   | 0.60 [0.20, 1.80]             |                               |
| Belghiti 2003    | 15         | 18    | 64         | 70    | 1.0%   | 0.47 [0.11, 2.09]             |                               |
| Bhangui 2016     | 25         | 31    | 279        | 340   | 2.1%   | 0.91 [0.36, 2.32]             |                               |
| Del Gaudio 2008  | 15         | 16    | 129        | 147   | 0.4%   | 2.09 [0.26, 16.81]            |                               |
| Faciutto 2008    | 5          | 5     | 28         | 32    | 0.2%   | 1.74 [0.08, 37.08]            |                               |
| Hu 2012          | 648        | 888   | 4534       | 6087  | 72.4%  | 0.92 [0.79, 1.08]             |                               |
| Hwang 2007       | 15         | 17    | 175        | 200   | 0.7%   | 1.07 [0.23, 4.97]             |                               |
| Kim 2008         | 13         | 15    | 28         | 31    | 0.6%   | 0.70 [0.10, 4.69]             |                               |
| Liu 2012         | 34         | 39    | 162        | 180   | 1.7%   | 0.76 [0.26, 2.18]             |                               |
| Margarit 2005    | 5          | 6     | 28         | 36    | 0.3%   | 1.43 [0.15, 14.05]            |                               |
| Moon 2012        | 12         | 17    | 152        | 169   | 1.9%   | 0.27 [0.08, 0.85]             |                               |
| Sapisochin 2010  | 10         | 17    | 29         | 34    | 1.8%   | 0.25 [0.06, 0.95]             |                               |
| Scotten 2008     | 15         | 20    | 52         | 73    | 1.3%   | 1.21 [0.39, 3.76]             |                               |
| Shan 2017        | 18         | 28    | 169        | 211   | 3.3%   | 0.45 [0.19, 1.04]             |                               |
| Shao 2008        | 12         | 15    | 57         | 62    | 1.0%   | 0.35 [0.07, 1.67]             |                               |
| Vasavada 2015    | 14         | 18    | 84         | 91    | 1.4%   | 0.29 [0.08, 1.13]             |                               |
| Vennarecci 2007  | 8          | 9     | 29         | 37    | 0.3%   | 2.21 [0.24, 20.35]            |                               |
| Wang 2016        | 46         | 76    | 199        | 295   | 7.5%   | 0.74 [0.44, 1.24]             |                               |
| Wu 2012          | 35         | 36    | 144        | 147   | 0.4%   | 0.73 [0.07, 7.22]             |                               |

Total (95% CI) 1288 / 8437 100.0% 0.86 [0.75, 0.98]

Heterogeneity: Chi²=17.68, df=18 (P=0.48); I²=0%
Test for overall effect: Z=2.23 (P=0.03)

### B

| Study or subgroup | SLT Events | Total | PLT Events | Total | Weight | Odds ratio M-H, fixed, 95% CI | Odds ratio M-H, fixed, 95% CI |
|------------------|------------|-------|------------|-------|--------|-------------------------------|-------------------------------|
| Adam 2003        | 9          | 17    | 133        | 195   | 1.8%   | 0.52 [0.19, 1.42]             |                               |
| Belghiti 2003    | 14         | 18    | 53         | 70    | 0.9%   | 1.12 [0.33, 3.87]             |                               |
| Bhangui 2016     | 13         | 31    | 182        | 340   | 3.1%   | 0.63 [0.30, 1.32]             |                               |
| Del Gaudio 2008  | 13         | 16    | 119        | 147   | 0.8%   | 1.02 [0.27, 3.82]             |                               |
| Faciutto 2008    | 5           | 5     | 22         | 32    | 0.1%   | 5.13 [0.26, 101.70]           |                               |
| Hu 2012          | 460        | 888   | 3354       | 6857  | 73.6%  | 0.87 [0.75, 1.00]             |                               |
| Hwang 2007       | 11         | 17    | 156        | 200   | 1.5%   | 0.52 [0.18, 1.48]             |                               |
| Liu 2012         | 30          | 39   | 146        | 180   | 2.1%   | 0.78 [0.34, 1.79]             |                               |
| Margarit 2005    | 4           | 6     | 22         | 36    | 0.4%   | 1.27 [0.21, 7.89]             |                               |
| Moon 2012        | 10          | 17    | 140        | 169   | 1.9%   | 0.30 [0.10, 0.84]             |                               |
| Sapisochin 2010  | 9           | 17    | 45         | 73    | 1.2%   | 0.16 [0.41, 3.25]             |                               |
| Scotten 2008     | 13          | 20    | 135        | 211   | 2.6%   | 0.65 [0.19, 1.44]             |                               |
| Shan 2017        | 15          | 28    | 135        | 211   | 2.6%   | 1.90 [0.48, 7.52]             |                               |
| Shao 2008        | 12          | 15    | 42         | 62    | 0.6%   | 0.64 [0.18, 2.22]             |                               |
| Vasavada 2015    | 14          | 18    | 77         | 91    | 1.0%   | 4.87 [0.55, 43.18]            |                               |
| Vennarecci 2007  | 8           | 9     | 23         | 37    | 0.2%   | 1.72 [0.07, 45.87]            |                               |
| Wang 2016        | 40          | 76    | 146        | 295   | 5.0%   | 1.13 [0.68, 1.88]             |                               |
| Wu 2012          | 29          | 36    | 127        | 147   | 1.7%   | 0.65 [0.25, 1.69]             |                               |

Total (95% CI) 1273 / 8376 100.0% 0.85 [0.76, 0.96]

Heterogeneity: Chi²=16.64, df=17 (P=0.48); I²=0%
Test for overall effect: Z=2.54 (P=0.01)
Figure 5. Overall survival outcomes between SLT group and PLT group: (A) 1-year, (B) 3-year, (C) 5-year.
To assess the outcome measurement of vascular complications, a total of 8172 patients were included from 9 studies [16,17,22,23,28,30,31,34,36]. The \( \chi^2 \) test revealed \( P=0.96 \) and \( I^2=0\%; \) meta-analysis using a fixed effect model revealed no statistically significant difference between SLT and PLT (OR: 1.32, 95% CI: 1.03 to 1.71, \( P=0.03 \)) Figure 14C.

**Vascular complications between SLT and PLT**

To assess the outcome measurement of vascular complications, a total of 8172 patients were included from 9 studies [16,17,22,23,28,30,31,34,36]. The \( \chi^2 \) test revealed \( P=0.96 \) and \( I^2=0\%; \) meta-analysis using a fixed effect model revealed no statistically significant difference between SLT and PLT (OR: 1.32, 95% CI: 1.03 to 1.71, \( P=0.03 \)) Figure 14C.

**Figure 6.** Overall survival outcomes for DDLT between SLT group and PLT group: (A) 1-year, (B) 3-year, and (C) 5-year.
### Study or subgroup

| Study or subgroup | SLT Events Total | PLT Events Total | Weight |
|------------------|-----------------|-----------------|--------|
| Hu 2012          | 27/29           | 339/360         | 16.6%  |
| Hwang 2007       | 15/17           | 175/200         | 15.3%  |
| Moon 2012        | 12/17           | 152/169         | 38.8%  |
| Vasavada 2015    | 14/18           | 84/91           | 29.3%  |
| **Total (95% CI)** | **81/820**     |                 | **100.0%** |

Heterogeneity: $\chi^2 = 3.10$, $df=3$ ($P=0.38$); $I^2 = 3$

Test for overall effect: $Z=2.13$ ($P=0.03$)

#### Odds ratio

| Study or subgroup | SLT Events Total | PLT Events Total | Weight |
|------------------|-----------------|-----------------|--------|
| Hu 2012          | 27/29           | 339/360         | 16.6%  |
| Hwang 2007       | 15/17           | 175/200         | 15.3%  |
| Moon 2012        | 12/17           | 152/169         | 38.8%  |
| Vasavada 2015    | 14/18           | 84/91           | 29.3%  |
| **Total (95% CI)** | **81/820**     |                 | **100.0%** |

Heterogeneity: $\chi^2 = 1.06$, $df=3$ ($P=0.79$); $I^2 = 0$

Test for overall effect: $Z=2.85$ ($P=0.004$)

#### Odds ratio

| Study or subgroup | SLT Events Total | PLT Events Total | Weight |
|------------------|-----------------|-----------------|--------|
| Hu 2012          | 22/29           | 309/360         | 30.9%  |
| Hwang 2007       | 11/17           | 156/200         | 24.0%  |
| Moon 2012        | 10/17           | 140/169         | 29.3%  |
| Vasavada 2015    | 14/18           | 77/91           | 15.7%  |
| **Total (95% CI)** | **81/820**     |                 | **100.0%** |

Heterogeneity: $\chi^2 = 0.32$, $df=3$ ($P=0.96$); $I^2 = 0$

Test for overall effect: $Z=3.31$ ($P=0.0009$)

#### Odds ratio

| Study or subgroup | SLT Events Total | PLT Events Total | Weight |
|------------------|-----------------|-----------------|--------|
| Hu 2012          | 22/29           | 309/360         | 27.6%  |
| Hwang 2007       | 9/17            | 144/200         | 26.3%  |
| Moon 2012        | 10/17           | 134/169         | 25.0%  |
| Vasavada 2015    | 12/18           | 77/91           | 21.0%  |
| **Total (95% CI)** | **81/820**     |                 | **100.0%** |

Heterogeneity: $\chi^2 = 0.32$, $df=3$ ($P=0.96$); $I^2 = 0$

Test for overall effect: $Z=3.31$ ($P=0.0009$)

### Figure 7.

Overall survival outcomes for LDLT between SLT group and PLT group: (A) 1-year, (B) 3-year, (C) 5-year.

### Discussion

PLT is a well-accepted ideal treatment strategy for patients with early stage HCC, but the lack of available organ donors requires the use of restrictive criteria to assure the optimal use of the available grafts. On the other hand, LR remains a valuable curative option for non-transplantable HCC patients or for those waiting for LT. However, the tumor recurrence rate is higher after LR within 5 years [38]. Thus, SLT after primary LR remains the ideal treatment for recurrent HCC and decompensated liver after primary LR [11,15,16]. Notwithstanding, the intensity of surgical difficulty during SLT and the potential for reduced OS is a concern for a large portion of experts. Substantial adhesions and portal collateral circulations are frequently experienced after earlier LR [16]. Likewise, because of adhesion, heedless dissection of adhesions around the liver may bring heavy bleeding at the dissection area. Moreover, because of adhesions, it’s also hard to separate a hepatic vein and the inferior vena cava. However, some studies have demonstrated that SLT has similar perioperative and postoperative complications as that of the PLT [22,23,31]. Furthermore, reports suggest that meticulous sharp dissection with a sufficient dissection plan can resolve the problem of excessive bleeding in cases of excessive adhesions [23,31]. Nevertheless, there are serious concerns among experts about the outcomes of SLT in comparison with the PLT, since most of the studies have reported conflicting results. However, there is still a need for a large multi-center study to compare the advantages and disadvantages of SLT and PLT.

Until now, few systematic reviews and meta-analysis have been conducted comprehensively to analyze the short-term
**Figure 8.** Overall survival outcomes for patients within Milan criteria between SLT group and PLT group: (A) 1-year, (B) 3-year, (C) 5-year.

| Study or subgroup | SLT Events | SLT Total | PLT Events | PLT Total | Weight | Odds ratio, 95% CI | Odds ratio, 95% CI |
|-------------------|------------|-----------|------------|-----------|--------|-------------------|-------------------|
| **A** | | | | | | | |
| Belghiti 2003 | 15 | 18 | 64 | 70 | 9.4% | 0.47 [0.11, 2.09] | | |
| Bhangui 2016 | 25 | 31 | 279 | 340 | 19.5% | 0.91 [0.36, 2.32] | | |
| Del Gaudio 2008 | 15 | 16 | 129 | 147 | 3.4% | 2.09 [0.26, 16.81] | | |
| Hwang 2007 | 8 | 10 | 139 | 158 | 7.2% | 0.55 [0.11, 2.77] | | |
| Kim 2008 | 9 | 10 | 28 | 31 | 3.0% | 0.96 [0.09, 10.47] | | |
| Margant 2005 | 5 | 6 | 28 | 36 | 2.9% | 1.43 [0.15, 14.05] | | |
| Sapisochin 2010 | 10 | 17 | 29 | 34 | 17.2% | 0.25 [0.06, 0.95] | | |
| Shan 2017 | 9 | 13 | 104 | 113 | 14.3% | 0.19 [0.05, 0.76] | | |
| Vennarecci 2007 | 8 | 9 | 29 | 37 | 2.7% | 2.21 [0.24, 20.35] | | |
| Wang 2016 | 24 | 30 | 86 | 101 | 17.0% | 0.70 [0.24, 1.99] | | |
| Wu 2012 | 35 | 36 | 144 | 147 | 3.4% | 0.73 [0.07, 7.22] | | |
| **Total (95% CI)** | 196 | 1214 | 100.0% | 0.68 [0.44, 1.04] | | | |
| **B** | | | | | | | |
| Belghiti 2003 | 14 | 18 | 53 | 70 | 7.0% | 1.12 [0.33, 3.87] | | |
| Bhangui 2016 | 13 | 31 | 182 | 340 | 25.7% | 0.63 [0.30, 1.32] | | |
| Del Gaudio 2008 | 13 | 16 | 119 | 147 | 6.4% | 1.02 [0.27, 3.82] | | |
| Hwang 2007 | 8 | 10 | 87 | 158 | 3.0% | 3.26 [0.67, 15.86] | | |
| Margant 2005 | 4 | 6 | 22 | 36 | 3.1% | 1.27 [0.21, 7.89] | | |
| Sapisochin 2010 | 9 | 17 | 26 | 34 | 11.9% | 0.35 [0.10, 1.19] | | |
| Shan 2017 | 7 | 13 | 96 | 113 | 13.3% | 0.21 [0.06, 0.69] | | |
| Vennarecci 2007 | 8 | 9 | 23 | 37 | 1.5% | 4.87 [0.55, 43.18] | | |
| Wang 2016 | 22 | 30 | 79 | 101 | 14.0% | 0.77 [0.30, 1.95] | | |
| Wu 2012 | 29 | 36 | 127 | 147 | 14.1% | 0.65 [0.25, 1.69] | | |
| **Total (95% CI)** | 186 | 1183 | 100.0% | 0.78 [0.55, 1.11] | | | |
| **C** | | | | | | | |
| Belghiti 2003 | 10 | 18 | 37 | 70 | 10.6% | 1.11 [0.39, 3.16] | | |
| Bhangui 2016 | 1 | 31 | 135 | 340 | 6.0% | 0.05 [0.01, 0.38] | | |
| Chenour 2009 | 13 | 18 | 101 | 136 | 10.2% | 0.90 [0.30, 2.71] | | |
| Del Gaudio 2008 | 10 | 16 | 107 | 147 | 10.4% | 0.62 [0.21, 1.83] | | |
| Hwang 2007 | 8 | 10 | 39 | 158 | 7.7% | 12.21 [2.49, 59.92] | | |
| Margant 2005 | 2 | 6 | 11 | 36 | 6.6% | 1.14 [0.18, 7.15] | | |
| Sapisochin 2010 | 9 | 17 | 22 | 34 | 9.8% | 0.61 [0.19, 2.00] | | |
| Shan 2017 | 6 | 13 | 93 | 113 | 9.7% | 0.18 [0.06, 0.61] | | |
| Vennarecci 2007 | 8 | 9 | 23 | 37 | 5.4% | 4.87 [0.55, 43.18] | | |
| Wang 2016 | 17 | 30 | 75 | 101 | 11.7% | 0.45 [0.19, 1.06] | | |
| Wu 2012 | 25 | 36 | 111 | 147 | 12.0% | 0.74 [0.33, 1.64] | | |
| **Total (95% CI)** | 204 | 1319 | 100.0% | 0.75 [0.40, 1.42] | | | |
and long-term outcomes of SLT and PLT. However, an earlier meta-analysis was reported but had only a few studies and had small total number of patients. Our meta-analysis includes 20 relatively high-quality studies conducted from 2003 to 2017, with a total 9879 patients (SLT=1306 and PLT=8573), thus we believe it is the first study of its type. In our meta-analysis, we found that SLT was superior and feasible in terms of OS and DFS compared to PLT, and we found that the incidence of postoperative complications, such as biliary complications, sepsis, and vascular complications of SLT were similar to that of PLT; however, there was a significantly higher rate of postoperative bleeding and operative mortality with the SLT group than the PLT group.

In the scenario of conflicting results from different studies, the most important finding regarding SLT was its post-transplant survival rate and DFS rate compared to PLT. Adam et al. [17] found that SLT was related to a higher risk of recurrence and a poorer outcome compared to PLT. Nonetheless, a study carried out in the same year by Belghiti et al. [22] found contrasting results and concluded that SLT and PLT were similar in terms of OS rates. Moreover, a study by Scatton et al. [24] showed that careful consideration of histological features of resected tumor specimens may be used as selection criteria for SLT, with similar survival and recurrence results as PLT. As reported earlier by Adam et al. [17], the poor results after SLT were basically because of increased operative mortality and excess bleeding at the time of surgery, because of surgical difficulties during dissecting the substantial adhesions and portal collateral circulations during LT. However, the other studies have suggested that meticulous sharp dissection with a sufficient dissection plan can resolve the problem of excessive bleeding [23,31].

Figure 9. Overall survival outcomes for patients beyond Milan criteria between SLT group and PLT group: (A) 1-year, (B) 3-year, (C) 5-year.
Figure 10. Disease-free survival outcomes between SLT group and PLT group: (A) 1-year, (B) 3-year, (C) 5-year.
Figure 11. Disease-free survival outcomes for DDLT between SLT group and PLT group: (A) 1-year, (B) 3-year, (C) 5-year.
As observed from pooled estimates of our meta-analysis, SLT showed superior 1-year, 3-year, and 5-year OS and DFS rates in comparison with PLT. After classifying data according to donor type, we found DDLT recipients showed no significant difference in 1-year and 3-year OS rates between the SLT and PLT groups. However, 5-year OS rates for DDLT recipients was superior in the SLT group compared to the PLT group. In LDLT recipients, SLT had superior 1-year, 3-year, and 5-year OS rates compared to PLT. Moreover, 1-year, 3-year, and 5-year DFS rates were also superior in SLT compared to PLT in both the DDLT and LDLT recipients. In addition, classifying data according to Milan criteria, our meta-analysis didn’t find any difference for OS and DFS rates between the SLT and PLT groups for patients within the Milan criteria. The meta-analysis for OS beyond the Milan criteria was also not significant between SLT and PLT groups. SLT after LR has the advantage that surgeons are aware of the histological status of the tumor, which allows surgeons to choose appropriate patients for SLT. Currently, there are no definitive answers as to why the OS and DFS rates of SLT patients surpassed those of PLT patients. One possible explanation is that after primary liver resection, there is downstaging of the tumor, and the patients presenting for SLT are mostly patients with Child A, lower MELD score, lower AFP level, and fewer nodules compared to PLT patients [25,26,39–41]. Interestingly, when we compared MELD score and pre-transplant AFP levels between SLT and PLT groups, we found both MELD score and pre-transplant AFP levels were significantly lower in SLT patients than in PLT patients. Thus, the meta-analysis of MELD score and pre-transplant AFP levels seems to justify our findings, that SLT is superior to PLT in terms of OS and DFS. However, our meta-analysis showed the SLT group had a higher number of nodules, but smaller size of tumors compared to the PLT group. The reason for a higher number of nodules can be explained in 2 ways: 1) local recurrence and 2) de novo HCC, as LR is associated with high tumor recurrence because it leaves diseased liver in a place where local recurrence might be from insufficient R1 resection or micro-vascular invasion from segmental portal circulation. Furthermore, de novo HCC is still present in the diseased liver after LR, leading to distant recurrence from the resection area [42]. These 2 phenomena might be responsible for a higher number of nodules in the SLT group. However, regular monitoring of HCC...
patients after LR might be the result of smaller tumors in the SLT group compared to the PLT group. These results should be reevaluated according to the recent transplant selection requirements. Additionally, these findings also showed that the patient selection standard for SLT demands careful consideration and redefinition. Moreover, our review of studies suggested that along with tumor size and numbers of tumors, the liver transplantation could be implemented for less aggressive and pathological well differentiated tumors. This meta-analysis also showed that SLT is similar to PLT for patients within and beyond Milan criteria, and can be performed safely after LR.

Moreover, concern regarding postoperative outcomes between SLT and PLT results showed that the rate of postoperative complications like biliary, sepsis, and vascular complications, were similar among SLT and PLT patients; however, postoperative bleeding and operative mortality was significantly high in the SLT group compared to the PLT group. The possible causes of
postoperative bleeding and operative mortality in SLT patients has already been discussed earlier in this article. Additionally, despite surgical difficulties in SLT, primary laparoscopic resection of the liver and postsurgical intra-abdominal anti-adhesive products are found to be effective in reducing adhesions and thereby minimizing the risks of complications in SLT [43,44].

Despite the high quality of the papers included in this meta-analysis, there are various shortcomings concerning our meta-analysis. First, there is a potential publication bias, because studies are less likely to outline negative findings and there are limited resources available to identify unpublished trials. Second, only English-language studies were included. Thus, the quality of outcomes was compromised to some extent, which is a typical reason for publication bias. In the future, high-quality randomized controlled trials with large sample size should be performed. However, this meta-analysis is still of great significance for comparing different outcomes between SLT and PLT and may prove beneficial for clinicians in choosing the appropriate treatment option.

| Study or subgroup | SLT       | PLT       | Odds ratio M-H, fixed, 95% CI |
|-------------------|-----------|-----------|-------------------------------|
| Adam 2003         | 17 (1.0)  | 11 (0.1)  | 0.10 (0.02, 0.49)             |
| Belghiti 2003     | 18 (0.5)  | 11 (0.1)  | 0.12 (0.03, 0.51)             |
| Hu 2012           | 88 (4.0)  | 62 (1.5)  | 1.04 (0.99, 1.00)             |
| Hwang 2007        | 5 (2.5)   | 10 (1.0)  | 0.82 (0.08, 8.00)             |
| Kim 2008          | 4 (1.5)   | 9 (1.0)   | 0.94 (0.80, 1.09)             |
| Liu 2012          | 39 (2.0)  | 33 (1.0)  | 0.14 (0.02, 0.99)             |
| Moon 2012         | 8 (0.5)   | 10 (0.3)  | 0.70 (0.08, 6.09)             |
| Vennarecci 2007   | 9 (0.2)   | 10 (0.1)  | 0.12 (0.02, 0.67)             |
| Wu 2012           | 4 (0.3)   | 5 (0.1)   | 0.09 (0.02, 0.54)             |
| Total (95% CI)    | 113 (0.2) | 77 (0.1)  | 1.00 (0.99, 1.00)             |
| Heterogeneity: Chi² = 2.1, df = 8 (P = 0.19) | Test for overall effect: Z = 3.1 (P = 0.00)

| Study or subgroup | SLT       | PLT       | Odds ratio M-H, fixed, 95% CI |
|-------------------|-----------|-----------|-------------------------------|
| Adam 2003         | 17 (1.0)  | 11 (0.1)  | 0.10 (0.02, 0.49)             |
| Belghiti 2003     | 18 (0.5)  | 11 (0.1)  | 0.12 (0.03, 0.51)             |
| Hu 2012           | 88 (4.0)  | 62 (1.5)  | 1.04 (0.99, 1.00)             |
| Hwang 2007        | 5 (2.5)   | 10 (1.0)  | 0.82 (0.08, 8.00)             |
| Kim 2008          | 4 (1.5)   | 9 (1.0)   | 0.94 (0.80, 1.09)             |
| Liu 2012          | 39 (2.0)  | 33 (1.0)  | 0.14 (0.02, 0.99)             |
| Moon 2012         | 8 (0.5)   | 10 (0.3)  | 0.70 (0.08, 6.09)             |
| Vennarecci 2007   | 9 (0.2)   | 10 (0.1)  | 0.12 (0.02, 0.67)             |
| Wu 2012           | 4 (0.3)   | 5 (0.1)   | 0.09 (0.02, 0.54)             |
| Total (95% CI)    | 113 (0.2) | 77 (0.1)  | 1.00 (0.99, 1.00)             |
| Heterogeneity: Chi² = 2.1, df = 8 (P = 0.19) | Test for overall effect: Z = 3.1 (P = 0.00)

| Study or subgroup | SLT       | PLT       | Odds ratio M-H, fixed, 95% CI |
|-------------------|-----------|-----------|-------------------------------|
| Adam 2003         | 17 (1.0)  | 11 (0.1)  | 0.10 (0.02, 0.49)             |
| Belghiti 2003     | 18 (0.5)  | 11 (0.1)  | 0.12 (0.03, 0.51)             |
| Hu 2012           | 88 (4.0)  | 62 (1.5)  | 1.04 (0.99, 1.00)             |
| Hwang 2007        | 5 (2.5)   | 10 (1.0)  | 0.82 (0.08, 8.00)             |
| Kim 2008          | 4 (1.5)   | 9 (1.0)   | 0.94 (0.80, 1.09)             |
| Liu 2012          | 39 (2.0)  | 33 (1.0)  | 0.14 (0.02, 0.99)             |
| Moon 2012         | 8 (0.5)   | 10 (0.3)  | 0.70 (0.08, 6.09)             |
| Vennarecci 2007   | 9 (0.2)   | 10 (0.1)  | 0.12 (0.02, 0.67)             |
| Wu 2012           | 4 (0.3)   | 5 (0.1)   | 0.09 (0.02, 0.54)             |
| Total (95% CI)    | 113 (0.2) | 77 (0.1)  | 1.00 (0.99, 1.00)             |
| Heterogeneity: Chi² = 2.1, df = 8 (P = 0.19) | Test for overall effect: Z = 3.1 (P = 0.00)
**Conclusions**

Compared with PLT, SLT had more postoperative bleeding and increased operative mortality. However, SLT was shown to have better 1-year, 3-year, and 5-year OS and DFS rates compared to PLT. As shown in the results of this meta-analysis of 9879 patients, SLT may be a better treatment strategy for recurrent HCC and for patients with compensated liver, whenever feasible, considering the severe organ limitation and the safety of SLT. However, PLT can be referred as a treatment strategy for HCC patients with cirrhotic and decompensated liver.

**Conflict of interests**

None.

**Abbreviations**

SLT – salvage liver transplantation; PLT – primary liver transplantation; HCC – hepatocellular carcinoma; OR – odds ratio; CI – confidence interval; OS – overall survival; DFS – disease free survival; PRISMA – preferred reporting items for systematic reviews and meta-analysis; SMD – standard mean difference.
References:

1. El-Serag HB, Davila JA, Petersen NJ, McGlynn KA: The continuing increase in the incidence of hepatocellular carcinoma in the United States: An update. Ann Intern Med, 2003; 139: 817–23
2. El-Serag HB, Kanwal F: Epidemiology of hepatocellular carcinoma in the United States: Where are we? Where do we go? Hepatology, 2014; 60: 1767–75
3. Ferlay J, Soerjomataram I, Dikshit R et al: Cancer incidence and mortality worldwide: sources, methods and major patterns in GLOBOCAN 2012. Int J Cancer, 2015; 136: E359–86
4. Forner A, Llovet JM, Bruix J: Hepatocellular carcinoma. Lancet, 2012; 379: 1245–55
5. Bruix J, Sherman M: Management of hepatocellular carcinoma: An update. Hepatology, 2011; 53: 1020–22
6. Bhooi S, Sposito C, Germini A et al: The challenges of liver transplantation for hepatocellular carcinoma on cirrhosis. Transpl Int, 2010; 23(7): 712–22
7. de Villas V, Lo CM: Liver transplantation for hepatocellular carcinoma in Asia. Histol Histopathol, 2012; 27: 1231–41
8. Wong RJ, Cheung R, Ahmed A: Nonalcoholic steatohepatitis is the most rapidly growing indication for liver transplantation in patients with hepatocellular carcinoma in the U.S. Hepatology, 2014; 59: 2188–95
9. Yeh H, Smoot E, Schoenfeld DA, Markmann JF: Geographic inequity in access to organs for transplantation. Transplantation, 2011; 91: 479–86
10. Northup PG, Intagliata NM, Shah NL et al: Excess mortality on the liver transplant waiting list: Unintended policy consequences and Model for End-Stage Liver Disease (MELD) inflation. Hepatology, 2015; 61: 285–91
11. Cherqui D, Laurent A, Mocellin N et al: Liver resection for transplantable hepatocellular carcinoma: Long-term survival and role of secondary liver transplantation. Ann Surg, 2009; 250: 738–46
12. Salem R, Mazzaferrro V, Sango B: Yttrium 90 radioembolization for the treatment of hepatocellular carcinoma: Biological lessons, current challenges, and clinical perspectives. Hepatology, 2013; 58: 2188–97
13. Mazzaferrro V, Battiston C, Peronno S et al: Radiofrequency ablation of small hepatocellular carcinoma in cirrhotic patients awaiting liver transplantation: A prospective study. Ann Surg, 2004; 240: 900–9
14. Belghiti J, Carr BI, Greig PD et al: Treatment before liver transplantation for HCC. Ann Surg Oncol, 2008; 15(4): 993–1000
15. Majno PE, Saisin JP, Mentha G, Hadengue A: Primary liver resection and salvage transplantation or primary liver transplantation in patients with single, small hepatocellular carcinoma and preserved liver function: An outcome-oriented decision analysis. Hepatology, 2000; 31: 899–906
16. Wu L, Hu A, Tan N et al: Salvage liver transplantation for patients with recurrent hepatocellular carcinoma after curative resection. PLoS One, 2012; 7: e41820
17. Adam R, Azoulay D, Cestaing D et al: Liver resection as a bridge to transplantation for hepatocellular carcinoma on cirrhosis: A reasonable strategy? Ann Surg, 2003; 238: 508–19
18. Shan Y, Huang L, Xia Q: Salvage liver transplantation leads to poorer outcome in hepatocellular carcinoma compared with primary liver transplantation. Sci Rep, 2017; 7: 44652
19. Moher D, Liberati A, Tetzlaff J, Altman DG: Preferred reporting items for systematic reviews and meta-analyses: The PRISMA statement. Ann Intern Med, 2009; 151: 264–69, w64
20. Omby RL, Crocco E, Apecado A et al: Depression and risk for Alzheimer disease: Systematic review, meta-analysis, and metagression analysis. Arch Gen Psychiatry, 2006; 63: 330–38
21. Higgins JP, Thompson SG, Deeks J, Altman DG: Measuring inconsistency in meta-analyses. BMJ, 2003; 327: 557–60
22. Belghiti J, Cortes A, Abdalla EK et al: Resection prior to liver transplantation for hepatocellular carcinoma. Ann Surg, 2003; 238: 885–93
23. Hwang S, Lee S-G, Moon D-B et al: Salvage living donor liver transplantation after prior liver resection for hepatocellular carcinoma. Liver Transpl, 2007; 13: 741–46
24. Scattone O, Zalinski S, Terris B et al: Hepatocellular carcinoma developed on compensated cirrhosis: Resection as a selection tool for liver transplantation. Liver Transpl, 2008; 14: 779–88
25. Margaret C, Esclatnie A, Castells L et al: Resection for hepatocellular carcinoma: A good option in Child-Turcotte-Pugh class A patients with cirrhosis who are eligible for liver transplantation. Liver Transpl, 2005; 11: 1242–51
26. Del Gaudio M, Ercolani G, Ravolacci M et al: Liver transplantation for recurrent hepatocellular carcinoma on cirrhosis after liver resection: University of Bologna experience. Am J Transplant, 2008; 8: 1177–85
27. Wang P, Yu P, Li H et al: Prognosis for recipients with hepatocellular carcinoma of salvage liver transplantation versus those of primary liver transplantation: A retrospective single-center study. SpringerPlus, 2016; 5: 1809
28. Liu F, Wei Y, Wang W et al: Salvage liver transplantation for recurrent hepatocellular carcinoma within UCSF criteria after liver resection. PLoS One, 2012; 7: e48932
29. Facchello ME, Koneru B, Rocca JP et al: Surgical treatment of hepatocellular carcinoma beyond milan criteria. Results of liver resection, salvage transplantation, and primary liver transplantation. Ann Surg Oncol, 2008; 15: 1383–91
30. Hu Z, Zhou J, Xu X et al: Salvage liver transplantation is a reasonable option for selected patients who have recurrent hepatocellular carcinoma after liver resection. PLoS One, 2012; 7: e36587
31. Kim BW, Park YK, Kim YB et al: Salvage liver transplantation for recurrent hepatocellular carcinoma after liver resection: Feasibility of the Milan criteria and operative risk. Transplant Proc, 2008; 40: 3558–61
32. Vasavada BB, Chann L-C: Salvage transplantation for post-resection recurrence in hepatocellular carcinoma associated with hepatitis C virus etiology: A feasible strategy? Hepatoma Research, 2015; 1: 36–40
33. Bhangui P, Allard MA, Vibtet E et al: Salvage Versus primary liver transplantation for early hepatocellular carcinoma: Do both strategies yield similar outcomes? Ann Surg, 2016; 264(1): 155–63
34. Moon JI, Kwon CH, Jho JI et al: Primary versus salvage living donor liver transplantation for patients with hepatocellular carcinoma: Impact of microvascular invasion on survival. Transplant Proc, 2012; 44: 487–93
35. Sapisochin G, Bilbao I, Baisels J et al: Optimizing of liver transplantation as a treatment of intrahepatic hepatocellular carcinoma recurrence after partial liver resection: experience of a single European series. World J Surg, 2010; 34: 2146–54
36. Vennarecci G, Ettorre GM, Antonini M et al: First-line liver resection and salvage liver transplantation are increasing therapeutic strategies for patients with hepatocellular carcinoma and child a cirrhosis. Transplant Proc, 2007; 39: 1857–60
37. Shao Z, Lopez R, Shen B, Yang G-S: Orthotopic liver transplantation as a rescue operation for recurrent hepatocellular carcinoma after partial hepatectomy. World J Gastroenterol, 2008; 14: 4370–76
38. Minagawa M, Makuuchi M, Takayama T, Komudo N: Selection criteria for repeat hepatectomy in patients with recurrent hepatocellular carcinoma. Ann Surg, 2003; 238: 703–10
39. Cucchielli A, Ercolani G, Vivaldi M et al: Impact of model for end-stage liver disease (MELD) score on prognosis after hepatectomy for hepatocellular carcinoma on cirrhosis. Liver Transpl, 2006; 12: 966–71
40. Teh SH, Christein J, Donohue J et al: Hepatic resection of hepatocellular carcinoma in patients with cirrhosis. Model of End-Stage Liver Disease (MELD) score predicts perioperative mortality. J Gastrointest Surg, 2005; 9: 1207–15; discussion 1215
41. Schraiber LD, de Mattos AA, Zanotelli ML et al: Alpha-fetoprotein level predicts recurrence after transplantation in hepatocellular carcinoma. Medicine, 2016; 95: e2478
42. Belghiti J, Panis Y, Farges O et al: Intrahepatic recurrence after resection of hepatocellular carcinoma complicating cirrhosis. Medicine, 2016; 95: e2478
43. Del Gaudio M, Ercolani G, Vivarelli M et al: Impact of model for end-stage liver disease (MELD) score on prognosis after hepatectomy for hepatocellular carcinoma on cirrhosis. Liver Transpl, 2006; 12: 966–71
44. El-Serag HB, Davila JA, Petersen NJ, McGlynn KA: The continuing increase in the incidence of hepatocellular carcinoma in the United States: An update. Ann Intern Med, 2003; 139: 817–23
45. El-Serag HB, Zalinski S, Terris B et al: Hepatocellular carcinoma developed on compensated cirrhosis: Resection as a selection tool for liver transplantation. Liver Transpl, 2008; 14: 779–88