Systematic Review and Meta-Analysis

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# Systematic review of treatment strategy for recurrent hepatocellular carcinoma

## Salvage liver transplantation or curative locoregional therapy

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**Abstract**

**Aims:** The aim of our systematic review was to compare the efficacy of salvage liver transplantation (SLT) versus curative locoregional therapy (CLRT) for patients with recurrent hepatocellular carcinoma (HCC).

**Methods:** Studies comparing the SLT with CLRT for patients with recurrent HCC were selected from database of PubMed, EMBASE, and Cochrane library. The outcomes including overall survival, disease-free survival, and complications were abstracted. Individual and pooled odds ratio (OR) with 95% confidence interval of each outcome was analyzed.

**Results:** Seven retrospective studies involving 840 patients were included. There is no difference between SLT and CLRT group regarding the1- and 3-year overall survival rates. However, the 5-year overall survival and 1-, 3-, 5-year disease-free survival were significantly higher after SLT than after CLRT (OR = 1.62, 95% CI 1.09–2.39, $P = .02$; OR = 4.08, 95% CI 1.95–8.54, $P = .0002$; OR = 3.63, 95% CI 2.21–5.95, $P < .00001$; OR = 5.71, 95% CI 2.63–12.42, $P < .0001$, respectively). But CLRT was associated with fewer complications and shorter hospital-stay compared with SLT. For SLT compared with repeat hepatectomy (RH), the subgroup analysis indicated that SLT group had a significantly higher 3- and 5-years disease-free survival than the RH group (OR = 3.23, 95% CI 1.45–7.20, $P = .004$; OR = 4.79, 95% CI 1.88–12.25, $P = .001$, respectively).

**Conclusion:** The efficacy of SLT may be superior to that of CLRT in the treatment of recurrent HCC. However, considering the similar overall survival rate and current situation of donor shortage, RH is still an important option for recurrence HCC.

**Abbreviations:** CI = confidence interval, CLRT = curative locoregional therapy, HBV = hepatitis B virus, HCC = hepatocellular carcinoma, IM = intrahepatic metastasis, MELD = model for end-stage liver disease, MO = multicentric occurrence, OR = odds ratio, RCT = random controlled trial, RH = repeat hepatectomy, SLT = salvage liver transplantation, TACE = transcatheter arterial chemoembolization, UCSF = University of California, San Francisco.

**Keywords:** hepatocellular carcinoma, locoregional therapy, meta-analysis, salvage liver transplantation

## 1. Introduction

The burden of hepatocellular carcinoma (HCC) is expected to increase in the future in conjunction with the high prevalence of hepatitis B virus (HBV) in Asia and sub-Saharan Africa and with the rising incidence of hepatitis C virus (HCV) infections, alcoholic liver disease, and steatohepatitis in developed countries.[1] The mainstay of curative treatment for HCC is hepatectomy. With advances in surgical techniques and perioperative care, the results of hepatectomy for HCC have greatly improved.[2] Nonetheless, long term survival after hepatectomy remains unsatisfactory because of the high incidence of intrahepatic recurrence (up to 68%–98% of patients).[3] Thus, effective therapeutic strategies for intrahepatic recurrence are critical to prolonging survival after hepatectomy for HCC. For resectable recurrent HCC, repeat hepatectomy (RH) remains the preferred option.[4] However, RH is not possible in many patients because of location or size of the tumor, or the severity of the cirrhosis and portal hypertension. Radiofrequency ablation (RFA), transcatheter arterial chemoembolization (TACE) and percutaneous ethanol injection (PEI) are forms of locoregional therapy that have been used with curative intent (referred to as "curative locoregional therapy (CLRT)" include RH in this article) in patients who are not RH candidates. In the past 2 decades, CLRT has been reported to be safe and to prolong survival after intrahepatic recurrence.[5] Recently, salvage liver transplantation (SLT) was proposed as a curative option for the intrahepatic recurrence of HCC, but it is still not widely used because of the insufficient number of cadaveric donors and the limited availability of appropriate living donors.[6–8] Another potential reason for

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The authors alone are responsible for the content and writing of the paper.

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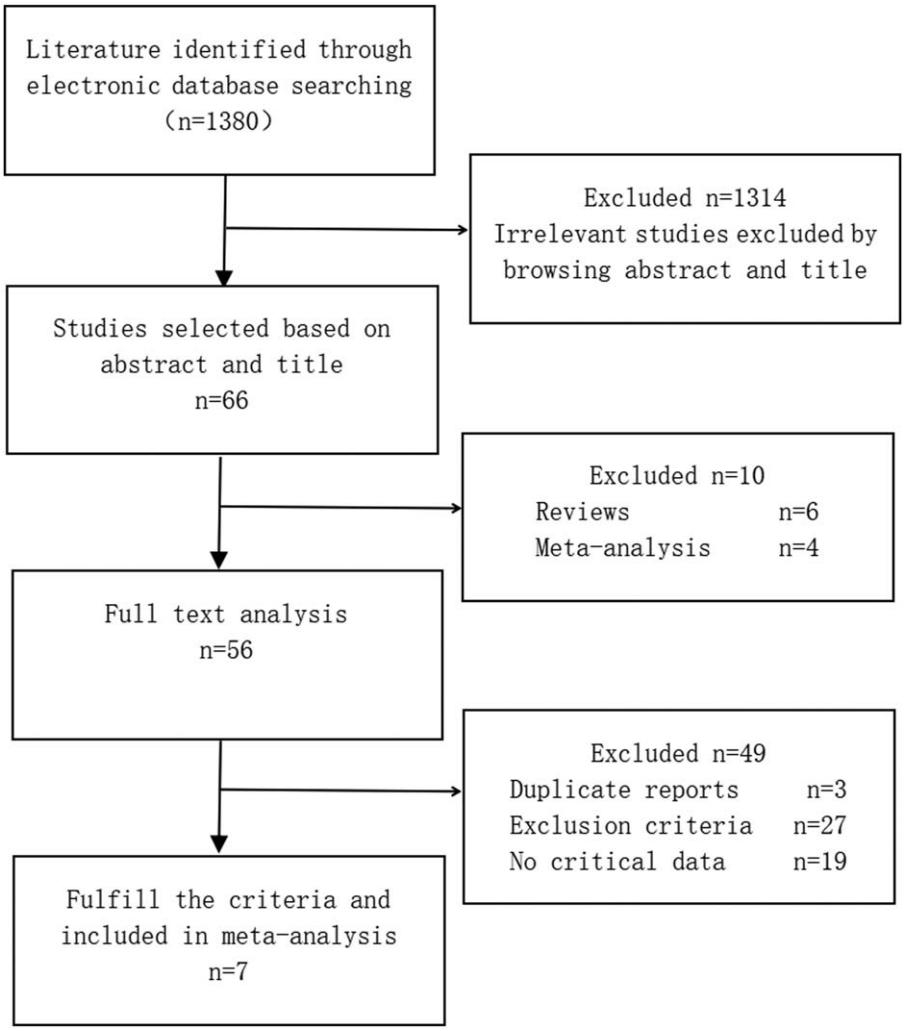


**Figure 1.** Flow chart showing selection of studies for meta-analysis.

excluding patients for SLT is that they are not fulfilling the criteria for the transplant. Some potential reasons such as ongoing alcohol abuse or other medical conditions making the liver transplant impossible. SLT may offer a good strategy for relieving patients with a good prognosis after HCC recurrence. Some researches have been conducted to compare the efficacy of the SLT with CLRT in the treatment of patients with recurrent HCC, but the results are still controversial.

Several retrospective cohort studies were newly conducted regarding the curative effect of SLT and CLRT in recent years.[9–15] Herein, we performed this systematic review using meta-analysis to compare SLT with CLRT in the treatment of recurrent HCC including these recently reported studies.

## 2. Methods

Ethics committee and institutional review board

This is a meta-analysis. Ethical approval was not necessary.

### 2.1. Literature search strategy

Two reviewers independently carried out a comprehensive search of PubMed, EMBASE, and Cochrane library. The key words in this strategy with Mesh heading: "recurrent", "salvage liver transplantation", "hepatocellular carcinoma". No restriction was set for languages or date of publication. The searches were limited to human subjects. Although meta-analysis has been commonly applied for evaluations of controversy trials especially of random controlled trials (RCTs), it is also available for retrospective studies. In order to obtain a more reliable conclusion, we included RCTs and all comparable retrospective studies.

### 2.2. Criteria for inclusion and exclusion

For inclusion in the meta-analysis, a study had to fulfill the following criteria:

(1) patients with recurrent HCC who were treated with SLT versus CLRT;
(2) Intent-to-treat analysis of SLT versus CLRT;
(3) For similar studies reported by the same institution and/or authors, only the most recent study with high quality was included in this analysis; and
(4) Included studies must report on at least one of the following outcomes: the overall survival of 1-, 3-, and 5-years, the

**Table 1**

**Characteristics of studies included in the meta-analysis.**

| Study | Period | Country / Region | Arms | No. patients | Age (mean ± SD) | Sex (Male/ Female) | Child-Pugh class (A/B/C) | MELD score | Tumor size (mean ± SD, mm) | Tumor amount (single/ multiple) | Recurrence time (months) | NOS score |
|---|---|---|---|---|---|---|---|---|---|---|---|---|
| Lim 2017 | 1994-2011 | France | SLT | 18 | 58 ± 9 | 14/4 | 17/1/0 | 7 ± 4 | 27 ± 22 | 11/7 | 19 ± 22 | 9 |
| | | | RH | 81 | 62 ± 9 | 67/14 | 75/6/0 | 8 ± 1 | 20 ± 9 | 27/54 | 38 ± 13 | |
| Zhang 2017 | 2007-2016 | China | SLT | 36 | 46.97 ± 10.22 | 31/5 | NA | 4.44 ± 3.16 | 44.3 ± 39.3 | 25/11 | 28.50 ± 15.46 | 8 |
| | | | RH/RFA | 116 | 50.23 ± 11.71 | 99/17 | NA | 4.33 ± 2.38 | 30.8 ± 19.0 | 84/32 | 20.24 ± 19.69 | |
| Du 2016 | 2004-2010 | China | SLT | 19 | 51.47 ± 8.50 | 17/2 | NA | NA | 34.5 ± 10.0 | 15/4 | NA | 7 |
| | | | RH | 53 | 56.23 ± 9.71 | 44/9 | NA | NA | 33.1 ± 10.5 | 49/4 | NA | |
| Yamashita 2015 | 1989-2012 | Japan | SLT | 13 | 56.2 ± 5.6 | 10/3 | 1/12 | NA | 25 ± 11 | NA | >12 | 8 |
| | | | RH | 146 | 68.2 ± 9.6 | 99/47 | 96/50 | NA | 19 ± 9 | NA | >12 | |
| Chan 2013 | 1993-2009 | Hong Kong | SLT | 19 | 50 | NA | NA | 10.7 | 38 | 6/13 | NA | 9 |
| | | | RH/RFA | 68 | 52/54 | NA | NA | 7.2/8.3 | 21/18 | 16/8 and 38/6 | NA | |
| Yong 2016 | 2001-2010 | Taiwan | SLT | 41 | 52.0 ± 6.9 | 34/7 | 33/8 | 8.5 ± 3.4 | NA | 27/14 | NA | 8 |
| | | | RFA/TACE/PEI | 170 | 59.1 ± 11.4 | 132/38 | 161/9 | 7.3 ± 1.4 | NA | 134/36 | NA | |
| Ng 2008 | 1989-2003 | Hong Kong | SLT | 12 | 51 | 12/0 | 6/4/2 | NA | NA | 8/4 | 34 | 8 |
| | | | RH/RFA/TACE/PEI | 48 | 53 | 42/6 | 47/1/0 | NA | NA | 36/12 | 17 | |

NA = not available, NOS = Newcastle-Ottawa scale, PEI = percutaneous ethanol injection, RFA radiofrequency ablation, RH = repeat hepatectomy, SD = standard deviation, SLT = salvage liver transplantation, TACE = transcatheter arterial chemoembolization.

disease-free survival of 1-, 3-, and 5-years and complications (including mortality and morbidity).

The exclusion criteria were as follows:

(1) nonhuman studies, abstracts, editorials, letters, case reports, expert opinions, reviews, and studies lacking control group;
(2) studies in which patients were diagnosed as other malignant liver tumors instead of HCC, such as cholangiocellular carcinomas or liver metastases; and
(3) studies not clearly reporting the outcomes of interest attributed to each specific intervention.

### *2.3. Data extraction and quality assessment*

Data were extracted independently by 2 authors (H-LW and J-HZ) and cross-checked to reach a consensus. The following variables were extracted from each study:

(1) first author and year of the publication;
(2) study design and patients characteristics;
(3) clinical outcomes.

The primary endpoint was efficacy, including overall and disease-free survival at 1-, 3-, and 5-years. The secondary endpoints included complications and hospital-stay. The quality of all selected articles was assessed by using the 9-star Newcastle-Ottawa Scale.

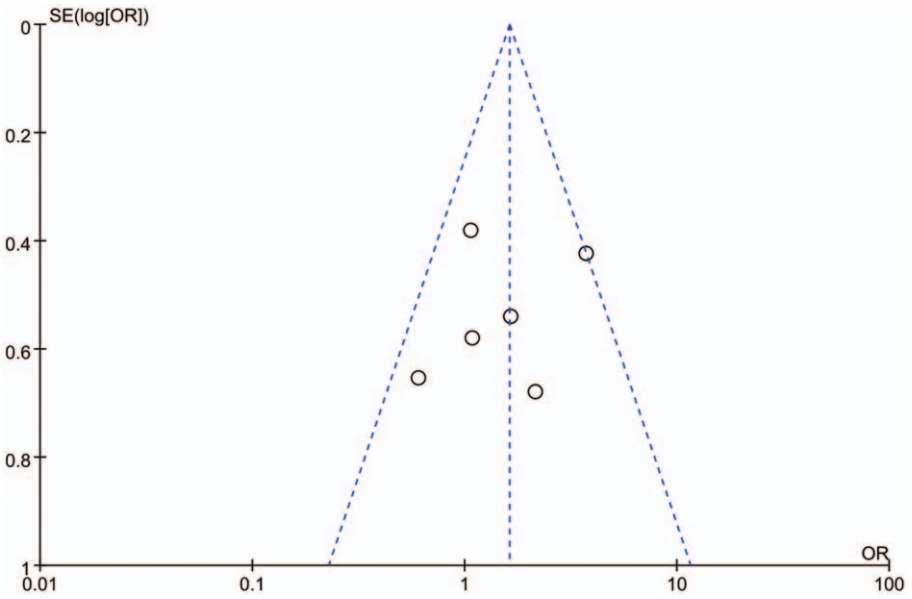


**Figure 2.** Funnel plot for overall survival at 5 years for SLT versus CLRT. CLRT = curative locoregional therapy, SLT = salvage liver transplantation.

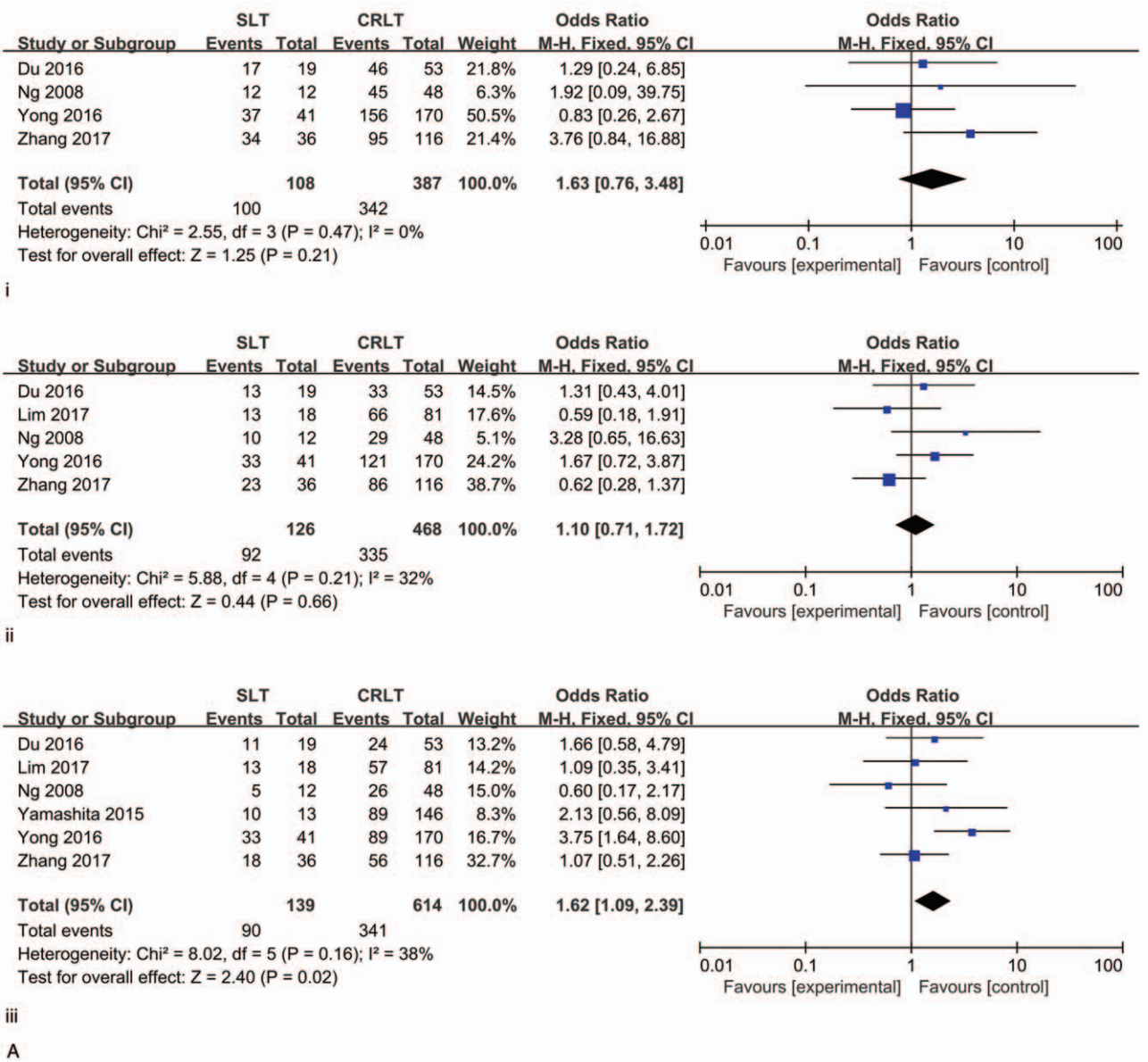


**Figure 3.** (A) Meta-analysis of SLT versus CLRT on 1-,3-, and 5-year overall survival rates. (i) 1-year overall survival (ii) 3-year overall survival (iii) 5-year overall survival. (B) Meta-analysis of SLT versus RH on 1-,3-, and 5-year overall survival rates. (i) 1-year overall survival (ii) 3-year overall survival (iii) 5-year overall survival. CLRT = curative locoregional therapy, RH = repeat hepatectomy, SLT = salvage liver transplantation.

### *2.4. Data synthesis and analysis*

The meta-analysis was performed by Review Manager (version 5.3), provided by the Cochrane Collaboration (The Nordic Cochrane Centre, Copenhagen). For dichotomous variables, odds ratio (OR) was estimated with a 95% confidence interval (CI). For continuous variables, weighted mean difference was calculated. The heterogeneity across each included study was explored by the Chi square ($\chi^2$) and $I^2$ statistic. $I^2 < 25\%$ was considered to reflect low heterogeneity, $25\% \leq I^2 \leq 50\%$ was considered to reflect moderate heterogeneity, and $I^2 > 50\%$ was considered to reflect high heterogeneity. Heterogeneity was considered substantially significant when the Cochrane $Q$ test $P < .10$, and random effect model was applied for meta-analysis; otherwise, fixed effect model was used. $P < .05$was considered statistically significant.

## 3. Results

### *3.1. Literature search*

A flow diagram of our literature search was shown in Figure 1. Total searches yielded 1380 entries. After screening based on titles and abstracts, 66 articles appeared to be potentially relevant. Meta-analysis and systematic reviews (10 articles) were then excluded. Among the remaining 56 studies, 49 were eliminated after the full-text analysis for the following reason: overlapping data or duplicated reports from the same study population (3 studies), lack of critical data (19 studies), and matching one of the exclusion criteria (27 studies). In the end, a total of 7 studies were selected, all of them are comparable retrospective studies.

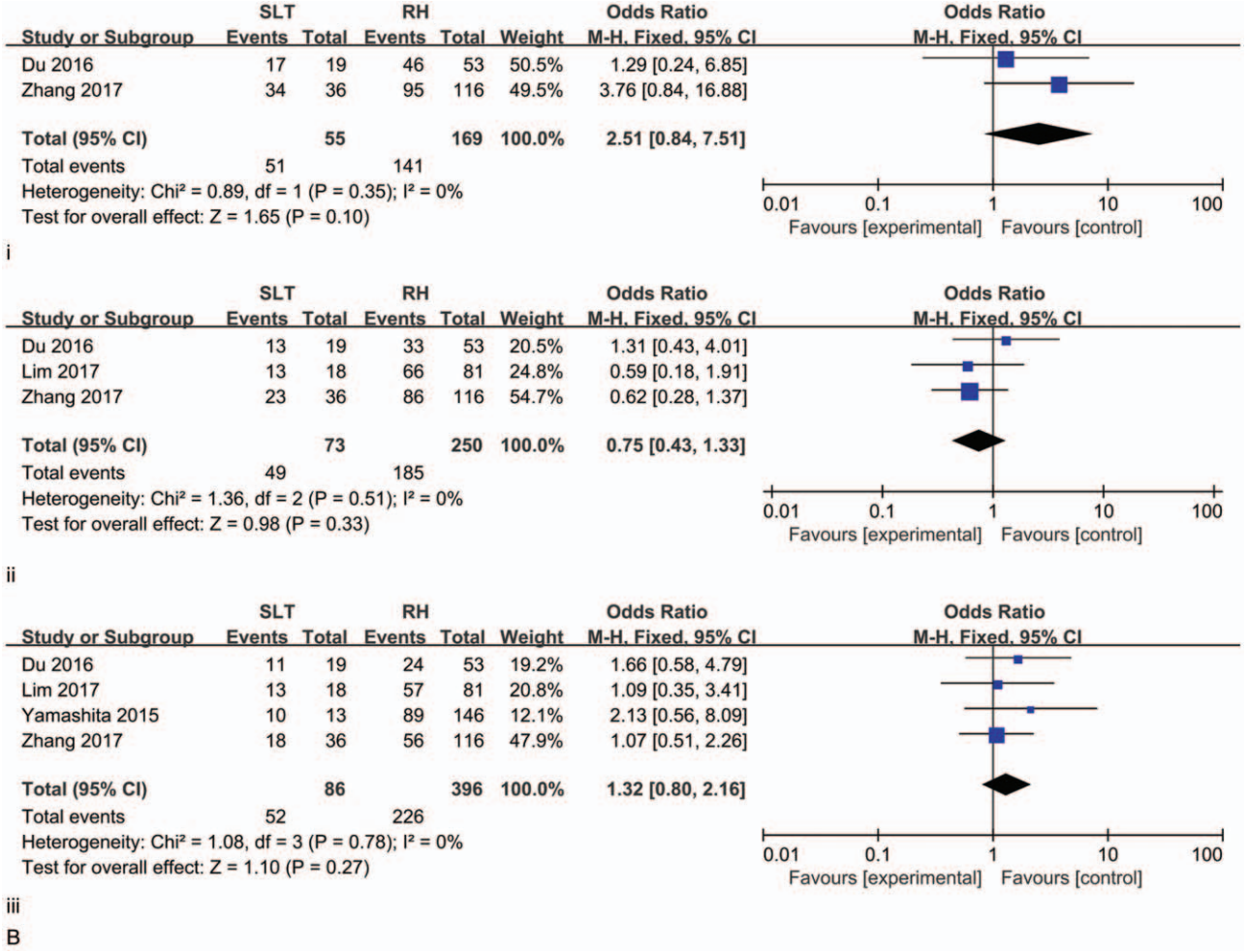


**Figure 3.** (Continued)

### 3.2. Study characteristics

The baseline characteristics of included studies are summarized in Table 1. The 7 studies were published between 2008 and 2017 and involved a total of 840 patients. 158 patients were treated with SLT and 682 patients who were treated with CLRT. Of these 7 studies, 5 were conducted in China (include HongKong and Taiwan), 1 in Japan, 1 in France. The mean age was 52.1 and 57.2 years in the SLT and CLRT groups; 84.9% and 78.7% were males respectively. The patients had a mean MELD score of 7.6 and 6.7 and were Child-Pugh class A in 67.8% and 85.1% in the SLT and CLRT groups respectively.

RH was used in 6 studies, RFA in 4 studies, transcatheter arterial chemoembolization (TACE) in 2 studies, PEI in 2 studies. In all studies, the SLT was compared to CLRT which was with deceased donor liver transplant in 5 studies and live donor liver transplant in 2 studies. Most patients were within Milan criteria in all studies.

### 3.3. Quality of the included studies

For the quality assessment of the 7 retrospective studies, a modification of the Newcastle-Ottawa scale was used. Full-text of all the 7 articles was downloaded and reviewed scrupulously. Both SLT and CLRT groups of each study were from the same center during the same period. Table 1 lists the detail assessment results of the 7 retrospective studies. Figure 2 illustrates symmetrical funnel plots of the included studies, which suggested no obvious publication bias exist in the present meta-analysis.

### 3.4. Overall survival rates

Most studies reported the overall survival. No significant difference was observed between SLT group and CLRT group in 1- and 3-year overall survival rates (OR = 1.63, 95% CI 0.76–3.48, $P = .21$; OR = 1.10, 95% CI 0.71–1.72, $P = .66$, respectively). But in the 5-year overall survival, SLT group is better than CLRT group (OR = 1.62, 95% CI 1.09–2.39, $P = .02$; Fig. 3a).

Subgroup analysis for SLT versus RH: there was also no significant difference between SLT group and RH group (1-year overall survival OR = 2.51, 95% CI 0.84–7.51, $P = .10$; 3-year overall survival OR = 0.75, 95% CI 0.43–1.33, $P = .33$; 5-year overall survival OR = 1.32, 95% CI 0.80–2.16, $P = .27$; Fig. 3b).

### 3.5. Disease-free survival

There were significant differences between the 2 groups on 1-, 3-, and 5-year disease-free survival. The SLT group had a significantly higher disease-free survival than the CLRT group

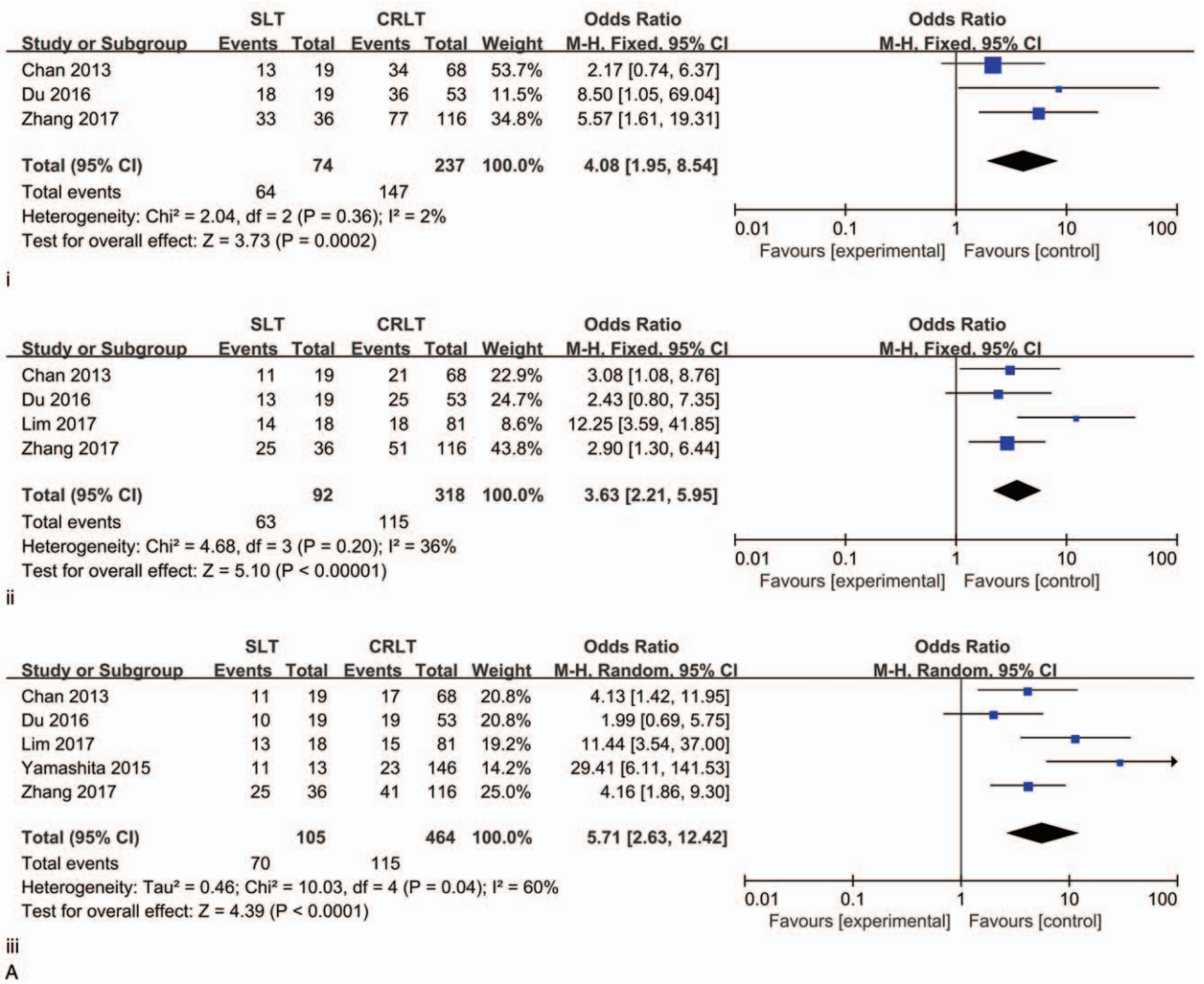


**Figure 4.** (A) Meta-analysis of SLT versus CLRT on 1-,3-, and 5-year disease-free survival rates. (i) 1-year disease-free survival (ii) 3-year disease-free survival (iii) 5-year disease-free survival. (B) Meta-analysis of SLT versus RH on 1-,3-, and 5-year disease-free survival rates. (i) 1-year disease-free survival (ii) 3-year disease-free survival (iii) 5-year disease-free survival. CLRT = curative locoregional therapy, SLT = salvage liver transplantation.

(1-year OR = 4.08, 95% CI 1.95–8.54, $P < .001$; 3-year OR = 3.63, 95% CI 2.21–5.95, $P < .001$; 5-year OR = 5.71, 95% CI 2.63–12.42, $P < .001$; Fig. 4a).

Subgroup analysis for SLT versus RH: there was significant difference between the 2 groups on 3- and 5-year disease-free survival rates, and the SLT group had a significantly higher disease-free survival than the RH group (OR = 3.23, 95% CI 1.45–7.20, $P = .004$; OR = 4.79, 95% CI 1.88–12.25, $P = .001$; Fig. 4b).

### 3.6. Treatment complications

Two studies reported the intraoperative mean blood loss. The intraoperative blood loss was significantly larger in the SLT group ($P < .001$; Fig. 5a). These 2 studies also reported the mean hospital-stay. The SLT group had significant longer hospital-stay than CLRT group ($P < .001$; Fig. 5b). The complications after SLT included symptomatic pleural effusion, bleeding peptic ulcer and biliary anastomotic site stricture. Most studies reported mortality at the time of follow-up, the causes of death included terminal malignancy, uncontrolled sepsis, and gastrointestinal tract bleeding, and so on.

### 3.7. Sensitivity analysis and publication bias

High heterogeneity was found concerning 5-year disease-free survival and in the subgroup analysis of 3- and 5-year disease-free survival. The sensitivity analysis was performed by eliminating 1 study in each turn, all the result consistent with the primary outcome. Publication bias was assessed using the Begg and Egger test. No significant publication bias was found for the overall survival. The funnel plot of 5-year overall survival was almost visually symmetrical (Fig. 2). The publication bias was not assessed for the others, because only a small number of studies reported those outcomes.

## 4. Discussions

Liver transplantation and hepatectomy are the best methods to treat with HCC. Currently, the internationally commonly used standard for liver transplantation is the Milan criteria proposed

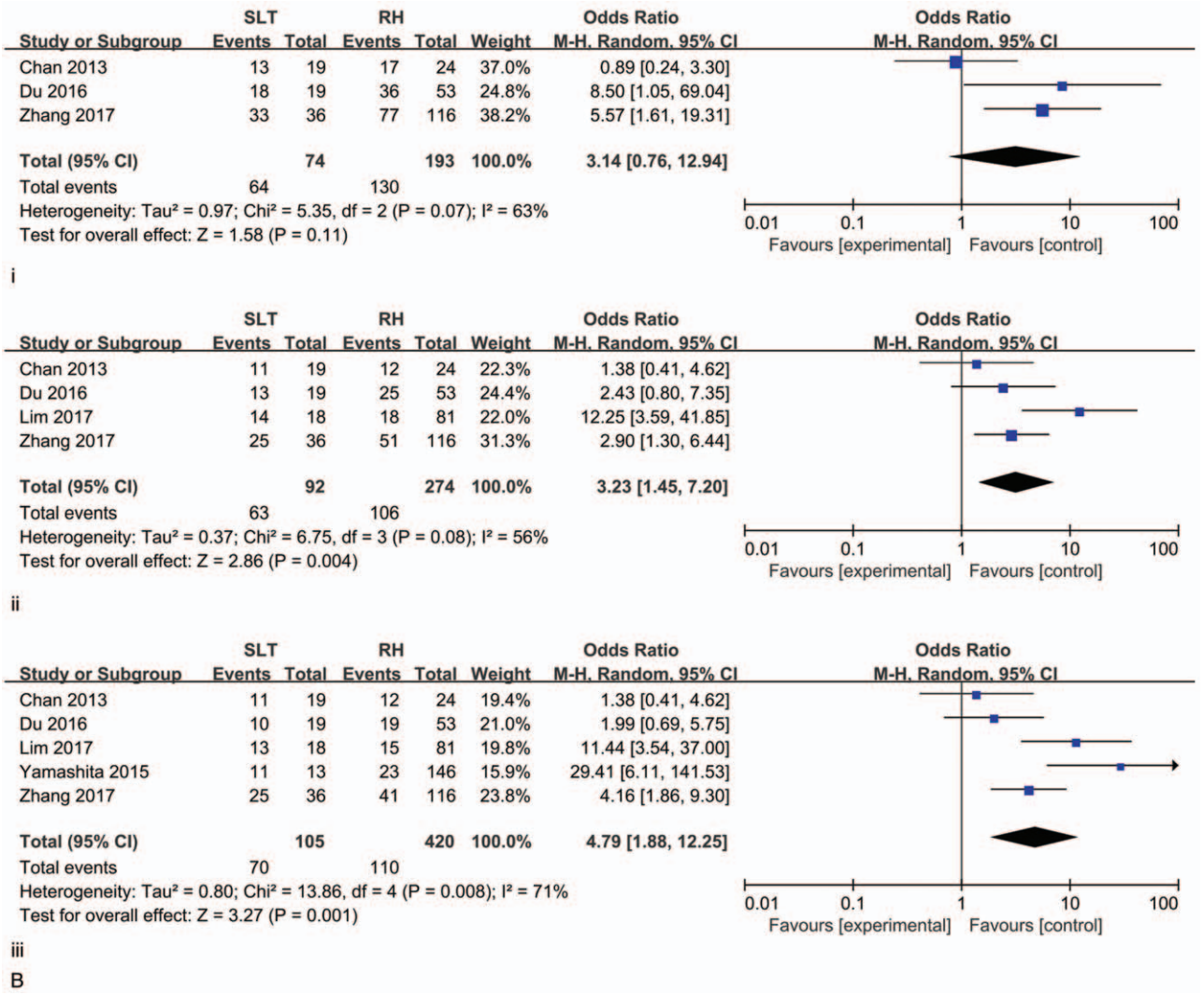


**Figure 4.** (Continued)

by Mazzaferro in 1996.[16] The criteria for eligibility for transplantation were the presence of a tumor 5 cm or less in diameter in patients with single HCC and no more than 3 tumor nodules, each 3 cm or less in diameter, in patients with multiple tumors. For patients with HCC who meet the Milan criteria, the 5-year survival rate after liver transplantation can reach 70% meanwhile with a recurrence rate less than 10% to 15%.[17] Due to the limitation of donor, liver transplantation cannot be timely applied to all HCC patients meeting Milan criteria. Majno' research estimated that 30% of small HCCs would outgrow Milan criteria within each 6-month time interval (5% per month). So they advised offer liver resection first and liver transplantation for tumor recurrence or deteriorating liver function (SLT).[18] However, there are still no standard patient inclusion criteria for SLT. Zhang researched Milan criteria, University of California, San Francisco (UCSF) criteria and model for end-stage liver disease (MELD) score as predictors of salvage liver transplantation. They found that the MELD score and Milan/UCSF criteria were effective in predicting the prognosis of SLT and when the recurrent lesions of HCC within the Milan criteria, SLT could be performed with a good prognosis.[19] de Haas' research suggested that the best candidates for SLT are patients with a higher MELD score, no preoperative TACE, no postoperative complications after initial resection, and low T-stage in the resected specimen.[20] The studies in our research included patients almost within Milan criteria.

Most providers consider liver transplantation to be the better treatment modality than surgical resection or other forms of locoregional therapy done with curative intent, to treat early-stage HCC, even though many studies have shown that surgical resection provides good overall survival in these patients. Murali AR's research[21] have done the meta-analysis locoregional therapy with curative intent versus primary liver transplant for HCC. However, the focus of our work is on SLT which is very different from Murali AR's work, and this is also the major contribution of our work. Our meta-analysis shows that 5-year overall survival rate and 1, 3, and 5-year disease-free survival are better after SLT compared to all types of CLRT (hepatectomy, RFA, TACE, PEI) when these are analyzed together as group. In the study of Chan's they evaluated the efficacy of SLT, RH, and RFA for patients with postoperative tumor recurrence and they showed that SLT and RH led to comparable survival outcomes, but both treatments led to significantly better survival outcomes than RFA.[12] This will leave the conclusion uncertain. To address

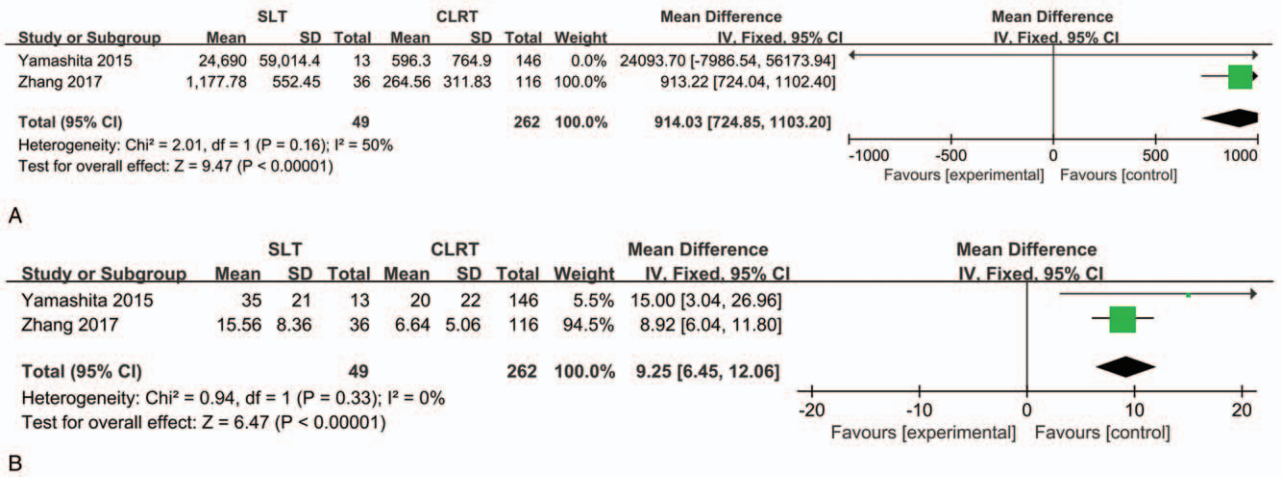


**Figure 5.** (A) Meta-analysis of SLT versus CLRT on blood loss. (B) Meta-analysis of SLT versus CLRT on hospital-stay. CLRT = curative locoregional therapy, SLT = salvage liver transplantation.

these confounding factors, we did subanalyses of studies that compared SLT and RH. Subanalysis of studies that only included SLT compared with RH. Meta-analysis shows that 2 groups have equal overall survival and 1-year disease-free survival. Nevertheless, SLT has better 3and 5-year disease-free survival. Obviously, disease-free survival following SLT was better compared with CLRT due to the following factors: achieving the safest possible resection margin by total hepatectomy; resecting clinically undetectable, existing distant micro-metastases in the remnant liver; and curing underlying liver disease preventing de novo HCC development in the remaining liver.[22] In addition, this means that patients in the SLT group had fewer procedures and treatments and likely had better quality of life than those in the CLRT group.

The time interval to recurrence is regarded as a useful marker for differentiating the recurrence pattern of HCC just like intrahepatic metastasis (IM) or multicentric occurrence (MO). IM, characterized by early tumor recurrence within 12 months, may spread from the primary cancer through the portal vein or result from disease left behind in the remnant liver; in contrast, MO means late recurrence is more likely to be associated with de novo tumor formation more than 12 months later.[23,24] More importantly, the time to recurrence is an independent prognostic factor for predicting the prognosis of HCC patients suffering recurrence.[14,25] In our included studies, only Zhang' made subgroup analyses about IM group and MO group. They found that the disease-free survival values of patients with MO in the SLT group were better than those of patients in the CLRT group. However, regarding IM, the 1-, 3-, and 5-year disease-free survival of patients in the SLT group and in the CLRT group were not significantly different.[10] Yamashita's study included patients all belonged to MO, they also testified SLT was better than CLRT about disease-free survival.[11] Ng's study focused on patients with stage II tumors at the primary resection or intrahepatic tumor recurrence within 12 months of the primary resection (IM) was performed to compare the overall survival outcome between the SLT and CLRT groups. Under this condition, patients in the SLT group had significantly better overall survival than did those in the CLRT group.[14] In other included studies they did not make IM and MO group clearly. Because of this we could not made subgroup analysis about IM and MO. So we still need more studies to prove SLT compared with CLRT in these 2 kinds of patients.

There are several limitations that should be considered in this meta-analysis. First, the number of included studies is few, and none of high quality randomized controlled studies were included for evaluation. Then, potential confounding factors may decrease the reliability of results, even the well-analyzed cohort studies. Second, several indirect data acquisition methods were used in the meta-analysis, which may have effect on our outcomes. Third, high heterogeneity existed in the analysis in which sensitivity analysis did not show a consistent outcome. Fourth, most included studies' patients had different backgrounds in 2 groups, usually, patients in SLT group had worse tumor characteristics than in CLRT group. Fifth, the included 7 studies which have been conducted in Asia except of 1 in Europe. The prevalence of HBV-associated liver cirrhosis is much higher in Asia compared to Europe and the US where alcohol and non-alcoholic steatohepatitis (NASH) are the most prevalent causes of liver cirrhosis. While HBV-associated HCC is usually developing without preexisting cirrhosis patients with other causes HCC usually has a much worse liver function. Above reason may lead to a narrow represent activeness of the conclusion. Therefore, we expect that more researchers will perform large, well-designed randomized controlled trials to clarify which treatment is most effective against recurrent HCC.

In conclusion, the efficacy of SLT is superior to that of CLRT in the treatment of recurrent HCC. However, considering the similar overall survival rate and current situation of donor shortage, RH is still an important option for recurrent HCC.

## Author contributions

**Conceptualization:** Hong-Liang Wang.
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**Supervision:** Le-Qun Li.
**Validation:** Le-Qun Li.

**Visualization:** Bang-De Xiang.
**Writing – original draft:** Hong-Liang Wang.
**Writing – review & editing:** Jian-Hong Zhong, Dun-Chang Mo.

## References


[1] El-Serag HB. Hepatocellular carcinoma. N Engl J Med 2011;365:1118–27.
[2] Zhong JH, Ke Y, Gong WF, et al. Hepatic resection associated with good survival for selected patients with intermediate and advanced-stage hepatocellular carcinoma. Ann Surg 2014;260:329–40.
[3] Chan DL, Alzahrani NA, Morris DL, et al. Systematic review of efficacy and outcomes of salvage liver transplantation after primary hepatic resection for hepatocellular carcinoma. J Gastroenterol Hepatol 2014;29:31–41.
[4] Mise Y, Hasegawa K, Shindoh J, et al. The feasibility of third or more repeat hepatectomy for recurrent hepatocellular carcinoma. Ann Surg 2015;262:347–57.
[5] Gbolahan OB, Schacht MA, Beckley EW, et al. Locoregional and systemic therapy for hepatocellular carcinoma. J Gastrointest Oncol 2017;8:215–28.
[6] Fuks D, Dokmak S, Paradis V, et al. Benefit of initial resection of hepatocellular carcinoma followed by transplantation in case of recurrence: an intention-to-treat analysis. Hepatology 2012;55:132–40.
[7] 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.
[8] Wu L, Hu A, Tam N, et al. Salvage liver transplantation for patients with recurrent hepatocellular carcinoma after curative resection. PLoS One 2012;7:e41820.
[9] Lim C, Shinkawa H, Hasegawa K, et al. Salvage liver transplantation or repeat hepatectomy for recurrent hepatocellular carcinoma: an intent-to-treat analysis. Liver Transpl 2017;23:1553–63.
[10] Zhang X, Li C, Wen T, et al. Treatment for intrahepatic recurrence after curative resection of hepatocellular carcinoma: Salvage liver transplantation or re-resection/radiofrequency ablation? A Retrospective Cohort Study. Int J Surg 2017;46:178–85.
[11] Yamashita Y, Yoshida Y, Kurihara T, et al. Surgical results for recurrent hepatocellular carcinoma after curative hepatectomy: Repeat hepatectomy versus salvage living donor liver transplantation. Liver Transpl 2015;21:961–8.
[12] Chan AC, Chan SC, Chok KS, et al. Treatment strategy for recurrent hepatocellular carcinoma: salvage transplantation, repeated resection, or radiofrequency ablation. Liver Transpl 2013;19:411–9.
[13] Yong CC, Tsai MC, Lin CC, et al. Comparison of salvage living donor liver transplantation and local regional therapy for recurrent hepatocellular carcinoma. World J Surg 2016;40:2472–80.
[14] Ng KK, Lo CM, Liu CL, et al. Survival analysis of patients with transplantable recurrent hepatocellular carcinoma: implications for salvage liver transplant. Arch Surg 2008;143:68–74.
[15] Du Suming, Xiaojin Z, Yi J. Comparative effect of salvage liver transplantation and repeated hepatectomy for recurrent hepatocellular carcinoma. J Reg Anat Oper Surg 2016;26:409–12.
[16] Mazzaferro V, Regalia E, Doci R, et al. Liver transplantation for the treatment of small hepatocellular carcinomas in patients with cirrhosis. N Engl J Med 1996;334:693–9.
[17] Forner A, Reig M, Bruix J. Hepatocellular carcinoma. Lancet 2018;391:1301–14.
[18] Majno PE, Sarasin FP, Mentha G, et al. 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.
[19] Zhang HM, Jiang WT, Pan C, et al. Milan criteria, University of California, San Francisco, criteria, and model for end-stage liver disease score as predictors of salvage liver transplantation. Transplant Proc 2015;47:438–44.
[20] de Haas RJ, Lim C, Bhangui P, et al. Curative salvage liver transplantation in patients with cirrhosis and hepatocellular carcinoma: an intention-to-treat analysis. Hepatology 2018;67:204–15.
[21] Murali AR, Patil S, Phillips KT, et al. Locoregional therapy with curative intent versus primary liver transplant for hepatocellular carcinoma: systematic review and meta-analysis. Transplantation 2017;101: e249–57.
[22] Poon RT, Fan ST, Ng IO, et al. Significance of resection margin in hepatectomy for hepatocellular carcinoma: A critical reappraisal. Ann Surg 2000;231:544–51.
[23] Imamura H, Matsuyama Y, Tanaka E, et al. Risk factors contributing to early and late phase intrahepatic recurrence of hepatocellular carcinoma after hepatectomy. J Hepatol 2003;38:200–7.
[24] Kumada T, Nakano S, Takeda I, et al. Patterns of recurrence after initial treatment in patients with small hepatocellular carcinoma. Hepatology 1997;25:87–92.
[25] Hu Z, Zhou J, Li Z, et al. Time interval to recurrence as a predictor of overall survival in salvage liver transplantation for patients with hepatocellular carcinoma associated with hepatitis B virus. Surgery 2015;157:239–48.