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*Original Article*

# Effectiveness and safety of liver transplantation for surgically unresectable hilar cholangiocarcinoma: a meta-analysis

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**Abstract:** Surgical resection (SR) was the standard of care for hilar cholangiocarcinoma (HCCA). But there have been no standard research results as to whether liver transplantation (LT) was an option for the treatment of unresectable HCCA patients nowadays. For that reason, a meta-analysis was performed in order to evaluate the effectiveness and safety of LT when compared to conventional SR. Of 578 studies from MEDLINE, EMBASE, and the Cochrane Library until 2015, 8 were included in the present study. The R0 resection rate, overall survival (OS) and mortality were evaluated. Subgroup analysis was performed according to the use of neoadjuvant therapy in LT patients (subgroup I: no neoadjuvant therapy; subgroup II: neoadjuvant therapy). No significant differences were noted in the 1-, 3-, and 5-year OS and mortality between the LT patients and SR patients. However, the R0 resection rate were significantly higher in the LT group (odds ratio (OR) =4.92, 95% confidence interval (CI) =2.57-9.44, *P*<0.001). In the subgroup analysis, LT achieved significantly higher rates of 1-year OS (OR=2.45, 95% CI=1.03-5.84, *P*=0.043), 3-year OS (OR=2.73, 95% CI=1.51-4.96, *P*=0.001), 5-year OS (OR=6.86, 95% CI=1.15-41.06, *P*=0.035), R0 resection (OR=7.22, 95% CI=1.17-44.48, *P*<0.001) and equivalent mortality from subgroup II. The results from subgroup I were in accord with overall analyses. In conclusion, there is no convincing evidence for the effectiveness and safety of LT in patients with surgically unresectable HCCAs when compared to conventional SR. However, LT combined with neoadjuvant therapy should be applied in patients with surgically unresectable HCCAs if a liver was available for transplantation.

**Keywords:** Liver transplantation, surgical resection, hilar cholangiocarcinoma, prognosis, meta-analysis

## Introduction

Hilar cholangiocarcinoma (HCCA), a relatively rare malignant tumor accounting for approximately 2% of human malignancies and two-thirds of all biliary tract tumors, is usually diagnosed at an advanced stage accordingly with a notoriously high mortality [1, 2]. Surgical resection (SR) has been reported to be the primary and most effective therapy for HCCAs [3]. However, SR is feasible in a minority of cases, because HCCA patients are usually diagnosed at an advanced stage with parenchymal damage or local irresectability [4, 5]. They had an identical prognosis to inoperable patients and survival with those unresectable HCCA patients were only 12-16 months after palliative therapy [6]. Thus, some authors had proposed liver transplantation (LT) as an emerging therapy for those unresectable HCCAs [7]. All requirements for negative resection margins could be negated by LT following en-bloc resection of the liver, bile ducts and hilar lymphatics. To date, relevant clinical outcomes still revealed unclearly on whether LT was a proper option for those surgically unresectable HCCAs when compared to conventional SR. Several studies reported that the prognosis of unresectable HCCAs in LT had been even better than patients in conventional SR, but opposite results were obtained by

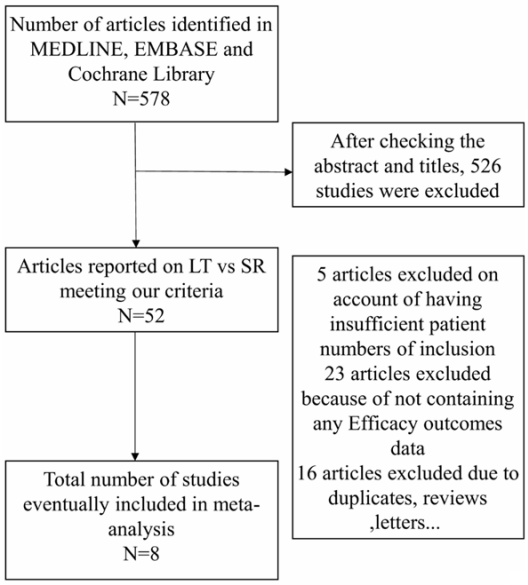


**Figure 1.** Flow-chart of the process for the inclusion of the meta-analysis.

some others. It was urgently needed to clarify the role of LT for surgically unresectable HCCAs. We performed a meta-analysis of all available observational studies to determine whether we can regard LT as an option for surgically unresectable HCCAs whenever possible by comparing it to SR, which is the standard treatment for HCCA [3]. No prospective or randomized controlled study comparing LT and SR has been reported because of ethical and logistical obstacles [8].

## Materials and methods

### *Search strategy*

The MEDLINE, EMBASE, and Cochrane Library databases were searched for articles published in English until 2015 using the following key words "hilar cholangiocarcinoma OR proximal bile duct carcinoma OR Klatskin tumor", "resection OR surgery" and "liver transplantation". The lists of references and bibliographies in primary study publications were reviewed to ensure that the search was comprehensive and to identify any potentially useful study reports.

### *Inclusion and exclusion criteria*

All studies that evaluated LT versus SR for the treatment of HCCAs, with a clear documentation of the characteristics of the patients with records of at least one of the outcomes of interest, were considered for inclusion. Only the latest published study containing the updated data was included when a series of trials from the same institution or author contained an obvious overlap of patient data. Abstracts without full text, reviews, cases series without a control group, case reports, and studies with <5 patients undergoing LT were excluded.

### *Data extraction*

Data of all the outcomes of interest were extracted independently by two reviewers (X. F. Y. and J. X. T.). When the article presented the outcomes in the form of Kaplan-Meier survival curves and the survival rates were unavailable to extract directly through the main text, we used the Engauge software to obtain specific data from the curves. Discrepancies between the data were resolved by discussion and consensus. For any unresolved discrepancies, another reviewer (H. Q. Y.) acted independently to resolve disagreements.

### *Outcome measurement and quality assessment*

Efficacy and safety outcomes of LT and SR included the R0 resection rate, 1-, 3-, and 5-year overall survival (OS) and mortality. The quality of all the studies used in this meta-analysis was assessed using the modified Newcastle-Ottawa Scale (NOS) [9, 10]. The number of stars in this scale ranges from zero to nine.

### *Statistical analysis*

The $I^2$ and chi-square ($\chi^2$) tests were used to assess heterogeneity [11]. A random-effects model was used to calculate the pooled OR if $I^2$>50% and $P$<0.10, otherwise, the data were assessed using a fixed-effects model [12]. Subgroup analysis was conducted to explore the effect of neoadjuvant therapy to the results and the sources of heterogeneity. Sensitivity analyses were performed to explore the statistical heterogeneity. Funnel plots were carried out to evaluate the potential publication bias. Statistical analyses were performed using Stata V.12.0 (Stata Corporation, College Station, TX, USA).

## Results

### *Literature search and description of eligible studies*

We identified 429 articles from MEDLINE, 139 from EMBASE and the Cochrane Library, and

**Table 1.** Summary of characteristics and quality of selected studies

| Study (yr) | Country | Enrolled periods (yr) | Study design | Neoad-ju-vant therapy | Arms | Simples size (n) | Sex (M/F) | R0 resection rates (%) | TNM (I, II/ III, IV) | Follow-up time (months) | NOS score |
|---|---|---|---|---|---|---|---|---|---|---|---|
| Pichlmayr et al [1996] [13] | Germany | 1975-1993 | R | No | LT | 25 | - | - | 9/16 | - | 6 |
| | | | | | SR | 125 | | | 50/75 | | |
| Iwatsuki et al [1997] [14] | America | 1981-1994 | R | No | LT | 20 | - | | 3/17 | Median: 81.6 (15.6-178.8) | 8 |
| | | | | | SR | 34 | | | 9/25 | | |
| Rea et al [2005] [15] | America | 1993-2004 | R | Yes | LT | 38 | 28/10 | 82 | NA | - | 6 |
| | | | | | SR | 26 | 14/12 | 59 | | | |
| Hidalgo et al [2007] [16] | England | 1993-2003 | R | No | LT | 12 | 8/4 | 97 | 10/2 | Median: 21.7 | 7 |
| | | | | | SR | 44 | 24/20 | 88 | 19/15 | | |
| Kaiser et al [2010] [17] | Germany | 1993-2002 | R | No | LT | 7 | 4/3 | 75 | 7/0 | Median: 32 | 6 |
| | | | | | SR | 7 | 3/4 | 45 | 7/0 | | |
| Robles et al [2010] [18] | Spain | 1988-2008 | R | No | LT | 11 | 10/1 | - | 4/7 | - | 8 |
| | | | | | SR | 29 | 14/15 | | 8/21 | | |
| Hong et al [2011] [19] | America | 1985-2009 | R | No | LT | 13 | 8/5 | 100 | - | - | 8 |
| | | | | | SR | 7 | 4/3 | 22 | | | |
| Croome et al [2015] [20] | America | 1993-2013 | R | Yes | LT | 54 | 40/14 | 69 | - | Median: 26 | 8 |
| | | | | | SR | 99 | 64/35 | 57 | | Median: 43 | |

LT, liver transplantation; SR, surgical resection; R, retrospective studies; M/F, male/female; LNM, lymph node metastasis; TNM, TNM staging; NOS, Newcastle-Ottawa Scale.

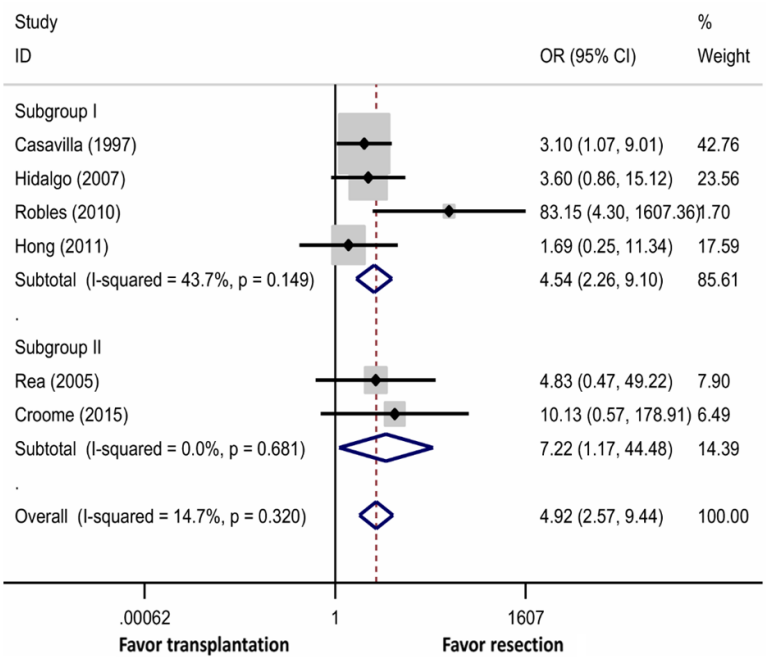


**Figure 2.** Meta-analysis of studies on R0 resection rate in HCCAs and subgroups: CI, confidence interval.

10 from a manual search of reference lists. Based on the titles, abstracts, and full texts, most of these articles did not suit our analysis. The screening process is presented in **Figure 1**. Of the studies identified, eight unique non-randomized trials met our inclusion criteria and were included in our meta-analysis [13-20]. The studies included a total of 579 patients (198 in the LT group and 371 in the SR group) (**Table 1**). According to the NOS, three articles received six stars, one received seven stars, and four received eight stars (**Table 1**).

*R0 resection rate*

R0 resection means a complete surgical resection with negative resection margins. Six studies [14-16, 18-20] assessed the R0 resection rate. Our meta-analysis found there was a significant difference regarding R0 resection rate favoring transplanted procedure than resected procedure (91 vs. 69%; OR=4.92, 95% CI=2.57-9.44, $P$<0.001; **Figure 2**; **Table 2**), and no significant heterogeneity between studies ($I^2$=14.7%; **Table 2**).

*1-, 3-, and 5-year OS*

The 1-, 3-, and 5-year OS were assessed in seven [13-18, 20], seven [13-18, 20], and six studies [13-16, 18, 20], respectively. Among all the studies, no significant differences were noted in the 1-year (77 vs. 72%; OR=1.13, 95% CI=0.72-1.76, $P$=0.067; **Figure 3**), 3-year (54

**Table 2.** Summary outcomes of meta-analyses for the treatment of HCCA patients with liver transplantation versus surgical resection

| Outcome | Therapy | Article numbers | Percent (%) | | Effect models | Odds ratio (OR) | 95% confidence interval (CI) | Significance *P* value | Heterogeneity | |
|---|---|---|---|---|---|---|---|---|---|---|
| | | | Transplant | Resection | | | | | $I^2$ (%) | *P* value |
| 1 year OS | | 7 (13-18, 20) | 77 | 72 | Fixed | 1.13 | 0.72-1.76 | 0.067 | 13.2 | 0.329 |
| Subgroup | Subgroup I | 5 (13, 14, 16-18) | 63 | 67 | Fixed | 0.80 | 0.47-1.37 | 0.411 | 0.0 | 0.722 |
| | Subgroup II | 2 (15, 20) | 91 | 81 | Fixed | 2.45 | 1.03-5.84 | 0.043 | 0.0 | 0.851 |
| 3 years OS | | 7 (13-18, 20) | 54 | 43 | Random | 1.11 | 0.76-1.62 | 0.587 | 74.2 | 0.001 |
| Subgroup | Subgroup I | 5 (13, 14, 16-18) | 33 | 38 | Fixed | 0.53 | 0.31-0.91 | 0.021 | 31.7 | 0.210 |
| | Subgroup II | 2 (15, 20) | 75 | 51 | Fixed | 2.73 | 1.51-4.96 | 0.001 | 40.5 | 0.195 |
| 5 years OS | | 6 (13-16, 18) | 48 | 30 | Random | 1.98 | 0.67-5.84 | 0.218 | 79.8 | 0 |
| Subgroup | Subgroup I | 4 (13, 14, 16, 18) | 24 | 28 | Random | 0.96 | 0.34-2.76 | 0.940 | 56.8 | 0.074 |
| | Subgroup II | 2 (15, 20) | 71 | 33 | Random | 6.86 | 1.15-41.06 | 0.035 | 83.8 | 0.013 |
| R0 resection | | (14-16, 18-20) | 91 | 69 | Fixed | 4.92 | 2.57-9.44 | 0.000 | 14.7 | 0.320 |
| Subgroup | Subgroup I | (14, 16, 18, 19) | 81 | 44 | Fixed | 4.54 | 2.26-9.10 | 0.033 | 43.7 | 0.149 |
| | Subgroup II | (15, 20) | 99 | 91 | Fixed | 7.22 | 1.17-44.48 | 0.000 | 0.0 | 0.681 |
| Mortality | | (13-15, 17, 18) | 12 | 10 | Fixed | 1.09 | 0.50-2.38 | 0.826 | 0.0 | 0.966 |
| Subgroup | Subgroup I | (13, 14, 17, 18) | 13 | 10 | Fixed | 1.12 | 0.47-2.64 | 0.802 | 0.0 | 0.905 |
| | Subgroup II | (15) | 7 | 12 | Fixed | 0.99 | 0.15-6.36 | 0.988 | - | - |

HCCA, hilar cholangiocarcinoma; LT, liver transplantation; SR, surgical resection; Subgroup I, LT vs. SR; Subgroup II, LT + neoadjuvant therapy vs. SR; Fixed, fixed-effects model; Random, random-effects model; OS, overall survival.

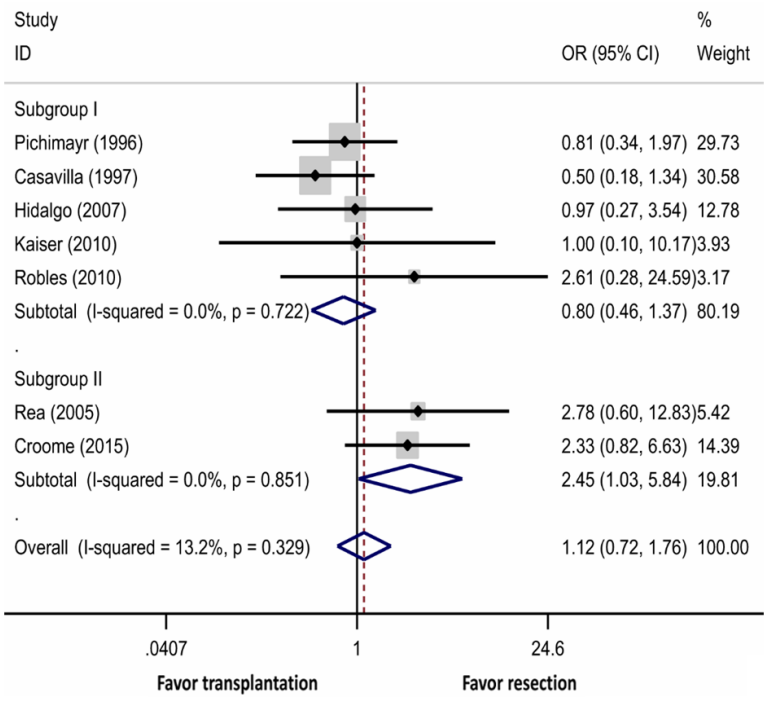


**Figure 3.** Meta-analysis of studies on 1-year overall survival (OS) in HCCAs and subgroups: CI, confidence interval.

vs. 43%; OR=1.11, 95% CI=0.76-1.62, *P*=0.587), and 5-year (48 vs. 30%; OR=1.98, 95% CI=0.67-5.84, *P*=0.218; **Figure 5**) OS between the LT and SR groups (**Table 2**). Significant heterogeneity was noted in the 3- and 5-year OS ($I^2$=74.2% and $I^2$=79.8%; **Table 2**).

*Mortality*

In our meta-analysis, five studies [13-15, 17, 18] reported the mortality. It showed that there was no significant difference in mortality between LT recipients and SR recipients (12 vs. 10%; OR=1.12, 95% CI=0.47-2.63, *P*=0.826; **Figure 6**; **Table 2**). No evidence of heterogeneity was noted in studies ($I^2$=0%; **Table 2**).

*Subgroup analysis and sensitivity analysis*

Among all the studies, eight compared the outcomes of LT and those of SR, including six [13, 14, 16-19] studies discussing the LT without neoadjuvant therapy (subgroup I) and two [15, 20] discussing the LT combined with neoadjuvant therapy (subgroup II). It showed that the 1-year (91 vs. 81%; OR=2.45, 95% CI=1.03-5.84, *P*=0.043; **Figure 3**), 3-year (75 vs. 51%; OR=2.73, 95% CI=1.51-4.96, *P*=0.001; **Figure 4**), and 5-year (48 vs. 30%; OR=6.86, 95% CI=1.15-41.06, *P*=0.035; **Figure 5**) OS were all higher in the LT patients than in the SR patients from subgroup

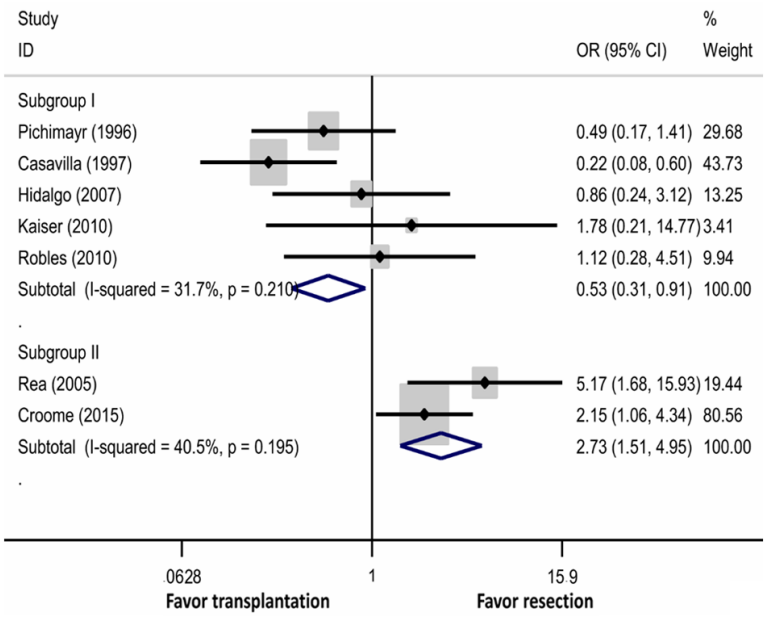


**Figure 4.** Meta-analysis of studies on 3-year overall survival (OS) in subgroups: CI, confidence interval.

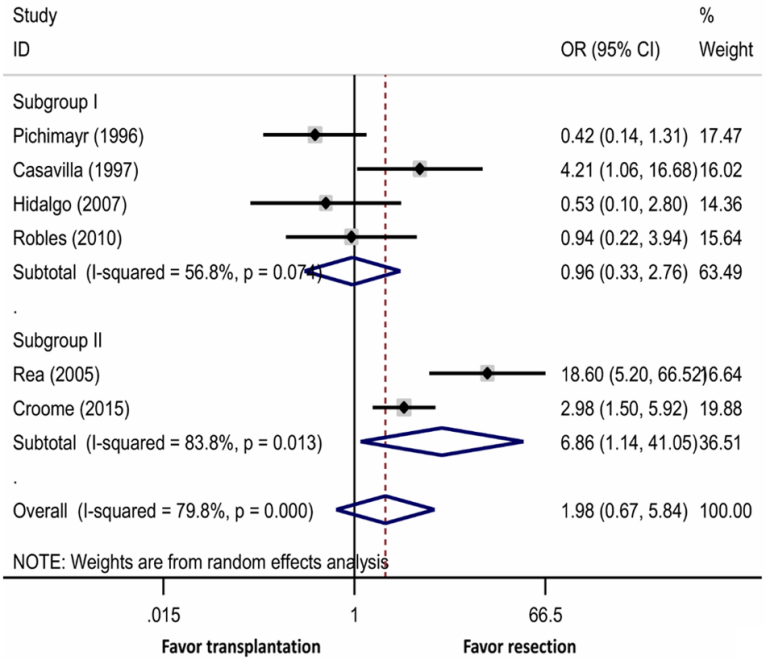


**Figure 5.** Meta-analysis of studies on 5-year overall survival (OS) in HCCAs and subgroups: CI, confidence interval.

II (**Table 2**); but no significant differences were noted from subgroup I. In addition, the evaluation of R0 resection rate and mortality were not changed in subgroups. The heterogeneity of 3-year OS became not obvious after subgroup analysis (**Table 2**). Furthermore, the curve of OS rates in 1-, 3- and 5-year in two groups were similar from subgroup I but appeared to distinctly improve in LT patients from subgroup II (**Figure 7**).

The sensitivity analysis which was performed by exclusion of each particular study in each pooled analysis did not change the substantive conclusions.

*Publication bias*

Funnel plots were carried out to evaluate the possible publication bias. The Begg's funnel plots didn't show any significant asymmetry, nor did the results of Egger's tests in OS, R0 resection rate and mortality analysis (all $P>0.05$; **Figure 8**).

## Discussion

To our knowledge, our study is the first to evaluate the efficacy and safety of LT for the treatment of unresectable HCCAs when compared to patients in conventional SR. In fact, LT had a number of advantages over conventional SR. It has a high potential for achieving complete tumor removal, and it could remove not only the tumor, but also the underlying liver disease in most surgically unresectable patients [21]. Although several previous st udies [13-20] have attempted to compare LT with SR in order to determine whether LT can be considered an option for surgically unresectable HCCAs, the role of LT in patients with surgically unresectable HCCAs remains controversial.

HCCA has been reported to be the most common type of cholangiocarcinoma, accounting for 60-70% of cases [1]. In the initial period of

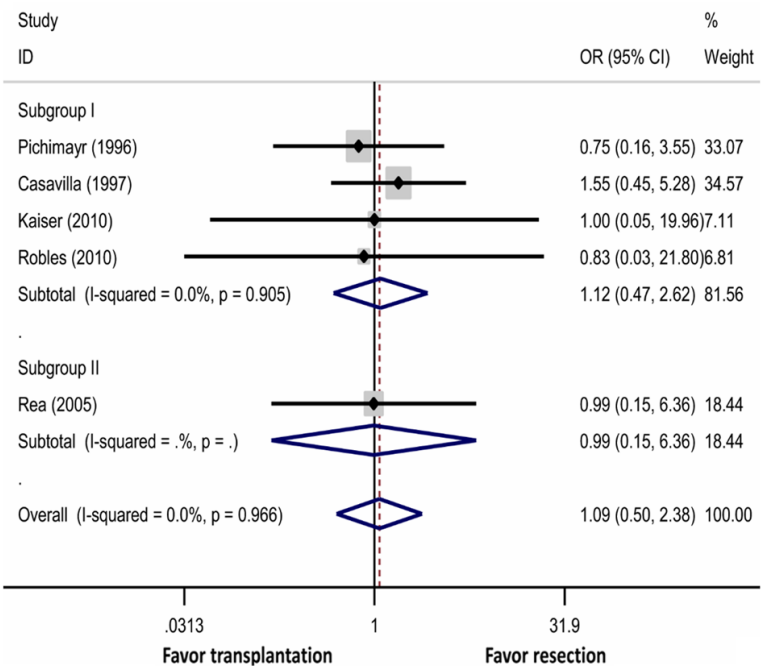


**Figure 6.** Meta-analysis of studies on mortality in HCCAs and subgroups: CI, confidence interval.

LT adoption, almost all the unresectable HCCA patients who underwent LT died within 1 or 2 years and a high tumor recurrence rate was noted [7, 22]. The outcomes were much worse with LT than with conventional SR. However, with the improvement in the surgical technique and perioperative management of LT, several recent studies have reported increases in the long-term survivals after LT. In 1997, Iwatsuki et al [14] performed a retrospective study with 72 HCCA patients (38 unresectable patients underwent LT and 34 resectable patients underwent SR), and reported 1-, 3-, and 5-year survival rates of 58%, 39%, and 39% and 74%, 34%, and 9% in patients who underwent LT and those who underwent SR, respectively. Furthermore, 11 patients who underwent LT and 3 patients who underwent SR survived for over 5 years. It appeared that the curative effects of LT for unresectable HCCAs were equivalent to conventional SR. In our overall analysis, no differences in all the OS and mortality were noted between the LT and SR groups; nonetheless, the R0 resection rate was higher in the LT group than in the SR group. It supported the advantage of LT that might achieve more effective R0 resection rate [21]. For HCCA patients, it has been demonstrated that R0 resection was the most important independent prognostic factor for survivals in various studies [23-26]. However, it should be noted that there were significant heterogeneities in the 3- and 5-year OS analyses. In order to explore the sources of heterogeneity and the benefits of neoadjuvant therapy, we compared LT with or without neoadjuvant therapy for unresectable HCCAs to patients in conventional SR and discussed the curative effects in the subgroups.

In 2005, Rea et al [15] reported that unresectable HCCA patients had excellent long-term survival rates after LT. The authors found that the 5-year survival rate was approximately 80% after LT in patients who were diagnosed with unresectable HCCAs. The survival outcomes were better with LT than with conventional SR, which reflected the results of the subgroup II analysis. The subgroup meta-analysis revealed significantly higher 1-, 3-, and 5-year OS and R0 resection rate in unresectable patients with HCCAs undergoing LT combined with neoadjuvant therapy than in patients undergoing conventional SR. On account of the immature experiences of transplantation in some institutions, the inappropriate indications in choosing the correct patients for transplant [27], and the delaying risks associated with immune suppression, which include infectious complications and toxicities [28], an increase in mortality used to be observed in patients who received transplant. Interestingly enough, no obviously difference was found on mortality between two groups in subgroup II. Thus, it revealed that LT combined with neoadjuvant therapy for unresectable HCCAs might have been superior to HCCA patients in conventional SR, as the overall survivals were higher and more effective R0 resection rate was obtained in LT patients. Otherwise, Compared with SR, the curve of OS rates in 1-, 3- and 5-year showed a distinct improvement in LT patients from subgroup II, demonstrating the long-term oncological benefits of LT with neoadjuvant therapy for unresectable HCCAs [29].

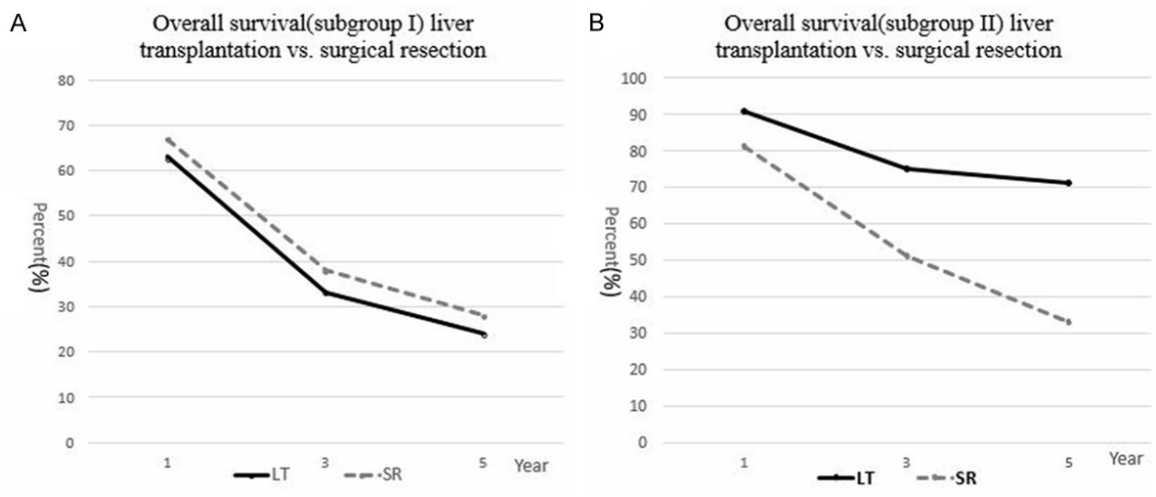


**Figure 7.** Summary graphs for tendency of overall survival rate at 1-, 3- and 5-years in subgroup I (A) and subgroup II (B).

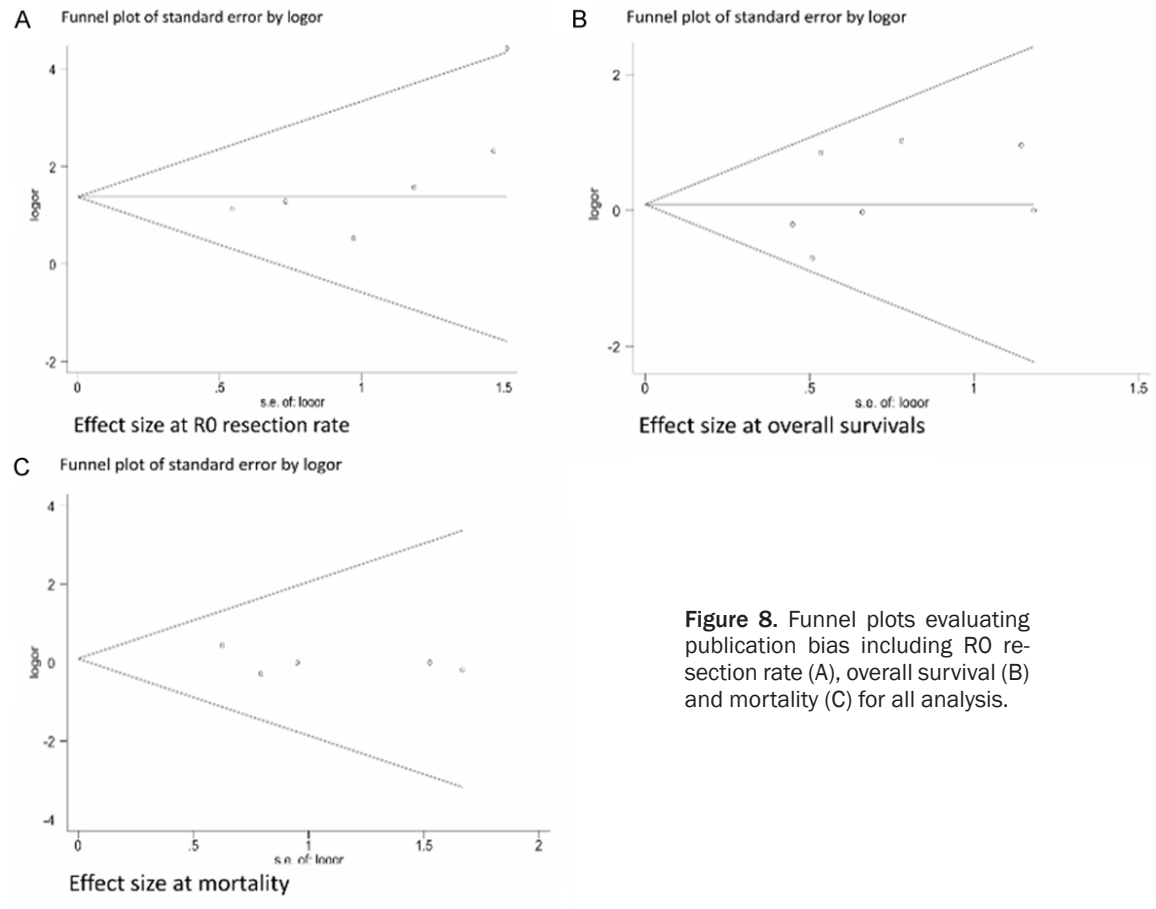


**Figure 8.** Funnel plots evaluating publication bias including R0 resection rate (A), overall survival (B) and mortality (C) for all analysis.

Therefore, LT combined with neoadjuvant therapy should be applied for surgically unresectable HCCAs if a liver is available for transplantation. Further studies were needed to evaluate whether LT combined with neoadjuvant therapy can be considered the first-line treatment for HCCA patients. On the other hand, there were no differences in the overall survivals between LT patients and SR patients from subgroup I. Besides, the changes in the OS rates with time

were similar between the two groups. Thus, in comparison to conventional SR, there is no convincing evidence for the use of LT alone in patients with surgically unresectable HCCAs because the pooled data did not demonstrate a survival advantage for LT without neoadjuvant therapy as well as the following problem. That the shortage of available organs for LT make it require carrying out rewardingly. And a delay in LT has been shown to significantly reduce the long-term survival of patients with HCCA [30, 31].

The present study had some limitations that may have caused bias in the analysis. First, considering the shortage liver resources worldwide, drop-outs are inevitable. Strictly speaking, intention-to-treat analysis has to be followed [32]. Second, definitive conclusions of the present meta-analysis were not possible because of the retrospective included studies and a tendency towards the selective transplant patients with advanced disease (T3, T4) (**Table 2**). Third, source of heterogeneity was present in 5-year OS, but no exact source of it was found from subgroup analysis or sensitivity analysis. Despite these limitations, a comprehensively study was performed to explore the value of LT for surgically unresectable HCCAs.

In summary, there is no convincing evidence that LT could be applied for surgically unresectable HCCAs when compared to SR, which was the mainstay and best treatment for HCCAs. However, when combined LT with neoadjuvant therapy, it was obviously effective for the treatment of unresectable HCCA patients. In the future, a comprehensive, randomized controlled trial will be needed to confirm the appropriate use of LT for the treatment of HCCAs.

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## Disclosure of conflict of interest

None.

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