



Comparison Between Salvage Liver Transplantation and Repeat Liver Resection for Recurrent Hepatocellular Carcinoma: A Systematic Review and Meta-analysis

I.D. Kostakis^{a,*}, N. Machairas^a, A. Prodromidou^a, P. Stamopoulos^a, Z. Garoufalia^a,
I. Fouzas^b, and G.C. Sotiropoulos^a

^a2nd Department of Propaedeutic Surgery, Laiko General Hospital, National and Kapodistrian University of Athens, Medical School, Athens, Greece; and ^bDivision of Transplantation, Department of Surgery, Aristotle University of Thessaloniki, Hippokratio General Hospital, Thessaloniki, Greece

ABSTRACT

Introduction. Repeat liver resection (RLR) has been adopted by surgeons as the first-line treatment in the case of intrahepatic recurrence of hepatocellular carcinoma (HCC), whereas salvage liver transplantation (SLT) is considered a second-line option. The aim of our study was to evaluate the results of SLT and RLR for HCC.

Methods. We searched for articles published up to December 1, 2017, in the PubMed database that compared SLT with RLR for HCC. We extracted data about patient and tumor characteristics, operative and postoperative outcomes, and survival and performed a meta-analysis.

Results. Patients who underwent SLT had somewhat larger liver lesions (mean difference: 0.73 cm, 95% confidence interval [CI]: 0.29–1.18, $P = .001$; $I^2: 0\%$, $P = .82$). Moreover, salvage liver transplantation resulted in higher blood loss, longer operating time, longer hospital stay, and higher postoperative morbidity (risk ratio [RR]: 2.45, 95% CI: 1.6–3.75, $P < .0001$; $I^2: 0\%$, $P = .58$) than RLR, whereas there was no significant difference in terms of postoperative mortality (RR: 6.48, 95% CI: 0.51–82.54, $P = .15$; $I^2: 61\%$, $P = .08$). On the other hand, SLT led to longer disease-free survival (DFS) than RLR (HR: 0.42, 95% CI: 0.25–0.7, $P = .0009$; $I^2: 63\%$, $P = .03$), but there was no significant difference in regard to overall survival (OS) (HR: 0.82, 95% CI: 0.55–1.23, $P = .34$; $I^2: 0\%$, $P = .62$).

Conclusions. SLT seems to be inferior to RLR regarding operative and postoperative results but presents a significant advantage in terms of DFS over RLR.

HEPATOCELLULAR carcinoma (HCC) is the fifth most frequent malignancy in men and the ninth most frequent malignancy in women worldwide [1]. Liver transplantation (LT) and liver resection are 2 treatment modalities that have curative intent for HCC, with the former offering the best results in terms of survival and recurrence [2,3]. In the case of operable recurrent HCC, repeat liver resection (RLR) is adopted as a first-line treatment. On the other hand, salvage liver transplantation (SLT), which was first described by Majno et al, is considered a second-line treatment, mainly due to the shortage of organs [4,5]. The objective of our systematic review and meta-analysis was to compare SLT with RLR as

treatment methods in patients who underwent liver resection for HCC and now their disease has relapsed.

METHODS

Search Strategy

We searched for articles published up to December 1, 2017, in the PubMed database. We used the following key words for this search:

*Address correspondence to Ioannis D. Kostakis, MD, PhD, 2nd Department of Propaedeutic Surgery, “Laiko” General Hospital, 17 AgiouThoma Street, 11527 Athens, Greece. E-mail: Ioannis.Kostakis@gmail.com

“hepatocellular carcinoma,” “recurrence,” “recurrent,” “liver transplantation,” “salvage,” and “resection.”

Inclusion and Exclusion Criteria

We included only original articles written in English and referring to patients with recurrent HCC who had undergone liver resection initially and compared SLT with RLR as a treatment approach. We excluded case reports, reviews, and original articles that referred only to SLT or RLR or other treatment modalities or written in languages other than English.

Review and Analysis

We extracted data about gender, age, cirrhosis status, tumor number, tumor size, operative time, blood loss, length of hospital stay, postoperative morbidity and mortality, and disease-free and overall survival.

Statistical Analysis

Review Manager version 5.3 was used for the meta-analysis. Risk ratio (RR) was used for the assessment of dichotomous variables and mean difference for the assessment of continuous variables hazard ratio (HR) for the assessment of survival. Due to the expected interstudy heterogeneity, the random effects model was chosen in all cases. The inverse variance method was chosen for comparisons between dichotomous variables, as well as between continuous variables, and the generic inverse variance method was chosen in case of survival analysis. Higgin's I^2 statistic was used for the assessment of statistical heterogeneity. Ninety-five percent confidence intervals (CI) were noted for all results. We calculated mean values and standard deviations based on to the equations proposed by Hozo et al [6] when they were not mentioned in the studies. Moreover, we calculated log HR and its standard error (SE) based on the equations proposed by Parmar et al [7] when they were not reported in the studies. Results were considered statistically significant when the P value was less than .05.

RESULTS

Search Results

Out of the 73 articles retrieved during our search, 7 studies were included in our analysis [8–14], whereas 66 articles were excluded (Fig 1). Three studies were of Chinese origin [9,11,12], 1 of Japanese origin [10], 1 of Korean origin [13], 1 of French origin [14], and 1 of combined French and Japanese origin [8]. There were 3 prospective [8,9,12] and 4 retrospective studies [10,11,13,14].

Patient and Tumor Characteristics

These 7 studies included 516 patients with recurrent HCC. One hundred and eight patients underwent SLT, while 408 patients underwent RLR [8–14], even though there were some patients who also underwent radiofrequency ablation in the study conducted by Zhang et al [9]. There were not sufficient data about the percentage of cirrhotic patients in most studies. However, the percentage of cirrhotic patients in the SLT group ranged between 66.7% and 100% [8,9,12], while this percentage ranged between 53.1% and 71.6% in the RLR group [8,9]. The same applies for the number of hepatic lesions. The percentage of patients with multiple tumors was 30.6% to 68.4% in the SLT [9,11,13], whereas this percentage was 27.6% to 33.3% in the RLR [9,11]. As far as the size of the tumors is concerned, the average tumor diameter ranged between 1.8 cm and 4.4 cm in the SLT group [8–13], while this ranged between 1.9 cm and 3.3 cm in the RLR group [8–11]. Patients who underwent SLT had somewhat larger liver lesions than patients who underwent RLR (mean difference: 0.73 cm, 95% CI: 0.29–1.18, $P = .001$; $I^2: 0\%$, $P = .82$) [8–11].

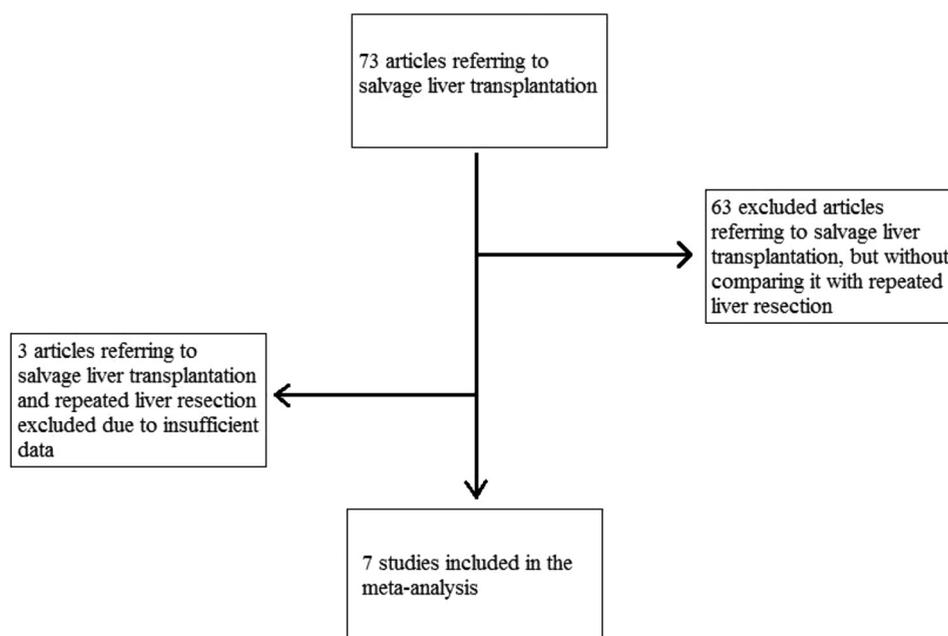


Fig 1. Study flowchart.

Operative Outcomes

There were not sufficient data about the operative times in most studies. However, Yamashita et al [10] and Ng et al [12] showed that SLT lasts significantly longer than RLR. Yamashita et al [10] reported a mean duration of 862.9 minutes for SLT and a mean duration of 229.1 minutes for RLR, while Ng et al [12] reported a median duration of 840 minutes for SLT and a median duration of 210 minutes for RLR. The same applied for blood loss. However, in those studies that mentioned the amount of blood loss, it was significantly higher in SLT than in RLR [9,10,12]. Specifically, Zhang et al [9] and Yamashita et al [10] reported a mean blood loss of 1178 mL and 24,690 g for SLT, respectively, whereas their mean blood loss was 265 mL and 596 g for RLR, respectively. Moreover, Ng et al [12] mentioned a median blood loss of 400 mL for RLR.

Postoperative Outcomes

There were not sufficient data about duration of hospitalization in most studies. However, Zhang et al [9] showed a mean length of hospital stay of 15.6 days for SLT, whereas this was 6.6 days for RLR. Furthermore, Yamashita et al [10] reported a mean length of hospital stay of 35 days for SLT, while this was 20 days for RLR. As far as postoperative morbidity is concerned, SLT resulted in higher rates of complications than RLR (RR: 2.45, 95% CI: 1.6–3.75, $P < .0001$; $I^2: 0\%$, $P = .58$) [9,10,12]. The same results remained when we removed the study conducted by Zhang et al [9], which also included some cases treated with radiofrequency ablation, from the analysis (RR: 2.24, 95% CI: 1.4–3.58, $P = .0007$; $I^2: 0\%$, $P = .6$) [10,12]. In regard to postoperative mortality, there is a higher rate of deaths after SLT than after RLR, but this difference did not reach statistical significance (RR: 6.48, 95% CI: 0.51–82.54, $P = .15$; $I^2: 61\%$, $P = .08$) [8–10,12–14]. The same results remained after the removal of the study conducted by Zhang et al [9] from the analysis (RR: 6.48, 95% CI: 0.51–82.54, $P = .15$; $I^2: 61\%$, $P = .08$) [8,10,12–14].

Survival

Concerning disease-free survival (DFS), there was an advantage of SLT, as it provided longer DFS at 5 years after operation than RLR (HR: 0.42, 95% CI: 0.25–0.7, $P = .0009$), even though there was some degree of heterogeneity among the studies ($I^2: 63\%$, $P = .03$) [8–12] (Fig 2). The results were

similar when the study conducted by Zhang et al [9], which also included some cases treated with radiofrequency ablation, was removed from the analysis (HR: 0.41, 95% CI: 0.2–0.84; $I^2: 70\%$, $P = .02$) [8,10–12]. However, there was no significant difference between SLT and RLR in terms of overall survival (OS) at 5 years after operation (HR: 0.82, 95% CI: 0.55–1.23, $P = .34$; $I^2: 0\%$, $P = .62$) [8–10] (Fig 3). The results were similar when the study conducted by Zhang et al [9] was removed from the analysis (HR: 0.66, 95% CI: 0.35–1.22, $P = .18$; $I^2: 0\%$, $P = .77$) [8,10].

DISCUSSION

Majno et al presented the first report of SLT for recurrent HCC [5]. Several case reports followed, indicating the feasibility of SLT as a treatment method for patients with intrahepatic recurrence of HCC that underwent liver resection as a first-line therapy [15–18]. According to those studies, the average operating time ranges from 7 to 10 hours [15–17], and the average blood loss ranges from 1.5 liters to 3 liters [15–18]. In a large study conducted by Hu et al [17], which included 888 cases of SLT, several types of postoperative complication were reported; intra-abdominal collection or abscess was detected in about 31% of patients, while intra-abdominal bleeding occurred in approximately 7% of patients. In the same study, postoperative infections were observed in about 30% of cases [17]. The rates of biliary complications, renal failure and vascular complications were 18%, 3%, and 4%, respectively [17]. In addition, the rates of postoperative mortality ranged between 2.1% and 11.8% [15,18]. Regarding the duration of hospitalization after transplantation, the median length of hospital stay is between 31 and 41 days [17,19]. As far as survival is concerned, the 5-year DFS rates vary greatly among studies, ranging between 37.8% and 86% [17–21], whereas the 5-year overall survival rates range between 46.6% and 88% [15–19].

There are also studies comparing SLT with other treatment strategies for HCC; a lot of studies have compared SLT for recurrent HCC with primary LT as the first surgical treatment for HCC [22]. A recent meta-analysis, conducted by Xiong et al [22], which compared SLT with primary LT, showed that SLT resulted in longer operating time, higher blood loss, increased recurrence rates, and poorer survival

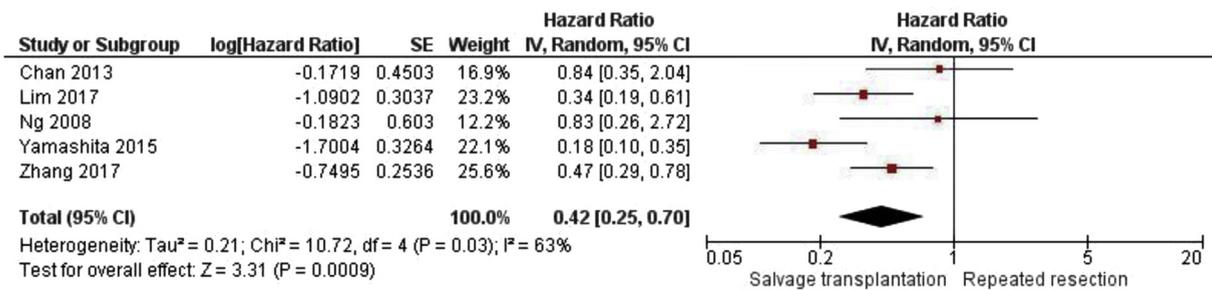


Fig 2. Five-year disease-free survival.

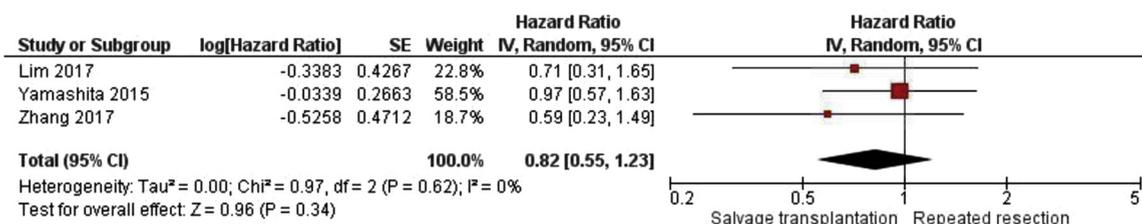


Fig 3. Five-year overall survival.

than primary LT, whereas there was no significant difference between the two treatment options in regard to postoperative morbidity, mortality, and duration of hospitalization. Furthermore, a few studies have proposed that LT could also be performed in patients who have undergone liver resection for HCC, and the histopathological examination of surgical specimens shows high-risk features, instead of waiting for tumor recurrence in order to proceed to SLT [18,23,24].

Our meta-analysis is the first attempt to evaluate SLT versus RLR for recurrent HCC. According to our findings, SLT is inferior to RLR regarding operative and postoperative results, but it has an advantage over RLR when disease-free survival is concerned.

REFERENCES

- [1] Torre LA, Bray F, Siegel RL, Ferlay J, Lortet-Tieulent J, Jemal A. Global cancer statistics, 2012. *CA Cancer J Clin* 2015;65:87–108.
- [2] Menahem B, Lubrano J, Duvoux C, Mulliri A, Alves A, Costentin C, et al. Liver transplantation versus liver resection for hepatocellular carcinoma in intention to treat: an attempt to perform an ideal meta-analysis. *Liver Transpl* 2017;23:836–44.
- [3] Xu XS, Liu C, Qu K, Song YZ, Zhang P, Zhang YL. Liver transplantation versus liver resection for hepatocellular carcinoma: a meta-analysis. *Hepatobiliary Pancreat Dis Int* 2014;13:234–41.
- [4] Lucidi V, Gustot T, Moreno C, Donckier V. Liver transplantation in the context of organ shortage: toward extension and restriction of indications considering recent clinical data and ethical framework. *Curr Opin Crit Care* 2015;21:163–70.
- [5] Majno PE, Sarasin FP, 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.
- [6] Hozo SP, Djulbegovic B, Hozo I. Estimating the mean and variance from the median, range, and the size of a sample. *BMC Med Res Methodol* 2005;5:13.
- [7] Parmar MK, Torri V, Stewart L. Extracting summary statistics to perform meta-analyses of the published literature for survival endpoints. *Stat Med* 1998;17:2815–34.
- [8] Lim C, Shinkawa H, Hasegawa K, Bhangui P, Salloum C, Gomez Gavara C, et al. Salvage liver transplantation or repeat hepatectomy for recurrent hepatocellular carcinoma: an intent-to-treat analysis. *Liver Transpl* 2017;23:1553–63.
- [9] Zhang X, Li C, Wen T, Peng W, Yan L, Yang J. 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.
- [10] Yamashita Y, Yoshida Y, Kurihara T, Itoh S, Harimoto N, Ikegami 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.
- [11] Chan AC, Chan SC, Chok KS, Cheung TT, Chiu DW, Poon RT, et al. Treatment strategy for recurrent hepatocellular carcinoma: salvage transplantation, repeated resection, or radiofrequency ablation? *Liver Transpl* 2013;19:411–9.
- [12] Ng KK, Lo CM, Liu CL, Poon RT, Chan SC, Fan ST. Survival analysis of patients with transplantable recurrent hepatocellular carcinoma: implications for salvage liver transplant. *Arch Surg* 2008;143:68–74.
- [13] Choi GH, Kim DH, Kang CM, Kim KS, Choi JS, Lee WJ, et al. Prognostic factors and optimal treatment strategy for intrahepatic nodular recurrence after curative resection of hepatocellular carcinoma. *Ann Surg Oncol* 2008;15:618–29.
- [14] Shen BY, Li HW, Regimbeau JM, Belghiti J. Recurrence after resection of hepatocellular carcinoma. *Hepatobiliary Pancreat Dis Int* 2002;1:401–5.
- [15] Wang P, Pu Y, Li H, Shi B, Zheng S, Zhong L. 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.
- [16] Qu W, Zhu ZJ, Sun LY, Wei L, Liu Y, Zeng ZG. Salvage liver transplantation for hepatocellular carcinoma recurrence after primary liver resection. *Clin Res Hepatol Gastroenterol* 2015;39:93–7.
- [17] Hu Z, Zhou J, Xu X, Li Z, Zhou L, Wu J, 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.
- [18] Lin CC, Elsarawy AM, Li WF, Lin TL, Yong CC, Wang SH, et al. Liver transplantation for high risk hepatocellular carcinoma after liver resection: a sequential or salvage approach? *Ann Transplant* 2017;22:602–10.
- [19] Lee S, Hyuck David Kwon C, Man Kim J, Joh JW, Woon Paik S, Kim BW, et al. Time of hepatocellular carcinoma recurrence after liver resection and alpha-fetoprotein are important prognostic factors for salvage liver transplantation. *Liver Transpl* 2014;20:1057–63.
- [20] Harimoto N, Yoshida Y, Kurihara T, Takeishi K, Itoh S, Harada N, et al. Prognostic impact of des-γ-carboxyl prothrombin in living-donor liver transplantation for recurrent hepatocellular carcinoma. *Transplant Proc* 2015;47:703–4.
- [21] Yoshizumi T, Ikegami T, Yoshiya S, Motomura T, Mano Y, Muto J, et al. Impact of tumor size, number of tumors and neutrophil-to-lymphocyte ratio in liver transplantation for recurrent hepatocellular carcinoma. *Hepatol Res* 2013;43:709–16.
- [22] Xiong Q, Geng TT, He L, Gao H. Harm and benefits of salvage transplantation for hepatocellular carcinoma: an updated meta-analysis. *Transplant Proc* 2016;48:3336–47.
- [23] Ferrer-Fàbrega J, Forner A, Llicioni A, Miquel R, Molina V, Navasa M, et al. Prospective validation of ab initio liver transplantation in hepatocellular carcinoma upon detection of risk factors for recurrence after resection. *Hepatology* 2016;63:839–49.
- [24] Sala M, Fuster J, Llovet JM, Navasa M, Solé M, Varela M, et al. High pathological risk of recurrence after surgical resection for hepatocellular carcinoma: an indication for salvage liver transplantation. *Liver Transpl* 2004;10:1294–300.