Impact of multiple liver resections prior to salvage liver transplantation on survival in patients with recurrent HCC

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ABSTRACT

Objectives: Salvage liver transplantation (SLT) is a controversial technique that has been reported to be acceptable for the management of patients with recurrent hepatocellular carcinoma (HCC) after primary hepatic resection (HR). However, whether the number of times liver resection is performed has an impact on survival after SLT has not yet been reported.

Design: Retrospective study.

Setting: The level of care is primary and the study was carried out at only 1 centre.

Participants: The study included 59 patients who underwent SLT for HCC from September 2001 to December 2012. 51 patients underwent HR only once before SLT, while the remaining 8 patients underwent HR more than once before SLT (HR=2 [7], HR=3, [1]).

Primary and secondary outcome measures: In this study, the 1-year, 3-year and 5-year overall and tumour-free survival outcomes between the 2 groups were compared.

Results: There were no significant differences between patients who underwent HR once and those who underwent HR more than once with respect to overall or tumour-free survival after receiving SLT. The 1-year, 3-year and 5-year overall survival rates for patients who underwent HR once were 72.9%, 35.3% and 35.5% vs 50%, 50% and 50%, respectively (p=0.986), while the 1-year, 3-year and 5-year tumour-free survival rates for those who underwent HR more than once were 66.3%, 55.3% and 44.4% vs 40%, 40% and 40%, respectively (p=0.790).

Conclusions: There was no significant difference in the survival rate of patients who underwent HR once and those who underwent HR more than once prior to SLT and those who underwent HR more than once after SLT. This suggests that SLT is a reasonable choice for patients who suffer from recurrent HCC after HR.

Trial registration number: This is a retrospective study and no registry or number is required.

INTRODUCTION

Hepatocellular carcinoma (HCC) is a disease with increasing worldwide morbidity1 as a consequence of the prolongation of human life. Increasing attention is being devoted to improving the quality of life for HCC incidence in this ageing population, and mortality rates continue to rise.2 Many clinical studies have focused on the most effective therapeutic regimen for patients who develop HCC.3 At present, hepatic resection (HR) and liver transplantation (LT) are two major curative options available for patients with operable, advanced HCC.4 LT is acknowledged as the primary and optimal strategy available for patients with end-stage liver diseases and/or concomitant HCC,6 as it removes the tumour in situ as well as the tissue that has cancerous potential. Sapisochin et al7 reported significantly better long-term actuarial survival in patients who underwent LT compared with those who received HR. The relatively poor outcome associated with HR was due to the result of a high HCC recurrence rate. However, the shortage of living-donor organs due to the escalating demand resulting from the increased incidence of HCC is a serious issue.8,9

Under these circumstances, salvage LT (SLT) was proposed by Majno et al,10 which is defined as LT after primary HR (PHR), and has been proven an acceptable
management strategy for patients with developed recurrent HCC.\textsuperscript{11} \textsuperscript{12} Conversely, the effectiveness of SLT remains doubtful for patients with tumours of greater invasive potential and in patients who have had to undergo more than one surgery. Furthermore, immunosuppression after LT is likely to be a significant challenge for patients who have previously undergone PHR. Although the SLT approach remains controversial, it has been shown that the overall survival following SLT does not differ from that of primary LT (PLT).\textsuperscript{13} In addition, SLT relieves the stress of organ shortage and extends patient lifespan. In the People’s Republic of China, the shortage of living donors is an extreme problem, and HCC often recurs following PHR before donors have been matched. In this situation, we typically perform a second liver resection (LR) surgery with the intention of prolonging survival until an appropriate donor can be found.

To the best of our knowledge, whether the number of HRs performed prior to SLT has any impact on overall or tumour-free survival has not previously been reported. Thus, the aim of this study is to evaluate the overall and tumour-free survival between patients who underwent HR only once and those who underwent HR more than once prior to SLT. The results of this study may offer insight into appropriate clinical management strategies for these patients.

\textbf{METHODS}

\textbf{Patients}

From September 2001 to November 2012, we performed a single-centre retrospective analysis involving 59 liver recipients, using data obtained from the First Affiliated Hospital of Zhejiang University.

The inclusion criteria were: adult (>18 years old); Chinese nationality; and patients with HCC who underwent previous hepatectomy and received SLT because of tumour recurrence.

The exclusion criteria were: patients with HCC who underwent previous hepatectomy and subsequent LT without record of tumour recurrence (due either to liver failure or as \textit{de principle} or bridge transplantation); recipients with other types of liver cancer (eg, cholangiocarcinoma); and loss to follow-up.

The 59 participants were divided into two groups based on the number of times they underwent HR before they received SLT: (1) recipients who underwent HR only once before SLT (HR1 group; \(n=51\)) and (2) recipients who underwent LR more than once before SLT (HR2 group; \(n=8\)). Within the latter group, seven patients underwent HR twice and one patient underwent HR three times.

The following variables were compared between these two groups: age, gender, recipient blood type, blood type incompatibility, preoperative \(α\)-fetoprotein (AFP) level, Model for End-Stage Liver Disease (MELD) score, Child-Pugh score, tumour status (including tumour number, diameter of the largest tumour, sum of tumour diameters and tumour–node–metastasis (TNM) staging) and macrovascular invasion. In addition, operative features (cold ischaemia time, warm ischaemia time and intraoperative blood loss) and post-transplant complications were also included.

The 1-year, 3-year and 5-year overall and tumour-free survival rates between the two groups after SLT were compared. Patient survival was further assessed by the Hangzhou criteria, which we have previously demonstrated to be a feasible candidate selection and prognostic approach for LT selection in HCC recipients.\textsuperscript{14} The Hangzhou criteria require that patients meet one of the following conditions: (1) total tumour diameter less than or equal to 8 cm and (2) total tumour diameter more than 8 cm with histopathological grade I or II and preoperative AFP level \(\leq 400\) ng/mL.\textsuperscript{14} \textsuperscript{15} Of the 59 patients, 32 recipients met the Hangzhou criteria, with 28 in the HR1 group and 4 in the HR2 group.

\textbf{Statistical analysis}

Descriptive statistics were expressed as mean (SD) or median (IQR). Recipient characteristics were compared using the Mann-Whitney \textit{U} test for continuous variables and Fisher’s Exact Test or Continuity Correction for binomial variables, where appropriate. Survival rates were assessed using Kaplan-Meier survival curves. Differences were considered statistically significant if the \(p<0.05\); all tests were two sided. All analyses were performed using SPSS 16.0 (SPSS Inc, Chicago, Illinois, USA).

\textbf{RESULTS}

\textbf{Patient groups and clinicopathological characteristics}

This study evaluated a total of 59 patients treated at our centre who received HR for HCC and later underwent SLT for recurrence. The only difference between these patients was the number of times they underwent HR before LT. Among these patients, 51 underwent only one resection (HR1 group, \(n=51\)), while 8 underwent HR more than once (HR2 group, \(n=8\)). Of the eight patients in the HR2 group, seven had one re-resection while the other patient had two (HR=2, \(n=7\); HR=3, \(n=1\)). Since the individual samples were not sufficiently large, we decided to combine all eight patients into one group (HR2).

There were no significant differences in general characteristics before SLT between HR1 and HR2 groups, such as gender (male/female: 43/8 vs 7/1, \(p=0.816\)), mean age (47.06±8.54 vs 48.13±7.55, \(p=0.799\)), transplant year (before 2008/after 2008: 19/32 vs 1/7, \(p=0.330\)) and blood type (\(p=0.166\)). The LT preoperative AFP level is a very important factor in the Hangzhou criteria. In this study, we found no difference in AFP level between the two groups (\(p=0.775\)): the AFP level in the HR1 group varied from 12.8 to 1176.1 ng/mL with a median of 232.6 ng/mL, while the range in the HR2 group was 32.1–756.2 ng/mL with a median of 323.7 ng/mL. Similarly, the MELD (median, 10 vs 10.5) and

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Child-Pugh scores (median, 7 vs 7) were not different between groups. As for the diameter of the largest tumour (IQR) and number of tumours, both groups were similar (p=0.602 and p=0.588, respectively). Finally, no differences were found in operative characteristics, including cold ischaemia time, warm ischaemia time and intraoperative blood loss. All statistics are shown in table 1.

Survival analysis of SLT

In this study, survival analysis, including overall survival and tumour-free survival, after SLT between patients who underwent HR only once (HR1 group) and those who underwent HR more than once (HR2 group), was compared. There was no significant difference between the two groups in terms of overall survival after SLT; the 1-year, 3-year and 5-year overall survival rates of recipients were 72.9%, 35.3% and 35.5% vs 50%, 50% and 50%, respectively (p=0.986; figure 1A). With respect to tumour-free survival, while survival in the HR2 group was inferior to the HR1 group, no statistically significant differences were detected between the two groups: the 1-year, 3-year and 5-year rates were 66.3%, 55.3% and 44.4% vs 40%, 40% and 40%, respectively (p=0.790; figure 1B).

For recipients fulfilling the Hangzhou criteria, the 1-year, 3-year and 5-year overall survival rates of the HR1 group were 88.4%, 68.0% and 68.0%, respectively, similar to those of the HR2 group (50.0%, 50.0% and 50.0%, respectively; p=0.150; figure 2A). The corresponding 1-year, 3-year and 5-year tumour-free survival rates for those meeting the Hangzhou criteria were 69.5%, 69.5% and 57.9%, respectively, in the HR1 group, and the 1-year and 3-year tumour-free survival rates were 100% and 50.0% in the HR2 group, respectively (p=0.833, figure 2B).

Complications of post-SLT

The complications of post-transplant were, mainly, postoperative infection, biliary complications, intraoperative bleeding, renal failure, vascular complications and acute rejection. Comparison of each complication shows there was no significant difference between HR1 and HR2 groups (p value >0.05). All detailed statistics are shown in table 2.

DISCUSSION

HCC is the most prevalent type of liver cancer. Curative treatments for HCC that have been used widely and proven effective include HR and LT. In addition, other treatment modalities, such as radiofrequency ablation (RFA) and transarterial chemoembolisation (TACE), should also be considered. Nonetheless, LT remains the most effective curative option for patients with HCC and cirrhosis,16 because it removes tumours and tissues that can cause other hepatic diseases. However, in certain areas with a high incidence of HCC and low organ donation rates, especially in the People’s Republic of China, LT is associated with significant waiting time and mortality. Using LT as a backup strategy, salvage LT (SLT) can be considered for patients with HCC who cannot receive LT immediately.

Table 1 Clinical characteristics of patients in the HR1 and HR2 groups before salvage liver transplantation

| Characteristic                                           | HR1 group | HR2 group | p Value |
|----------------------------------------------------------|-----------|-----------|---------|
| Gender (male/female)                                     | 43/8      | 7/1       | 0.816   |
| Age (year)                                               | 47.06±8.54| 48.13±7.55| 0.799   |
| Transplant year (before 2008/after 2008)                 | 19/32     | 1/7       | 0.330   |
| Blood type                                               |           |           | 0.166   |
| A                                                        | 17        | 1         |         |
| AB                                                       | 6         | 0         |         |
| B                                                        | 15        | 2         |         |
| O                                                        | 13        | 5         | 0.337   |
| Blood type incompatible                                  | 9         | 0         | 0.602   |
| Preoperative AFP level, median (IQR), ng/mL              | 232.6 (12.8–1176.1) | 323.7 (32.1–756.2) | 0.775 |
| MELD score                                               | 10 (7–15) | 10.5 (7–15.25) | 0.911   |
| TNM classification                                        |           |           | 0.504   |
| I                                                        | 13        | 2         |         |
| II                                                       | 11        | 3         |         |
| III                                                      | 19        | 1         |         |
| IV                                                       | 8         | 2         |         |
| Child-Pugh score                                         | 7 (5–9)   | 7 (5.25–9) | 0.781   |
| Diameter of largest tumour, median (IQR), cm             | 3 (2–5)   | 3 (2.13–4.38) | 0.602  |
| Number of tumours, median (IQR)                          | 2 (1–3)   | 2 (1–10.5) | 0.588   |
| Sum of tumour diameters, median (IQR), cm                 | 4.75 (3.00–7.88) | 4 (1.2–12.75) | 0.873   |
| Macrovascular invasion                                   | 18        | 1         | 0.381   |
| Cold ischaemia time (hours)                              | 8.8 (7–11.18) | 11.58 (7.48–12.48) | 0.163   |
| Warm ischaemia time (minutes)                            | 4.5 (3.5–5.00) | 5.00 (4.25–5.00) | 0.105   |
| Intraoperative blood loss (mL)                            | 2500 (1500–4500) | 5500 (2500–10 000) | 0.460   |

AFP, α-fetoprotein; HR, hepatic resection; MELD, Model for End-Stage Liver Disease; TNM, tumour node metastasis.
China, primary resection is the first-line of treatment for patients with HCC. HR for HCC may be performed with curative intentions following a free resection margin during surgery. Although this technique may lead to decreased perioperative mortality, the long-term survival is not as good as expected, with a rate of tumour recurrence as high as 70% within 5 years. Various factors, such as pathological aspects indicative of tumour invasiveness containing large tumour size, Child-Pugh score and presence of satellite nodules, account for this high recurrence rate. One positive clinical point for patients with HCC recurrence is that they have previously been evaluated for operative re-resection and LT if it was accessible. The evaluation protocol and selection criteria in LT management strategy are similar to those used in the treatment of primary HCC. The Milan criteria were acknowledged worldwide for decades and, recently, the Hangzhou criteria were proven suitable for LT as well. In the study by Ho et al., 12.4% patients with Child-Pugh class A chose re-resection as a treatment option and their 5-year survival was 72%. The remaining patients in the study chose non-surgical methods, including RFA, TACE and support treatment, and no differences were found in the 2-year and 5-year resection rates compared with re-resection. The study by Ho et al. also included nine patients who underwent LT after the first recurrence, which we call SLT, but the authors did not compare the survival rates of this group with the re-resection group.

SLT is a fairly new concept, first presented by Professor Bismuth et al. in 1999, and has been regarded as the quintessential complementary method of LT and HR as it alleviates the stress of organ donor shortage. Moreover, SLT extends the time a patient can wait for a donor liver and also provides better life-expectancy over HR.

During recent decades, whether SLT would achieve a curative effect similar to PLT has remained a bone of contention. Therefore, a number of studies have attempted to answer this question. Our previous research reported that there was no remarkable difference in survival rates between selected recipients of SLT and PLT. Similarly, Hu et al. claimed that, among recipients appropriately selected according to the Hangzhou criteria, 

![Figure 1](image1.png) **Figure 1** Comparison of overall and tumour-free survival between hepatic resection 1 (HR1) and HR2 groups; (A) overall survival, and (B) tumour-free survival.

![Figure 2](image2.png) **Figure 2** Comparison of overall and tumour-free survival between hepatic resection 1 (HR1) and HR2 groups within the Hangzhou criteria; (A) overall survival, and (B) tumour-free survival.
criteria, the 1-year, 3-year and 5-year overall survival rates of SLT recipients were similar to those of PLT recipients: 73.00%, 51.77% and 45.84% vs 74.49%, 55.10% and 48.81%, respectively (p=0.260). However, the 1-year, 3-year and 5-year disease-free survival rates of SLT recipients were inferior to those of PLT recipients (p=0.048).

Prior to our study, Poon and Fan performed similar research, investigating 107 patients who underwent LT after the first HR and SLT. Many factors might be considered to illustrate this difference, but none of the patients who underwent HR more than once prior to SLT were inferior to those of PLT recipients (p=0.048).

In addition, potential confounding factors were adjusted in the current study. Cirrhosis and other background hepatic disorders, such as metabolic disorders and hepatitis, are essential factors that should be taken into consideration during the decision-making process regarding whether it is feasible and whether patients are in a position to undergo surgery. Patients who previously underwent HR before SLT may have poor liver function and their general condition may also be poor; factors that can prevent them from undergoing another HR. In addition, recurrent tumours are not confined to one lobe of the liver; also, the tumour size may be greater than what is suitable for HR. Therefore, SLT may be the only option for patients with recurrent HCC.

Conversely, liver condition and regeneration in patients who accept HR more than once may enable them to undergo a second HR operation. With the presence of certain characteristically favourable histological factors, HR provides an excellent outcome with a low recurrence rate. Interestingly, nearly half of patients who undergo HR have a tumour size less than 2 cm, according to the sizing criteria set forth by Barcelona Clinic Liver Cancer (BCLC) prognosis staging. The drawback of HR is that many patients cannot meet the criteria and recurrence is a common phenomenon. However, based on the factors we aforementioned, we doubt whether repeated HRs would dramatically increase either the harm or the benefit of these patients, as the final outcome in patients with multiple HR is similar to that in patients who undergo only one HR.

We surmise that surgical resection extent is another factor that contributes to the lack of difference in survival between patients with single and multiple HR. For instance, the recurrent HCC tumours may be restricted to one lobe of the liver and lobectomy of a small area is associated with a good prognosis. Thus, even though a patient underwent multiple HRs, it does not necessarily mean that they had more liver area removed than a patient who only underwent one HR. In addition, the interval of HR recurrence might be an indication of higher invasion of HCC. In brief, all these complicated factors contribute to the single-factor model to decrease the likelihood of the current findings being attributed to selection bias.

Our study was retrospective, and all data were selected from a single centre, which limited our sample size. In addition, potential confounding factors were adjusted in the single-factor model to decrease the likelihood of the current findings being attributed to selection bias. Therefore, we plan to combine multicentre data in our further studies and analyse other factors in terms of cytobiology and histopathology, if possible.

On the basis of the outcomes of this study, we conclude that SLT is a reasonable approach to use to address the challenge of liver donor shortage and in patients who suffer from recurrent HCC after HR. The number of HR operations has little influence on
survival; therefore, treating recurrent HCC regardless of prior HR before SLT or to perform SLT directly after comprehensive evaluation of the general condition of the patients and the donor are both acceptable clinical practices.

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Contributors SZ and ZH were responsible for study concept and design. QZ and JX performed the experiments. QZ, JZ and ZL were responsible for peroperative management and recording clinical characteristics. QZ drafted the manuscript. ZH and SZ gave final approval for the version published.

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Competing interests None declared.

Patient consent Obtained.

Ethics approval The Committee of Ethics in Biomedical Research of Zhejiang University, China.

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Data sharing statement No additional data are available.

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REFERENCES

1. Yang JD, Roberts LR. Epidemiology and management of hepatocellular carcinoma. Infect Dis Clin North Am 2010;24:899–919, viii.
2. Altekruse SF, McGlynn KA, Reichman ME. Hepatocellular carcinoma incidence, mortality, and survival trends in the United States from 1975 to 2005. J Clin Oncol 2009;27:1485–91.
3. Facciputo ME, Koneru B, Roccia 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;15:983–91.
4. Jamagin WR. Management of small hepatocellular carcinoma: a review of transplantation, resection, and ablation. Ann Surg Oncol 2010;17:1226–33.
5. Rahbari NN, Mehrabi A, Mollberg NM, et al. Hepatocellular carcinoma: current management and perspectives for the future. Ann Surg 2011;253:453–69.
6. Wang ZX, Song SH, Teng F, et al. A single-center retrospective analysis of liver transplantation on 255 patients with hepatocellular carcinoma. Clin Transplant 2010;24:752–7.
7. Sapisochin G, Castells L, Dopazo C, et al. Single HCC in cirrhotic patients: liver resection or liver transplantation? Long-term outcome according to an intention-to-treat basis. Ann Surg Oncol 2013;20:1194–202.
8. Fomer A, Reig ME, de Lope CR, et al. Current strategy for staging and treatment: the BCLC update and future prospects. Semin Liver Dis 2010;30:61–74.
9. Bruix J, Sherman M. Management of hepatocellular carcinoma: an update. Hepatology 2011;53:1020–2.
10. Majno PE, Sarasin FP, Menthia 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;31:999–906.
11. 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:e38587.
12. 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;40:3538–61.
13. Hu Z, Wang W, Li Z, et al. Recipient outcomes of salvage liver transplantation versus primary liver transplantation: a systematic review and meta-analysis. Liver Transpl 2012;18:1316–23.
14. Xu X, Lu D, Ling Q, et al. Liver transplantation for hepatocellular carcinoma beyond the Milan criteria. GUT 2015.
15. Zheng SS, Xu X, Wu J, et al. Liver transplantation for hepatocellular carcinoma: Hangzhou experiences. Transplantation 2008;85:1726–32.
16. Mazzaferrro 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. Neeluf H, Makowiec F, Harder J, et al. Hepatic resection for hepatocellular carcinoma—results and analysis of the current literature. Zentrabtl Chir 2009;134:127–35.
18. Cucchielli A, Vitala A, Del Gaudio M, et al. Harm and benefits of primary liver resection and salvage transplantation for hepatocellular carcinoma. Am J Transplant 2010;10:619–27.
19. Ercolani G, Grazi GL, Ravaioi M, et al. Liver resection for hepatocellular carcinoma on cirrhosis: univariate and multivariate analysis of risk factors for intrahepatic recurrence. Ann Surg 2003;237:536–43.
20. Dahiya D, Wu TJ, Lee CF, et al. Minor versus major hepatic resection for small hepatocellular carcinoma (HCC) in cirrhotic patients: a 20-year experience. Surgery 2010;147:678–85.
21. Lung-Ping Poon R, Fan ST, Wong J. Risk factors, prevention, and management of postoperative recurrence after resection of hepatocellular carcinoma. Ann Surg 2000;232:10–24.
22. Ho CM, Lee PH, Shau WY, et al. Survival in patients with recurrent hepatocellular carcinoma after primary hepatectomy: comparative effectiveness of treatment modalities. Surgery 2012;151:700–9.
23. Bismuth H, Majno PE, Adam R. Liver transplantation for hepatocellular carcinoma. Semin Liver Dis 1999;19:311–22.
24. Can MF, Hughes CB. Primary liver transplantation vs liver resection followed by transplantation for transplantable hepatocellular carcinoma: liver functional quality and tumor characteristics matter. World J Gastrointest Surg 2013;5:5–8.
25. Chan DL, Alazhrani 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.
26. Guerrini GP, Gerunda GE, Montalti R, et al. Results of salvage liver transplantation. Liver Int 2014;34:96–104.
27. Tranchart H, Chirica M, Sepulveda A, et al. Long-term outcomes following aggressive management of recurrent hepatocellular carcinoma after upfront liver resection. World J Surg 2012;36:2684–91.
28. Poon RT, Fan ST. Resection prior to liver transplantation for hepatocellular carcinoma: a strategy of optimizing the role of resection and transplantation in cirrhotic patients with preserved liver function. Liver Transpl 2004;10:813–15.
29. Eguchi S, Kanematsu T, Arii S, et al. Recurrence-free survival more than 10 years after liver resection for hepatocellular carcinoma. Br J Surg 2011;98:552–7.
30. Nathan H, Schlicke RD, Choti MA, et al. Predictors of survival after resection of early hepatocellular carcinoma. Ann Surg 2009;249:799–805.
31. Fukus 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.
Correction

Hu Z, Zhang Q, Zhou J, et al. The Impact of Multiple Liver Resections Prior to Salvage Liver Transplantation on Survival in Patients with Recurrent HCC. BMJ Open 2015;5:e008429. The 5-year overall survival rate for patients who underwent HR once was 35.3%, not 35.5%, which is the same as the 3-year survival rate. The abstract should be corrected to read as follows:

There were no significant differences between patients who underwent HR once and those who underwent HR more than once with respect to overall or tumour-free survival after receiving SLT. The 1-year, 3-year and 5-year overall survival rates for patients who underwent HR once and those who underwent HR more than once were 72.9%, 35.3% and 35.3% vs 50%, 50% and 50%, respectively (p=0.986), while the 1-year, 3-year and 5-year tumour-free survival rates for these two groups were 66.3%, 55.3% and 44.4% vs 40%, 40% and 40%, respectively (p=0.790).

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