TRANSPLANT INTERNATIONAL

Transplant International ISSN 0934-0874

ORIGINAL ARTICLE

Living donor liver transplantation or resection for Child-Pugh A hepatocellular carcinoma patients with multiple nodules meeting the Milan criteria

Li Jiang,[1] Anque Liao,[2] Tianfu Wen,[1] Lunan Yan,[1] Bo Li[1] and Jiayin Yang[1]

1 Liver Transplantation Center, Department of Liver Surgery, West China Hospital of Sichuan University, Chengdu, Sichuan Province, China
2 Operating Theater, West China Hospital of Sichuan University, Chengdu, Sichuan Province, China

Keywords
hepatocellular carcinoma, living donor liver transplantation, Milan criteria, multiple nodules, resection.

Correspondence
Jiayin Yang MD, PhD, Liver Transplantation Center, Department of Liver Surgery, West China Hospital of Sichuan University, Chengdu, 610041 Sichuan Province, China.
Tel.: +86-28-85422871;
fax: +86-28-85422871;
e-mail: yangjiayinhx@163.com

Conflicts of interest
The authors have declared no conflict of interest.

Received: 23 December 2013
Revision requested: 24 January 2014
Accepted: 3 March 2014
Published online: 2 April 2014

doi:10.1111/tri.12297

Summary

The optimum primary treatment strategy for early hepatocellular carcinoma (HCC) patients with multiple nodules remains unclear. We aimed to compare the outcomes of living donor liver transplantation (LDLT) with that of liver resection (LR) for early Child-Pugh A HCC patients with multiple nodules meeting the Milan criteria. From January 2007 to July 2012, 67 of 375 patients with early HCC in our centre fulfilled the inclusion criteria (group LDLT, $n = 34$ versus group LR, $n = 33$). Patient and tumour characteristics, operative data, postoperative course and outcomes were analysed retrospectively. The postoperative mortality and rate of major complications were similar in both groups. The 5-year overall survival (OS; 76.5% vs. 51.2%, $P = 0.046$) and recurrence-free survival (RFS; 72.0% vs. 19.8%, $P = 0.000$) were better in group LDLT than that in group LR. The 5-year OS and RFS were similar between patients with tumours located in the same lobe (TSL) and those in the different lobes (TDL) after LDLT, whereas the 5-year RFS was better in patients with tumours in TSL (30.6% vs. 0%, $P = 0.012$) after LR. In conclusion, primary LDLT might be the optimum treatment for early HCC patients with multiple nodules meeting the Milan criteria.

Introduction

The debate concerning the best primary curative option for early hepatocellular carcinoma (HCC), defined as a single tumour <5 cm or a maximum of three total tumours with none more than 3 cm in patients (Milan criteria) [1] with Child-Pugh A cirrhosis, is continuing.

Liver transplantation (LT) has been advocated in patients with early HCC because it involves the largest possible hepatectomy and removal of underlying cirrhotic tissue, leading to a much lower recurrence. Satisfactory survival results were obtained in patients with early HCC meeting the Milan criteria with similar 5-year survival as those undergoing LT for nonmalignant liver diseases and low 5-year recurrence rate of <20% [2]. However, LT is not offered to all patients with early HCC as a result of the organ shortage and patients drop-off due to tumour progression while waiting for a donor organ. Fortunately, living donors are another source of organs and another means of reducing drop-out rate due to tumour progression [3]. On the other hand, some centres have been able to achieve acceptable outcomes with liver resection (LR), especially in well-preserved liver function HCC patients (Child-Pugh A) with long-term survival of 50–70% [4–7]. Moreover, proponents of LR further support its role in the current situation of organ shortage and long wait time. However, the main problem with LR is its high tumour-recurrence rate, which can reach 70–100% at 5 years [8–10]. Although outstanding outcomes have been observed with the use of radiofrequency ablation (RFA) in select patients,

particularly for tumours smaller than 3 cm [11,12], LT and LR continue to be universally considered the only curative options with good long-term outcomes.

Several studies have compared outcomes for patients with HCC meeting the Milan criteria treated with LR and LT [13–17]. Most of them showed the survival of patients with early HCC is similar between LR and LT; furthermore, recent studies even recommend LR for HCC patients with Child-Pugh A cirrhosis with a single nodule of no more than 5 cm as the first choice [7,18]. However, the majority of studies have mainly limited their analysis to early HCC patients with a single nodule. To the best of our knowledge, there are very few studies exclusively evaluating outcomes for another type of early HCC meeting the Milan criteria, that is, HCC patients with multiple nodules, treated with primary LR and living donor liver transplantation (LDLT).

The aim of our study was to try and define a better primary curative option (LDLT or LR) in Child-Pugh A HCC patients with multiple nodules meeting the Milan criteria based on their short- and long-term outcomes.

Patients and methods

Figure 1 shows the inclusion and exclusion criteria for the cohort. A total of 375 patients with HCC meeting the Milan criteria underwent surgical operations between January 2007 and July 2012 in our centre. Our general policy is to prioritize early Child-Pugh A HCC patients with multiple nodules meeting the Milan criteria for primary LT rather than LR and to offer LR to those patients who have no suitable donors in the short term. According to the different surgical procedures, they were initially divided into two groups: group LT (n = 113), which consisted of patients underwent LT; group LR (n = 262), which consisted of those underwent resection. After excluding two patients who were lost to follow-up, 34 patients with Child-Pugh B or C before transplantation, 24 patients with single nodule and 19 patients who underwent other treatments including resection, transcatheter arterial chemoembolization (TACE) and RFA before LT, 34 patients who underwent LDLT finally remained in group LT (so also named group LDLT). Similarly, 33 patients finally remained in group LR after excluding 16 patients (including 15 patients with a single nodule and one patient with multiple nodules) who were lost to follow-up, five patients with Child-Pugh B before resection and 208 patients with single nodule. To ensure the consistency for baseline data, all enrolled patients did not undergo other antitumour therapies before operation. They were monitored until October 2013 or their death, and their medical records were retrospectively reviewed. All organs were procured from living donors. Living donations were voluntary and altruistic in all cases, approved by the Ethics Committee of West China Hospital of Sichuan University, and in accordance with the ethical guidelines of the Declaration of Helsinki.

HCC diagnosis was based on pre-operative imaging including contrast enhanced computed tomography (CT) and/or magnetic resonance imaging (MRI), hepatitis B virus (HBV) background, tumour maker levels and the pathological profile.

The follow-up was routinely taken in the outpatient clinics. Abdominal ultrasonography was performed every month for the first half year, then every 3 months. CT scan or MRI was performed every 3 months for the first year and then every 6 months. Alpha-fetoprotein (AFP) measure was done every month for the first year and then every 3 months. The tumour recurrence was mainly based on radiographic evidence and/or AFP level. Patients diagnosed HCC recurrence were treated by the following alternatives including TACE, RFA, salvage LT, sorafenib [19], re-resection, radiotherapy and chemotherapy.

Using our database, we compared patient demographics, disease features, tumour characteristics, postoperative course and long-term outcomes in the group LR and group LDLT.

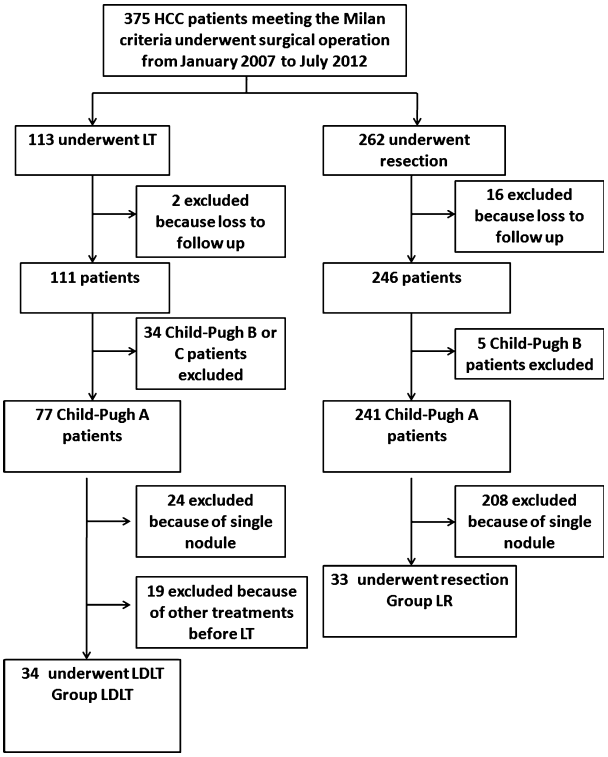

Fig. 1 Flow of study participants. HCC, hepatocellular carcinoma; LT, liver transplantation; LR, liver resection; LDLT, living donor liver transplantation.

Statistical analysis

SPSS 17.0 statistical software (SPSS Inc., Chicago, IL, USA) was used to analyse the relevant data. Categorical data were presented as number (per cent) and compared using Pearson chi-Square or Fisher's exact test. Continuous variables were expressed as the mean value ± SD and analysed using t-test. Overall patient survival and tumour-free survival rates were estimated by the Kaplan–Meier method, and differences between two groups were determined by log-rank test. $P < 0.05$ was considered statistically significant.

Results

Patient baseline characteristics

The baseline characteristics of the patients in both groups are summarized in Table 1. Portal hypertension (PH) was defined as the presence of oesophageal varices and/or a platelet count of less than 100 000 per μl in association with splenomegaly [20]. Of the 67 Child-Pugh A HCC patients with multiple nodules meeting the Milan criteria, 57 (85.1%) patients were male with a mean age of 48 years (29–74 years). The percentage of pre-operative antiviral therapy was higher in group LDLT in comparison with group LR (73.5% vs. 36.4%, $P = 0.002$). No differences existed between patients in group LDLT and group LR with respect to their age (46.9 ± 10.2 years vs. 48.5 ± 10.4 years, $P = 0.534$), the presence of PH (35.3% vs. 42.4%, $P = 0.549$) and cirrhosis (100% vs. 97.0%, $P = 0.493$), pre-operative Charlson comorbidity index (CCI), the percentage of male patients (85.3% vs. 84.8%, $P = 1.000$), the percentage of patients with pre-operative HBV DNA $< 10^3$ copies/ml (50.0% vs. 33.3%, $P = 0.167$) and HBV DNA $\geq 10^5$ copies/ml (20.6% vs. 24.2%, $P = 0.720$), and the percentage of patient with pre-operative AFP level <8 ng/ml (32.4% vs. 21.2%, $P = 0.304$), of with pre-operative AFP level ≥ 400 ng/ml (29.4% vs. 36.4%, $P = 0.545$) and of with pre-operative AFP level ≥ 800 ng/ml (14.7% vs. 24.2%, $P = 0.324$). The delay from diagnosis of HCC to LDLT was longer than that to LR (25.1 ± 7.0 vs. 4 ± 1.3 days, $P = 0.000$).

As shown in Table 2, there was no difference between the two groups regards as number of tumours, max diameter of tumour nodules, presence of microvascular invasion, presence of tumour cell on resection margin and the percentage of Edmonson grade 3–4 tumours.

Table 1. Baseline characteristics of the patients in group LDLT and group LR.

	Group LDLT ($n = 34$)	Group LR ($n = 33$)	*P* value
Age (mean ± SD, years)	46.9 ± 10.2	48.5 ± 10.4	0.534
Male	29 (85.3%)	28 (84.8%)	1.000
Pre-operative PH* (Presence)	12 (35.3%)	14 (42.4%)	0.549
Cirrhosis (Presence)	34 (100%)	32 (97.0%)	0.493
Pre-operative antiviral therapy	25 (73.5%)	12 (36.4%)	0.002
Pre-operative HBV DNA $< 10^3$ copies/ml	17 (50.0%)	11 (33.3%)	0.167
Pre-operative HBV DNA $\geq 10^5$ copies/ml	7 (20.6%)	8 (24.2%)	0.720
Pre-operative positive HBsAg	32 (94.1%)	32 (97.0%)	1.000
Pre-operative AFP level < 8 ng/ml	11 (32.4%)	7 (21.2%)	0.304
Pre-operative AFP level ≥ 400 ng/ml	10 (29.4%)	12 (36.4%)	0.545
Pre-operative AFP level ≥ 800 ng/ml	5 (14.7%)	8 (24.2%)	0.324
Delay from diagnosis of HCC to LR/LDLT (mean ± SD, days)	25.1 ± 7.0	4 ± 1.3	0.000
CCI score			
0	24 (70.6%)	21 (63.6%)	0.545
1	6 (17.6%)	8 (24.2%)	0.507
2	1 (2.9%)	2 (6.1%)	0.614
3	1 (2.9%)	1 (3.0%)	1.000
4	2 (5.9%)	1 (3.0%)	1.000

LDLT, living donor liver transplantation; LR, liver resection; SD, standard deviation; PH, portal hypertension; HBV DNA, hepatitis B virus deoxyribonucleic acid; HBsAg, hepatitis B surface antigen; AFP, alpha-fetoprotein; HCC, hepatocellular carcinoma; CCI, Charlson comorbidity index.
*Defined as the presence of oesophageal varices and/or a platelet count of less than 100 000 per μl in association with splenomegaly.

Operative characteristics and postoperative course

More patients in group LDLT required blood transfusions during the operation (32.4% vs. 6.1% in group LR, $P = 0.007$). No perioperative death (defined as death within 1 month of the surgical procedure) had occurred in both groups. The incidence of major complications (Clavien–Dindo ≥ Grade 3) was similar in group LDLT and group LR (17.6% vs. 6.1%, $P = 0.259$). The length of postoperative hospital stay was significantly longer in group LDLT than that in group LR (20.1 ± 4.3 vs. 10.2 ± 4.1 days, $P = 0.000$). The percentage of postoperative antiviral therapy was similar between group LDLT and LR (94.1% vs. 87.9%, $P = 0.427$; Table 3).

Survival and recurrence

The mean follow-up for group LDLT was 43.5 ± 22.1 months (range, 6–81), whereas it was 31.4 ± 15.5 months (range, 9–64) in group LR. During the follow-up period, six patients died in group LDLT and 12 patients died in

Table 2. Comparison of tumour characteristics between group LDLT and group LR.

	Group LDLT (n = 34)	Group LR (n = 33)	P value
Number of tumours (mean ± SD)	2.4 ± 0.5	2.3 ± 0.5	0.361
Maximum diameter of tumour nodules (mean ± SD, range, cm)	2.4 ± 0.5 (1.2–3)	2.6 ± 0.5 (1.5–3)	0.119
Tumour necrosis (Presence)	4 (11.8%)	5 (15.2%)	0.734
Microvascular invasion (Presence)	10 (29.4%)	13 (39.4%)	0.390
Tumour cell on resection margin (Presence)	—	None	
Edmonson grading (III, IV)	16 (47.1%)	13 (39.4%)	0.524

LDLT, living donor liver transplantation; LR, liver resection; SD, standard deviation.

Table 3. Comparison of operative characteristics and postoperative course between group LDLT and group LR.

	Group LDLT (n = 34)	Group LR (n = 33)	P value
Blood transfusion during the operation	11 (32.4%)	2 (6.1%)	0.007
Perioperative death	None	None	—
Postoperative major complications (Clavien–Dindo ≥ Grade 3; Presence)	6 (17.6%)	2 (6.1%)	0.259
Length of postoperative hospital stay (mean ± SD, days)	20.1 ± 4.3	10.2 ± 4.1	0.000
Postoperative antiviral therapy	32* (94.1%)	29 (87.9%)	0.427

LDLT, living donor liver transplantation; LR, liver resection; SD, standard deviation.
*All the patients used a prophylactic regimen with lamivudine and individualized low-dose intramuscular hepatitis B immunoglobulin after LDLT.

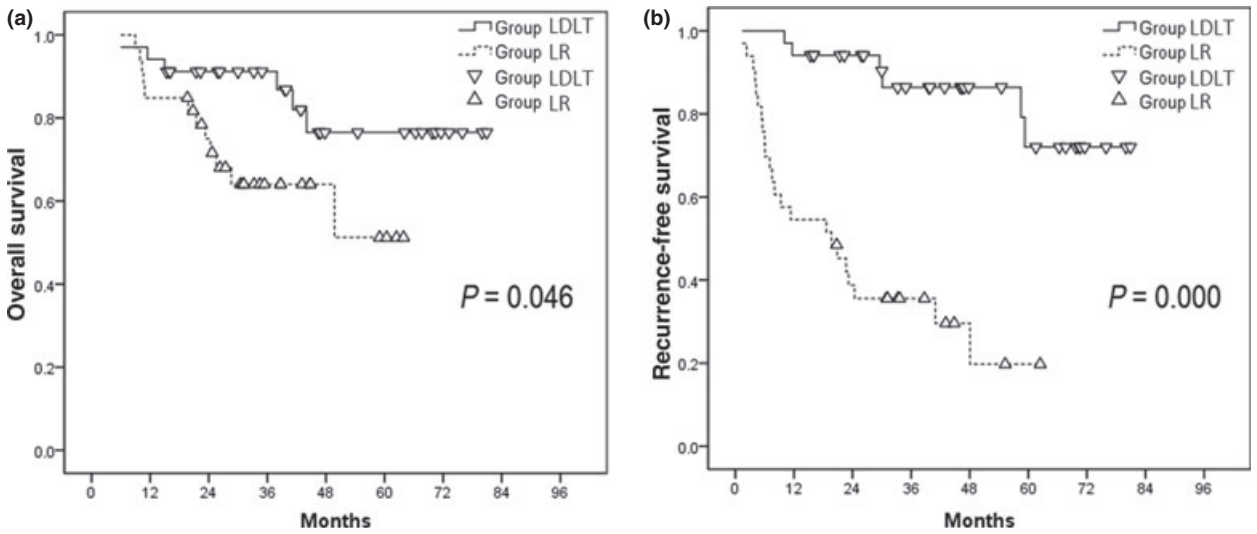

Fig. 2 (a) Cumulative postoperative overall survival rates for both groups; (b) cumulative postoperative recurrence-free survival rates for both groups (log-rank test). LDLT, living donor liver transplantation; LR, liver resection.

group LR, respectively. The 1-, 3- and 5-year overall survival (OS) rate was higher in group LDLT than that in group LR (94.1%, 91.2% and 76.5% vs. 84.8%, 64.0% and 51.2%, respectively, P = 0.046; Fig. 2a). Six (17.6%) patients occurred tumour recurrence in group LDLT, and the mean time to recurrence was 33.2 ± 21.7 months. However, 23 (69.7%) patients occurred tumour recurrence in group LR, and the mean time to recurrence was 13.2 ± 12.4 months. The 1-, 3- and 5-year recurrence-free survival (RFS) rate was significantly higher in group LDLT than that in group LR (94.1%, 86.4% and 72.0% vs. 54.5%, 35.6% and 19.8%, respectively, P = 0.000; Fig. 2b).

The influence of tumour location on survival

According to the tumour's location, we divided these patients into two groups: tumours in the same lobe (TSL) and tumours in the different lobes (TDL). In group LDLT,

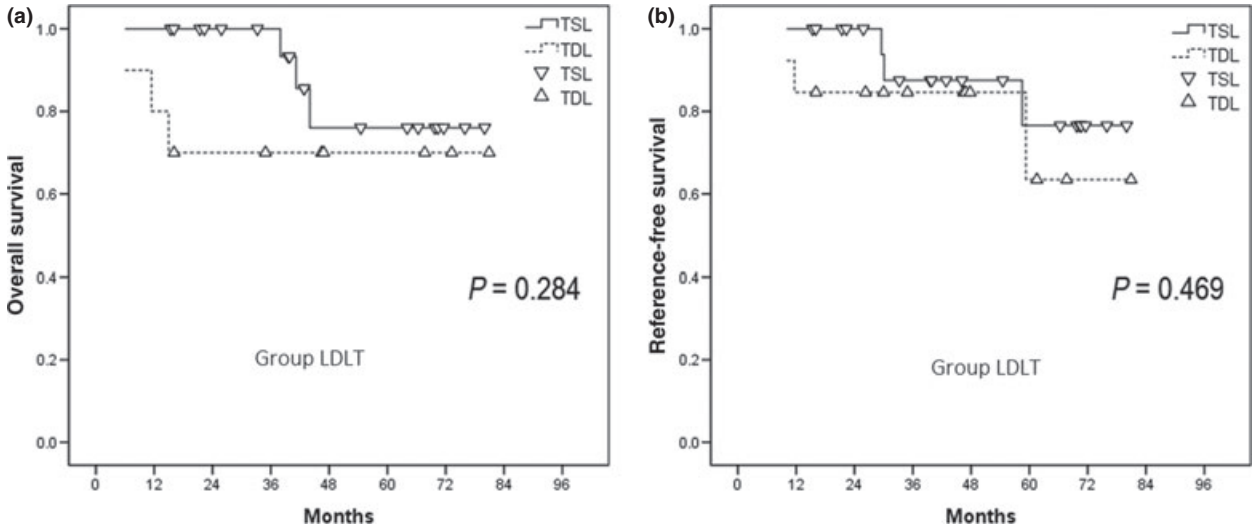

Fig. 3 (a) Cumulative overall survival rates between patients with multiple nodules located in the same lobe and those located in the different lobes after living donor liver transplantation; (b) Cumulative recurrence-free survival rates between patients with multiple nodules located in the same lobe and those located in the different lobes after living donor liver transplantation. TSL, the same lobe; TDL, the different lobes; LDLT, living donor liver transplantation.

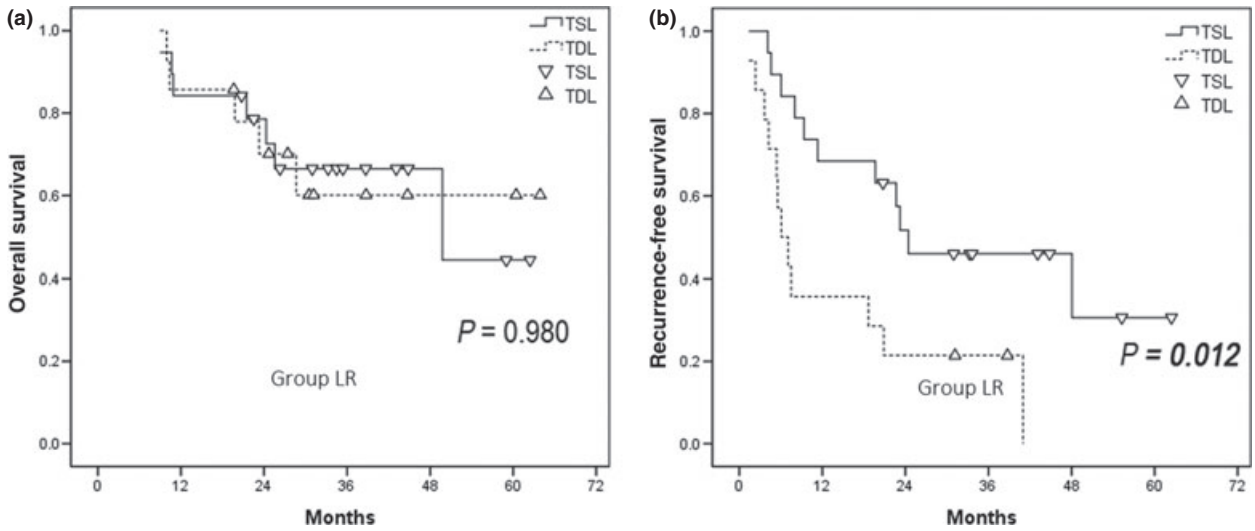

Fig. 4 (a) Cumulative overall survival rates between patients with multiple nodules located in the same lobe and those located in the different lobes after liver resection; (b) Cumulative recurrence-free survival rates between patients with multiple nodules located in the same lobe and those located in the different lobes after liver resection. TSL, the same lobe; TDL, the different lobes; LR, liver resection.

the 1-, 3- and 5-year OS rate was similar between TSL and TDL (100%, 100% and 76% vs. 80%, 70% and 70%, respectively, $P = 0.284$; Fig. 3a) and the 1-, 3- and 5-year RFS rate was also similar between TSL and TDL (100%, 87.5% and 76.6% vs. 92.3%, 84.6% and 63.5%, respectively, $P = 0.469$; Fig. 3b). In group LR, the 1-, 3- and 5-year OS rate was similar between TSL and TDL (84.2%, 66.5% and 44.3% vs. 85.7%, 60.1% and 60.1%, respectively, $P = 0.980$; Fig. 4a); however, the 1-, 3- and 5-year RFS rate was higher in TSL than that in TDL (68.4%, 45.9% and 30.6% vs. 35.7%, 21.4% and 0%, respectively, $P = 0.012$; Fig. 4b).

Discussion

Both LT and LR are available to patients with early HCC and well-preserved liver function. Certainly, the ideal test of the benefit of any therapy is a randomized prospective trial, but such studies are limited for patients with HCC. Thus, therapy strategies have been based on theoretical

analysis and retrospective investigations. Although the role of surgery with either LT or LR in the management of early HCC patients with well-preserved liver function is continuing to evolve, more and more studies show that LR offers 5-year survival similar to LT for early HCC patients with a single nodule up to 5 cm [7,18]. However, for early HCC patients with multiple nodules, the optimal management remains unclear because of very limited relevant literature reports. We hence design the study to evaluate the short- and long-term outcomes of early Child-Pugh A HCC patients with multiple nodules selected for LDLT and LR.

To focus on clinical outcomes relating to surgery rather than to other antitumour treatments, we exclusively excluded those patients who had underwent other antitumour therapies including RFA and TACE before surgery. We think the exclusion, by the present study, to keep the consistency of the baseline data between two groups may result in a more accurate analysis for OS and RFS. Because all liver grafts were from the living donors, the waiting time before LDLT became relatively fixed, with the mean delay from diagnosis of HCC to transplantation of 25.1 $\pm$ 7.0 days in group LDLT. Owing to pre-operative ethical approval process, the delay from diagnosis to surgery was longer in group LDLT than that in group LR, which may have a negative impact on the outcome of the transplanted group. Accordingly, the percentage of pre-operative antiviral therapy was higher in group LDLT in comparison with group LR (73.5% vs. 36.4%, $P = 0.002$).

Our study showed that no differences existed in perioperative outcomes between group LDLT and LR. We also confirmed the satisfactory results for liver resection obtained in the group LR, with no perioperative mortality and low incidence of major complications. Perioperative results after LDLT in those Child-Pugh A patients meeting the Milan criteria were also excellent, although LDLT is a more aggressive surgical procedure with longer postoperative stay compared with LR. In addition, with respect to the graft availability and waiting list priority, LDLT can effectively alleviate the shortage of deceased live supply and significantly shorten the waiting time before transplantation. Although the delay from diagnosis to surgery showed in this study was significantly longer in group LDLT in comparison with group LR, almost all patients did not had HCC tumour progression in the relatively fixed and short waiting time before transplantation (25.1 $\pm$ 7.0 days) even without any antitumour treatments. Therefore, primary LDLT may be considered as an alternative curative treatment for early HCC parallel to LR, which also can be performed without significant delay.

Our data revealed that the survival of early HCC patients with multiple nodules who underwent LDLT was better than that of patients who received LR. According to our analysis, the survival rates of Child-Pugh A patients with multiple HCCs who underwent LR were unsatisfactory. Their 5-year OS rate was 51.2%, which was worse than that of the early HCC patients with a single nodule (55–70%) [5,7,15,18]. Furthermore, a high recurrence rate is a major drawback of LR as a curative therapy. According to our data, the 5-year RFS was only 19.8%, which was significantly lower than that of our patients who underwent LDLT (72.0%). The high recurrence rate in the resection could be partly contributed to the underlying liver diseases, such as HBV and cirrhosis. Therefore, our study demonstrated that LDLT might be the preferred treatment choice to offer the chance of a cure for early HCC patients with multiple nodules. Reasons for this may include (i) LDLT results in the widest possible resection margin of the tumour, (ii) LDLT can remove the underlying cirrhotic liver tissue and oncogenic viral stimulus for the development of HCC, (iii) multiple lesions may represent intrahepatic metastasis or multicentric hepatocarcinogenesis, which is the most important predictor of recurrence [21,22], (iv) HBV has been shown to be an independent risk factor for HCC recurrence after LR [23]. Fortunately, our prophylaxis against HBV recurrence after LDLT using lamivudine and individualized low-dose hepatitis B immunoglobulin can lead to the 5-year HBV recurrence rate of <10% [24,25].

In addition, we preliminarily examined the influence of tumour location (all nodules located in the same lobe or different lobes) on HCC recurrence after LR or LDLT. Our data showed that no differences existed in OS and RFS between early HCC patients with multiple tumours located in the same lobe and those located in the different lobes after LDLT; however, patients with multiple nodules located in the same lobe had higher RFS rate than those located in the different lobes after LR, although no differences existed in OS between patients with multiple tumours located in the same lobe and those located in the different lobes after LR. Therefore, early HCC patients with multiple nodules located in the different lobes may be more suitable for LDLT. Moreover, it is very worthwhile to further investigate the influence of tumour distribution on survival and HCC recurrence in long-term, randomized, controlled, prospective trials.

Major weak points about this study include a small sample size, its retrospective nature and potential selection bias. Moreover, patients with hepatitis C virus infection or other chronic liver disease were not included in this analysis because of the small sample. It is for the reason of the small sample size that we did not identify independent prognostic factors of OS and RFS in all patients. However, this study, to the best of our knowledge, represents one of the largest cohorts to exclusively evaluate outcomes for early HCC patients with multiple nodules treated with primary LR and LDLT and provides adequate preliminary data to warrant future-related studies.

In conclusion, our experience shows that for the Child-Pugh A HCC patients with multiple nodules meeting the Milan criteria, LDLT might offer better long-term survival and lower HCC recurrence rates than LR; moreover, no differences existed in perioperative death and major complications between group LDLT and group LR. In addition, patients with multiple nodules located in the different lobes may have worse HCC recurrence-free survival than those located in the same lobe after LR. Further well-designed studies are still warrant to further confirm our conclusions.

Authorship

LJ: designed research and wrote manuscript. AL: involved in acquisition of data and performed research. TW: did the data analysis. LY: approved the submitted manuscript. BL: reviewed critically the manuscript. JY: participated in drafting the manuscript.

Funding

This study was supported by grants from the National Sciences and Technology Major Project of China (2012ZX10002-016) and (2012ZX10002-017), the National Natural Science Foundation of China (81170456) and Sichuan Province Technology Supporting Plan (2013SZ0023).

References

1. 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.
2. Figueras J, Jaurrieta E, Valls C, *et al.* Survival after liver transplantation in cirrhotic patients with and without hepatocellular carcinoma: a comparative study. *Hepatology* 1997; **25**: 1485.
3. Quintini C, Hashimoto K, Uso TD, Miller C. Is there an advantage of living over deceased donation in liver transplantation? *Transpl Int* 2013; **26**: 11.
4. Arii S, Yamaoka Y, Futagawa S, *et al.* Results of surgical and nonsurgical treatment for small-sized hepatocellular carcinomas: a retrospective and nationwide survey in Japan. The Liver Cancer Study Group of Japan. *Hepatology* 2000; **32**: 1224.
5. Poon RT, Fan ST, Lo CM, Liu CL, Wong J. Long-term survival and pattern of recurrence after resection of small hepatocellular carcinoma in patients with preserved liver function: implications for a strategy of salvage transplantation. *Ann Surg* 2002; **235**: 373.
6. Koniaris LG, Levi DM, Pedroso FE, *et al.* Is surgical resection superior to transplantation in the treatment of hepatocellular carcinoma? *Ann Surg* 2011; **254**: 527.
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.
8. 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.
9. Shah SA, Cleary SP, Wei AC, *et al.* Recurrence after liver resection for hepatocellular carcinoma: risk factors, treatment, and outcomes. *Surgery* 2007; **141**: 330.
10. Shah SA, Greig PD, Gallinger S, *et al.* Factors associated with early recurrence after resection for hepatocellular carcinoma and outcomes. *J Am Coll Surg* 2006; **202**: 275.
11. Choi D, Lim HK, Rhim H, *et al.* Percutaneous radiofrequency ablation for early-stage hepatocellular carcinoma as a first-line treatment: long-term results and prognostic factors in a large single-institution series. *Eur Radiol* 2007; **17**: 684.
12. Waki K, Aikata H, Katamura Y, *et al.* Percutaneous radiofrequency ablation as first-line treatment for small hepatocellular carcinoma: results and prognostic factors on long-term follow up. *J Gastroenterol Hepatol* 2010; **25**: 597.
13. Margarit C, Escartin A, Castells L, Vargas V, Allende E, Bilbao I. Resection for hepatocellular carcinoma is a good option in Child-Turcotte-Pugh class A patients with cirrhosis who are eligible for liver transplantation. *Liver Transpl* 2005; **11**: 1242.
14. Poon RT, Fan ST, Lo CM, Liu CL, Wong J. Difference in tumor invasiveness in cirrhotic patients with hepatocellular carcinoma fulfilling the Milan criteria treated by resection and transplantation: impact on long-term survival. *Ann Surg* 2007; **245**: 51.
15. Shah SA, Cleary SP, Tan JC, *et al.* An analysis of resection vs transplantation for early hepatocellular carcinoma: defining the optimal therapy at a single institution. *Ann Surg Oncol* 2007; **14**: 2608.
16. Facciuto ME, Rochon C, Pandey M, *et al.* Surgical dilemma: liver resection or liver transplantation for hepatocellular carcinoma and cirrhosis. Intention-to-treat analysis in patients within and outwith Milan criteria. *HPB (Oxford)* 2009; **11**: 398.
17. Bigourdan JM, Jaeck D, Meyer N, *et al.* Small hepatocellular carcinoma in Child A cirrhotic patients: hepatic resection versus transplantation. *Liver Transpl* 2003; **9**: 513.
18. Silva MF, Sapisochin G, Strasser SI, *et al.* Liver resection and transplantation offer similar 5-year survival for Child-Pugh-Turcotte A HCC-patients with a single nodule up to 5 cm: a multicenter, exploratory analysis. *Eur J Surg Oncol* 2013; **39**: 386.
19. Welker MW, Bechstein WO, Zeuzem S, Trojan J. Recurrent hepatocellular carcinoma after liver transplantation - an emerging clinical challenge. *Transpl Int* 2013; **26**: 109.
20. Bruix J, Sherman M. Management of hepatocellular carcinoma. *Hepatology* 2005; **42**: 1208.

21. Jonas S, Bechstein WO, Steinmüller T, *et al.* Vascular invasion and histopathologic grading determine outcome after liver transplantation for hepatocellular carcinoma in cirrhosis. *Hepatology* 2001; **33**: 1080.
22. Lim HY, Sohn I, Deng S, *et al.* Prediction of Disease-free Survival in Hepatocellular Carcinoma by Gene Expression Profiling. *Ann Surg Oncol* 2013; **20**: 3747.
23. Sasaki Y, Yamada T, Tanaka H, *et al.* Risk of recurrence in a long-term follow-up after surgery in 417 patients with hepatitis B- or hepatitis C-related hepatocellular carcinoma. *Ann Surg* 2006; **244**: 771.
24. Jiang L, Yan L, Li B, *et al.* Prophylaxis against hepatitis B recurrence posttransplantation using lamivudine and individualized low-dose hepatitis B immunoglobulin. *Am J Transplant* 2010; **10**: 1861.
25. Jiang L, Yan L, Wen T, *et al.* Hepatitis B prophylaxis using lamivudine and individualized low-dose hepatitis B immunoglobulin in living donor liver transplantation. *Transplant Proc* 2013; **45**: 2326.