June, 2013

Short- and long-term outcomes of third liver transplantation at single centre

Hideyi Tanaka, *Western University*
Mamoun Al Basheer, *Western University*
Jeffrey Shum, *Western University*
Michael Bloch, *Western University*
Roberto Hernandez Alejandro, *Western University*, et al.

Hepatol Int (2013) 7:728–733
DOI 10.1007/s12072-012-9364-5

ORIGINAL ARTICLE

Short- and long-term outcomes of third liver transplantation at single centre

Hideya Kamei · Mamoun Al-Basheer · Jeffrey Shum · Michael Bloch · Roberto Hernandez Alejandro · Vivian McAlister · William Wall · Douglas Quan

Received: 3 November 2011 / Accepted: 29 February 2012 / Published online: 14 March 2012

Abstract
Purpose Although three or more liver transplantation (LT)s in the same patient arouse not only medical but also ethical issues in the context of organ shortage, it is a fact that additional liver retransplantation (reLT) is the only lifesaving treatment option for those with graft failure after a second LT. However, little is known regarding the risks and benefits associated with a third LT.
Methods We analyzed fifteen cases of third LT and 48 of second LT performed between January 2000 and December 2010. Clinical outcomes were compared with those of second LT cases performed during the same period.
Results Model for end-stage liver disease (MELD) scores at transplant was similar between the two groups. As for surgical aspects, there was no significant difference in operative time or number of units of red blood cells transfused during the transplant procedures between the groups. Patient and graft survival after the third LT at 1, 3, and 10 years were 66.7, 51.9, and 44.4 %, and 66.7, 51.9, and 29.6 %, respectively. There was no significant difference in patient or graft survival between the groups. However, graft loss within 3 months after the third LT was significantly higher than that of second LT patients.
Conclusion Third LT cases showed acceptable short- and long-term outcomes that were not significantly inferior to those of a second LT. Careful patient care especially in the early phase after a third LT may be essential to improve the outcome.

H. Kamei (✉) · M. Al-Basheer · J. Shum · M. Bloch · R. H. Alejandro · V. McAlister · W. Wall · D. Quan
Multi-Organ Transplant Program, University Hospital of Ontario, London Health Science Centre, 339 Windermere Road, London, ON N6A 5A5, Canada
e-mail: kamei@med.nagoya-u.ac.jp

Keywords Third liver transplantation · Liver retransplantation · Donor shortage · Patient survival · Single centre analysis

Introduction

Liver transplantation (LT) has become a curative option for patients with end-stage liver disease, with acceptable results as 5-year patient and graft survival rates after LT have reportedly increased to 75 and 66 %, respectively [1]. However, a substantial number of patients who undergo LT develop graft failure for various reasons and require a second LT.

Second LT has been frequently discussed [2–10]. Despite strict patient selection, and improvements in surgical technique and post-transplant patient care, the results of second LT are inferior to those of primary LT, and a substantial number of patients experience irreversible graft failure following the second procedure [2, 5, 9, 10]. In addition, instances of recurrent disease have recently increased along with indications for a second LT [11]. Since disease can recur even after a second LT, the requirement of a third or subsequent LT may be growing in the near future. A third LT is theoretically considered to be associated with inferior results as compared to a second LT, because of surgical difficulties related to the previous two liver transplants, as well as, the longer duration of liver disease and immunosuppressive therapy. However, few reports have focused on more than two transplantation procedures performed in the same patient for recurring graft failure. Although a third LT is the only curative option for patients with liver failure after a second LT, a third procedure should be precluded if its results are anticipated to be unacceptable and significantly inferior to those of a second LT. This is because performance of more

than two transplantations in the same patient has medical and ethical issues in the context of the considerable disparity between donor availability and the demand for LT. To optimize the utility of three or more LTs, it is imperative to estimate the risks and benefits of a third procedure.

The purpose of the present study is to identify the indications, surgical aspects, and outcomes of a third LT and determine whether a third procedure is comparable to a second. We investigated short- and long-term outcomes of third LT, and compared them with those of second LT in patients treated at a single transplant centre during the same period. Given the fact that a second LT is associated with lower patient and graft survival than a primary LT, it is reasonable that the outcome of a third LT will also be inferior to that of primary LT. Therefore, it is more practical to compare third LT outcomes to second LT outcomes to determine if a third LT has equivalent acceptability to a second procedure, which is considered worthwhile despite the risk of poor outcome [2, 4, 6–8, 10].

Methods

Patients and methods

Between January 2000 and December 2010, 778 LTs were performed at London Health Science Centre, including 48 s LTs, 15 third LTs, and 2 fourth LTs. We retrospectively reviewed third LT cases in this cohort in regard to patient demographics, indications for the primary and third LTs, intervals between the primary, second, and third LTs, and creatinine level and model for end-stage liver disease (MELD) score at the time of the third procedure. As for the surgical aspects, we recorded the number of units of packed red blood cells transfused during the transplant and the duration of the operation. We also reviewed donor characteristics, including cold ischemia time (CIT) for the third LT. Finally, patient and graft survivals after the third LT were noted. Patients were examined on an as-needed basis and at least yearly. Preoperative and surgical technical aspects, and clinical outcomes of the third LTs were compared with those of the second LTs performed during the same period at our centre.

The hepatic veins were reconstructed by inferior vena cava replacement in most patients. A venovenous bypass was used selectively in patients, who were judged to be intolerant of caval occlusion, and the piggy-back technique was occasionally used. The bile duct was basically reconstructed in a duct-to-duct fashion, though a choledochojejunostomy was chosen when dictated by other circumstances at the discretion of the surgeon. All patients received similar immunosuppression, which consisted of tacrolimus (trough levels 8–12 ng/ml), mycophenolate mofetil, and scheduled tapering prednisone.

The livers for all second and third LTs were harvested from brain-dead donors. Four males and eleven females with a median age of 43 (15–82) years and median body weight of 64.5 (42.1–79) kg were donors for the third LTs, and 42 males and 6 females with a median age of 37 (14–84) years and a median body weight of 71.5 (36.5–102) kg were donors for the second LTs. The main cause of brain death of the donors in the third LT group was cerebrovascular accident in 9 cases, trauma in 3, anoxia in 1, and others in 2, while the main cause in the second LT group was trauma in 21 cases, cerebrovascular accident in 19, anoxia in 5, and others in 3.

The present review of patient medical records was approved by the ethics review board of the University of Western Ontario.

Statistical comparisons

Continuous variables are presented as a median (range) and compared using a Mann–Whitney U test. Survival curve estimates were calculated according to the Kaplan–Meier method and compared using a log-rank test. Fisher's exact test was used to compare categorical data. $P < 0.05$ was considered to be statistically significant.

Results

In the 15 patients who underwent 3 LTs, the primary liver disease (indication for the first LT) was primary sclerosing cholangitis (PSC) in 4 patients, hepatitis C virus (HCV)-related cirrhosis in 2, autoimmune hepatitis (AIH) in 2, alcoholic cirrhosis in 2, cryptogenic cirrhosis in 2, hepatitis B virus (HBV)-related cirrhosis in 1, Budd-Chiari syndrome in 1, and nonalcoholic steatohepatitis cirrhosis in 1. The indications for second and third LTs are shown in Table 1. HCV recurrence was not an indication for third LT.

Recipient and donor demographics were also compared between the second and third LT groups (Table 2). Eleven males and four females underwent third LT; their median age was 47 (21–67) years. Twenty-eight males and twenty females underwent second LT; their median age was 44 (19–69) years. Recipient age and sex in the third LT group were similar to those in the second LT group. There was no significant difference in donor age and weight between the groups, but female donors were significantly more frequent in the third LT group.

Pre- and post-transplant variables and surgical aspects were compared between the groups (Table 3). The median MELD score and creatinine level at transplant in the third

Table 1 Indications for second and third liver transplantation

	Second liver transplant ($n = 48$)	Third liver transplant ($n = 15$)
Chronic rejection	17	5
Recurrent disease	5[a]	4[b]
Hepatic arterial thrombosis	7	2
Biliary complication	7	1
Primary non-function	5	1
Severe acute rejection	3	0
Portal vein thrombosis	2	0
Other	2[c]	1[d]

[a] Primary sclerosing cholangitis in two patients, hepatitis C in two, autoimmune hepatitis in one

[b] Primary sclerosing cholangitis in two patients, autoimmune hepatitis in two

[c] Acute hepatitis B and liver injury after liver biopsy in one patient each

[d] Hepatic vein thrombosis and cholestatic liver disease in one patient each

Table 2 Recipient and donor demographics in the second and third liver transplantation groups

	Second liver transplant ($n = 48$)	Third liver transplant ($n = 15$)	p
Recipient age (years)[a]	44 (19–69)	47 (21–67)	0.33
Recipient sex (male/female)	28/20	11/4	0.29
Donor age (years)[a]	37 (14–84)	43 (15–82)	0.35
Donor sex (male/female)	42/6	4/11	0.001
Donor weight (kg)[a]	71.5 (36.5–102)	64.5 (42.1–79)	0.16

[a] Median with range

LT group were 25.4 (6.0–34.5) and 117 (32–230) μmol/l, respectively. These values were similar to those in the second LT group (MELD: 27.4, 7.4–40.0 and creatinine level: 113, 23–415 μmol/l). In the third LT group, the median interval between the primary and third LT was 2,829 (439–6,608) days, while that between the second and third LT was 1,247 (2–3,686) days. In the second LT group, the median interval between the primary and second LT was 496 days. The interval between primary and second LT in the second LT group did not significantly differ from the interval between the second and third LT in the third LT group. The waiting time on the transplant list for a third liver transplantation was a median 44 (1–533) days, while the median CIT in the third LT group was 445 (233–571) min. These variables were comparable between the second and third LT groups. As for the operative aspects, the median amount of red blood cell transfusion during the operation was 11.5 packed red cell units (0–40 Us) and 8 packed red cell units (0–30 U) in the second and third LT groups, respectively. The median time of operation in the third LT group, 515 (487–770) min, was similar to that in the second LT group (464, 195–733 min). The duration of hospital stay after transplantation was also similar (third LT group: 16, 8–108 days and second LT group 15, 3–300 days). However, graft loss within 3 months after the third LT (33.3 %) was significantly greater than that after the second LT (10.4 %) ($p = 0.034$).

Five patients in the second LT group received 10-year and longer follow-up. Of those, one patient died at 10.4 years after the second LT. Three patients received 10-year follow-up after the third LT and all of them survive. Patient and graft survival rates after 1, 3, 5, and 10 years in the third LT group were 66.7, 51.9, 44.4, and 44.4 %, and 66.7, 51.9, 44.4 and 29.6 %, respectively,

Table 3 Pre- and post-transplant variables and surgical aspects of second and third liver transplantation

	Second liver transplant ($n = 48$)	Third liver transplant ($n = 15$)	p
MELD[a] at transplant	27.4 (7.4–40.0)	25.4 (6.0–34.5)	0.30
Creatinine level at transplant (μmol/l)	113 (23–415)	117 (32–230)	0.68
Interval from first transplant (days)	496 (0–8,443)	2,829 (439–6,608)	0.02
Interval from previous transplant (days)	496 (0–8,443)	1,247 (2–3,686)	0.41
Wait time (days)	28 (1–1,312)	44 (1–533)	0.60
Cold ischemia time (min)	443 (202–844)	445 (233–571)	0.68
Red blood cell transfusion (U)	11.5 (0–40)	8 (0–30)	0.46
Operative time (min)	464 (195–733)	515 (487–770)	0.09
Hospital stay (days)[b]	15 (8–300)	16 (8–108)	0.64
Graft loss within 3 months	10.4 %	33.3 %	0.03

Values are expressed as median with range

[a] MELD, model for end-stage liver disease

[b] Patients who died within 30 days after transplantation without being discharged from the hospital were excluded

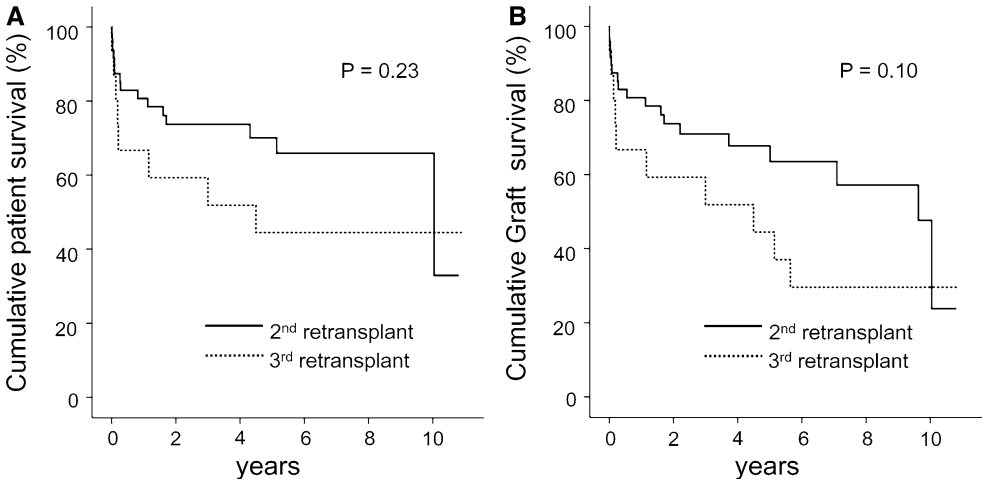

Fig. 1 Patient (**a**) and graft (**b**) survival after second (*solid line*) and third liver transplantation (*dotted line*). There were no significant differences in patient ($p = 0.23$) and graft survival ($p = 0.10$) between the second and third liver transplant groups

while those in the second LT group were 80.7, 73.7, 70.0 and 65.9 %, and 80.7, 71.0, 67.8 and 47.6 %, respectively. There was no significant difference in patient or graft survival between the groups (Fig. 1). The 5-year patient and graft survival in the third LT group were inferior to those in the second LT group, but the difference was not significant ($p = 0.089$ and 0.126, respectively).

Discussion

We retrospectively evaluated the short- and long-term outcomes of patients who underwent a third LT. Our findings showed that patient and graft survival after third LT were not significantly inferior to those after second LT. However, graft loss within 3 months after surgery was significantly higher after third LT than after second LT.

Advances in surgical techniques and medical care have significantly improved patient and graft survival after transplantation [1]. However, virtually all primary indications for LT can recur, and a subset of these patients develops graft failure [11]. In addition, a steady increase in the long-term survival of primary transplant recipients has resulted in an increasing population of individuals who may ultimately require additional grafts [11]. One model predicted that the number of repeat LT candidates will eventually outstrip the number of potential donors [12].

Currently, however, cases of a third LT after a second graft failure are uncommon, and repeat LT in this setting has only been pursued in a few large transplant centres. Given that repeat LT for the recurrence of disease and chronic biliary graft failure may increase further [11, 13], such diseases can recur even after a second LT. Some recent reports have noted that a second LT is associated with improved outcome [2, 4, 6–8, 10, 14], and second transplant recipients can survive long enough to develop graft failure from recurrent disease [11]. These trends can lead to an increase in the number of patients with graft failure following second LT and requiring a third LT. In fact, the percentage of third LTs in our centre was 0.64 % (5/787) from January 1981 to December 1997 [15], and then significantly increased to 1.93 % (15/778) in the period from January 2000 to December 2010.

For those with graft failure after a second procedure, a third LT is the only curative option. However, the issue of multiple LTs in a single patient is more controversial than second LT, as the growing discrepancy between the unchanging number of donor organs and rising number of potential liver transplant recipients has led to a dramatic increase in the number of patients on the waiting list and the duration of waiting, as well as number of deaths while on the list. Although it has been historically reported that an increased number of transplants in the same individual is related to worse survival [1, 6, 16, 17], few recent reports have focused on the outcomes of third LTs. Careful analysis of the potential benefits of a third LT in light of recent improvements in surgical and medical treatments is essential to justify its role in the current era of organ shortage. Given the fact that a second LT is associated with decreased patient and graft survival as compared with a primary LT [2–10], comparable outcomes between a third and primary LT cannot be expected. Thus, we evaluated the surgical aspects and short- and long-term outcomes of third LT in the present study, and compared them to those of second LT, which is currently regarded as acceptable despite its inferior outcomes as compared to primary transplantation.

MELD score and creatinine levels at transplant were similar between the two groups in our study. Although initially employed to predict short-term survival of patients with cirrhosis following a transjugular intrahepatic portosystemic shunt procedure [18], the MELD model is now

used to prioritize patients on the transplant waiting list. However, the MELD score does not consider liver allograft characteristics, and thus, its use to predict the survival of candidates for repeat LT is controversial. Some reports have suggested that at a given MELD score, repeat LT might be associated with a significantly higher mortality rate than that associated with the initial transplant [10, 19], while another study showed that at each MELD score, survival was worse for a second LT for the primary LT [20]. Others have also found that MELD greatly underestimates waiting list mortality among listed retransplant candidates [9].

The operative time in the present study for the third LT tended to be longer than that for the second LT, though the difference was not significant. Furthermore, the amount of red blood cells transfused during the operation was similar between the two groups, even though the third LT was expected to be more arduous than the second. These findings are in accordance with those of other studies [21, 22]. The degree of adhesion due to the previous surgery might not be associated with the number of transplantations, which encourages proceeding with a third LT.

The correlation of recipient survival with elapsed time between transplantation and retransplantation has been confirmed in other studies [9, 23]. In the present study, the interval between the primary and third LT was significantly longer than that between the primary and second LT. This result indicates that the duration of immunosuppression and liver disease was longer in patients who underwent a third LT than in those who underwent a second LT. The extended periods of immunosuppression and liver disease may have contributed to the significantly higher graft loss seen in the early phase after transplantation in the third LT patients, despite having similar surgical aspects and MELD scores to the second LT recipients. A high mortality rate within 30 days after transplantation in third LT recipients has also been reported in another study [21]. Thus, medical care in the early post-transplant phase is thought to be essential to improve the outcome of third LT.

In our study, patient and graft survival after 1, 3, and 10 years in the third LT group were 66.7, 51.9, and 44.4 %, and 66.7, 51.9, and 29.6 %, respectively. There were no significant differences in patient and graft survival, and duration of hospital stay between the second and third LT recipients. These results are consistent with those of other studies [21, 22].

Acceptable specific retransplantation survival rates, below which retransplantation should be avoided, have not been determined. It has been proposed that a 1-year survival rate of less than 40 % in repeat LT patients constitutes an unreasonable use of a donor organ when a primary LT recipient would be anticipated to have at least double the chance of survival [9, 11]. With these proposals in mind, we consider that a third LT is acceptable for patients with graft failure after a second LT.

Because of the limited number of patients in our study, we did not investigate risk factors related to the short- and long-term outcomes of third LT. Although numerous variables associated with outcomes of second LT have been suggested in some large studies [2, 3, 5, 6, 9, 23]; few have evaluated risk factors specific to third LT outcomes. Taner et al. [22] reported that patients who received a graft with a donor risk index score greater than 1.6 at the time of the third LT had a significantly lower survival rate, but failed to find a significant impact of MELD score, or interval between second and third LT on patient survival after the third LT. To improve outcomes, further investigations with a larger cohort are necessary to identify risk factors related to patient outcomes based on patient and graft selection for third LT.

In conclusion, we found that a third LT provided acceptable short- and long-term outcomes that were not significantly inferior to those of second LT. Further, the technical aspects of third LT were found to be similar to those of second LT. Thus, third LT should not be precluded for ethical or clinical reasons. Improved outcomes can be obtained by appropriate patient and graft selection, along with careful patient care, especially in the early phase after a third LT, since perioperative graft loss in these recipients was significantly higher than that in second LT recipients. A larger study to identify risk factors specific to third LT and associated with poor outcome would likely help to improve patient and graft survival.

References

1. Busuttil RW, Farmer DG, Yersiz H, et al. Analysis of long-term outcomes of 3200 liver transplantation over two decades: a single-center experience. Ann Surg 2005;241:905–916
2. Azoulay D, Linhares MM, Huguet E, et al. Decision for retransplantation of the liver: an experience- and cost-based analysis. Ann Surg 2002;236:713–721
3. Doyle HR, Morelli F, McMichael J, et al. Hepatic retransplantation–an analysis of risk factors associated with outcome. Transplantation 1996;61:1499–1505
4. Landaverde C, Berenguer M, Aguilera V, et al. Liver retransplantation: outcome analysis in 50 patients. Med Clin 2005;124:721–725
5. Markmann JF, Gornbein J, Markowitz JS, et al. A simple model to estimate survival after retransplantation of the liver. Transplantation 1999;67:422–430
6. Markmann JF, Markowitz JS, Yersiz H, et al. Long-term survival after retransplantation of the liver. Ann Surg 1997;226:408–418
7. Pfitzmann R, Benscheidt B, Langrehr JM, et al. Trends and experiences in liver retransplantation over 15 years. Liver Transpl 2007;13:248–257
8. Postma R, Haagsma EB, Peeters PM, et al. Retransplantation of the liver in adults: outcome and predictive factors for survival. Transpl Int 2004;17:234–240

9. Rosen HR, Prieto M, Casanovas-Taltavull T, et al. Validation and refinement of survival models for liver retransplantation. Hepatology 2003;38:460–469
10. Zimmerman MA, Ghobrial RM. When shouldn't we retransplant? Liver Transpl 2005;11:S14–S20
11. Biggins SW, Beldecos A, Rabkin JM, et al. Retransplantation for hepatic allograft failure: prognostic modeling and ethical considerations. Liver Transpl 2002;8:313–322
12. Wall WJ. Recurrent disease after liver transplantation: implications for the future. Liver Transpl Surg 1997;3:S62–S67
13. Adani GL, Baccarani U, Risaliti A, et al. A single-center experience of late retransplantation of the liver. Transplant Proc 2005;37:2599–2600
14. Ghabril M, Dickson R, Wiesner R. Improving outcomes of liver retransplantation: an analysis of trends and the impact of hepatitis C infection. Am J Transplant 2008;8:404–411
15. Kumar N, Wall WJ, Grant DR, et al. Liver retransplantation. Transplant Proc 1999;31:541–542
16. Bilbao I, Figueras J, Grande L, et al. Risk factors for death following liver retransplantation. Transplant Proc 2003;35:1871–1873
17. Jain A, Reyes J, Kashyap R, et al. Long-term survival after liver transplantation in 4,000 consecutive patients at a single center. Ann Surg 2000;232:490–500
18. Malinchoc M, Kamath PS, Gordon FD, et al. A model to predict poor survival in patients undergoing transjugular intrahepatic portosystemic shunts. Hepatology 2000;31:864–871
19. Watt KD, Menke T, Lyden E, et al. Mortality while awaiting liver retransplantation: predictability of MELD scores. Transplant Proc 2005;37:2172–2173
20. Watt KD, Lyden ER, McCashland TM. Poor survival after liver retransplantation: is hepatitis C to blame? Liver Transpl 2003;9:1019–1024
21. Akpinar E, Selvaggi G, Levi D, et al. Liver retransplantation of more than two grafts for recurrent failure. Transplantation 2009;88:884–890
22. Taner CB, Balci D, Willingham DL, et al. Long-term outcomes after third liver transplant. Exp Clin Transplant 2011;9:98–104
23. Rosen HR, Madden JP, Martin P. A model to predict survival following liver retransplantation. Hepatology 1999;29:365–370