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ORIGINAL ARTICLE

Outcomes in right liver lobe transplantation: a matched pair analysis

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Summary

Split liver transplantation (SLT) has proven to be an effective technique of increasing the donor pool and thereby reducing adult and paediatric waiting list mortality. There remains concern regarding complications in adult recipients. Here, we compare SLT with matched whole liver grafts. Adult recipients of primary extended right lobe grafts (ERL) were matched to recipients of whole liver transplantations (WLTs) according to the following criteria: model of end-stage liver disease (MELD) score, recipient age, indication for liver transplantation and year of transplantation. Twenty-seven pairs of recipients were transplanted for chronic liver disease. The overall 30-day patient survival rates after ERL and WLT were 88.9% and 92.5% and 3-year survival rates after SLT and WLT were 77.8% and 85.2% respectively (log-rank = 0.38). Two patients with SLTs had hepatic artery thromboses and were retransplanted with none from the WLT group. The prevalence of a biliary leak was higher among the SLT group ($n = 4$) compared with none in the WLT group ($P = 0.05$). Patients with preoperative hyponatraemia showed a trend towards poorer survival after SLT compared with WLT. Our data suggest that SLT with extended right liver lobes, although not significantly different, shows a trend towards a poorer outcome.

Introduction

Split liver transplantation (SLT) has become a standard technique to increase the donor organ pool so as to address the current national donor:recipient imbalance. *Ex situ* splitting of a donor liver into an extended right lobe (ERL) graft and left lateral segment resulting in two transplantable organs for an adult and a paediatric recipient respectively. The outcome following left lateral segment liver transplantation in children has been excellent [1]. There have been a number of studies comparing matched SLT and whole liver transplant (WLT) recipients [2–5]. In the absence of a randomized controlled trial, which may be ethically questionable, matched pair analyses of SLT and WLT have been previously carried out by one centre [6,7]. This is performed to overcome the criticism for good results in SLT, which is that ERL grafts may be allocated to 'healthier' recipients resulting in a selection bias.

The model of end-stage liver disease (MELD) score has been validated as a good predictor of survival without transplantation [8]. In an attempt to make a direct comparison of SLT to WLT, we report for the first time the outcomes of a matched pair analysis using the MELD score for matching SLT and WLT recipients.

Method

We retrospectively analysed outcomes in ERL transplantation from January 2000 until June 2006. Donor livers considered for splitting is based on (i) donor age <50, (ii) body weight >40 kg, (iii) ICU stay <5 days, (iv)

minimal inotropic support, (v) preretrieval good liver function, (vi) macroscopic quality of graft at retrieval and (vii) suitable anatomy.

Following a standard retrieval operation at the donor hospital, the *ex situ* splitting procedure is performed at our centre. Hilar and Hepatic venous anatomy is delivered before the decision to split. No on-table cholangiography is routinely performed. Bipolar diathermy at a high setting was used for parenchymal transaction approximately 1 cm to the right of the falciform ligament. Suture/ligation of ductal and vascular branches was performed. All splits resulted in a left lateral segment (segment II and III) and ERL (I and IV–VIII) graft. The left lateral graft includes left hepatic vein, left or segmental hepatic ducts, left portal vein and often the left hepatic artery. The ERL graft includes inferior vena cava, common bile duct, main portal vein and right hepatic artery.

The ERL allocation is based on recipient size, severity of disease, general medical condition and urgency on transplant waiting list. An ERL recipient was matched to a whole liver recipient based on (i) recipient age, (ii) MELD score, (iii) indication for transplantation and (vi) year of transplantation by an independent observer blinded to the patient outcome.

Outcomes studied included vascular and biliary complications and overall patient and graft survival. Vascular complications included hepatic artery stenosis/thrombosis, portal vein thrombosis, biliary complications included biliary leak (anastamotic and nonanastamotic) and strictures requiring intervention.

Kaplan–Meier plots, Fishers exact test and Mann–Whitney *U*-test were used to compare survival, categorical and continuous variables. A *P*-value <0.05 was considered statistically significant.

Results

Between January 2000 and June 2006, 739 Liver Transplants were performed at our centre: 632 adult and 84 paediatric transplants. Sixty-one split liver transplants were performed during this time: 32 paediatric and 29 adult transplants. Twenty-nine adult recipients received an ERL graft and underwent matching with the WLT cohort. Twenty-seven ERL graft recipients were successfully matched to the WLT group on recipient age, MELD and cause of liver failure and included in this study.

Donor demographics

Donor demographics are included in Table 1. In general, organs from younger and more stable donors were considered to undergo splitting. Unsurprisingly, donors in the ERL category were generally younger than the matched group of WLT group with a mean age of 39.9 and 46.7 years and requirement for inotropic support in 17% and 21% respectively ($P = 0.08$ and $P = 0.21$).

Table 1. Donor demographics.

	WLT ($N = 27$)		SLT ($N = 27$)		
Characteristics	Mean	Range	Mean	Range	*P*-value
Age (years)	46.7	19–79	39.9	15–54	0.08
Body weight (kg)	71.9	55–90	72.6	52–84	0.8
Bilirubin (μmol/l)	13.0	4–50	13.2	5–32	0.93
ALT (U/l)	35	12–82	40	10–62	0.39
Alk phos (IU/l)	117	42–194	122	36–240	0.74
Inotropic support (%)	21		17		0.21
Retrieval sodium (mmol/l)	143	130–165	149	132–164	0.40
Cold ischaemic time (minutes)	602	206–1094	675	459–892	0.09

All splitting procedures were performed *ex situ*. Although not statistically significant, this has resulted in a prolonged cold ischaemic time (CIT) in the SLT group (Table 1). Otherwise, the two groups were comparable for donor demographics.

Recipient characteristics

The ERL and WLT groups were well matched for recipient age, MELD score and causes of liver failure (Table 2). The mean MELD score was 16 in both groups with the leading causes of liver failure being primary biliary cirrhosis (29.6%), primary sclerosing cholangitis (29.6%) and alcoholic cirrhosis (18.5%).

Table 2. Recipient characteristics.

Characteristics	WLT ($N = 27$)	SLT ($N = 27$)	*P*-value
Age [years; mean (range)]	53.4 (34–74)	52.1 (22–68)	0.76
MELD score [mean (range)]	16.4 (8–32)	16.0 (7–36)	0.83
Sex (M:F)	12:15	16:11	0.41
Indications			
Alcoholic cirrhosis	10/54		NA
Hepatocellular carcinoma	2/54		
Hepatitis C	4/54		
Neuroendocrine tumour	2/54		
Hyperoxalosis	2/54		
Primary biliary cirrhosis	16/54		
Primary sclerosing cholangitis	16/54		
Chronic rejection	2/54		

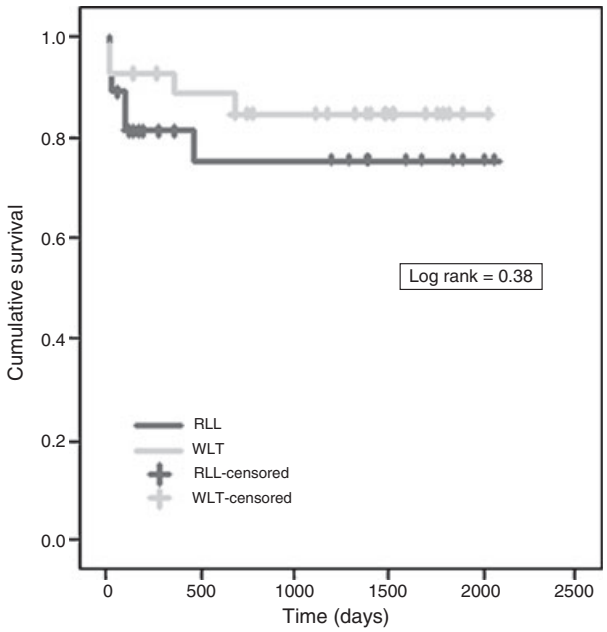

Figure 1 Patient survival after ERL and WLT transplantation.

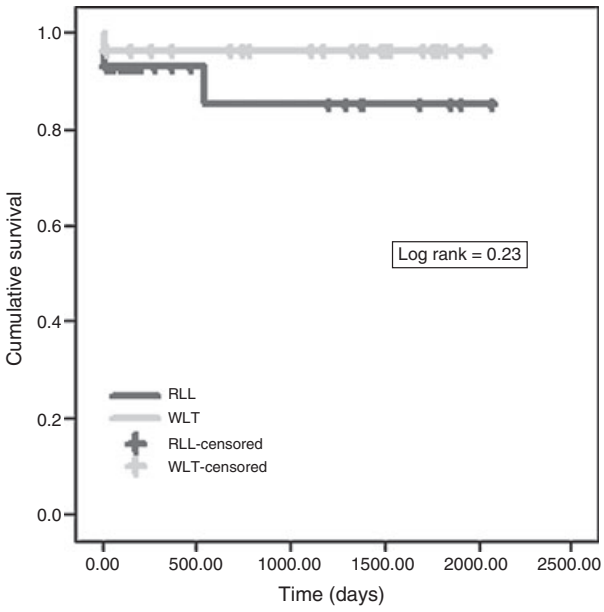

Figure 2 Graft survival after ERL and WLT transplantation.

Outcome

There was no primary nonfunction in either group. The 30-day survival was 88.9% and 92.5% in the ERL and whole graft recipients respectively. With a median follow-up of 42 months, the 3-year overall patient survival for the ERL group was 77.8% and WLT group was 85.2% (log-rank = 0.38) (Fig. 1). The 3-year graft survival for the ERL and WLT recipients was 88.9% and 96.3% respectively (log-rank = 0.23) (Fig. 2).

The vascular and biliary complications are listed in Table 3. Two patients in the ERL group developed hepatic artery thrombosis. They were both relisted and successfully regrafted. One patient developed portal vein thrombosis following WLT, died waiting for a regraft.

There were significantly more biliary leaks in the ERL group with four patients developing biliary leaks from the transected hepatic parenchyma and one anastamotic leak compared to no leaks in the WLT group ($P = 0.05$). The patient with parenchymal biliary leaks settled with conservative management while the patient with the anastamotic leak required a biliary reconstruction. There were fewer biliary strictures in the ERL group ($n = 1$) compared with the WLT group ($n = 3$) with one and two patient in each group, respectively, requiring reconstructive surgery. One patient, with a biliary stricture, in the WLT group retained good graft function following 6 months of a trial of stenting.

We performed a subset analysis of survival of patients with pretransplant hyponatraemia and compared survival in ERL and WLT patients. This revealed a trend towards a poorer survival in patients who were hyponatraemic pretransplant, though not statistically significant (log-rank = 0.21). Statistical significance may not have been achieved because of the small numbers in each category (Table 4). However, the observed trend was indeed remarkable (Figs 3 and 4).

Table 3. Vascular and biliary complications of ERL and WLT groups.

Complication	WLT ($N = 27$)	ERL ($N = 27$)	*P*-value
Vascular thrombosis	1 (Portal V Thrombosis)	2 (Hep A Thrombosis)	1.0
Treatment	Relisted and deceased	Regrafted ($N = 2$)	
Biliary			
Leak	0	5 (20.8%)	0.05
Anastomotic (treatment)		1 (reconstructed)	
Nonanastomotic (treatment)		4 (conservative)	
Stricture	3	1	0.61
Treatment	Stented ($N = 1$), Reconstructed ($N = 2$)	Reconstructed ($N = 1$)	

Table 4. Overall survival of hypo-and normo-natraemic ERL and WLT recipients.

	Hyponatraemic	Normonatraemic
ERL recipient (fraction; % survival)	2/6; 33	19/21; 90
WLT recipient (fraction; % survival)	10/11; 91	13/16; 81

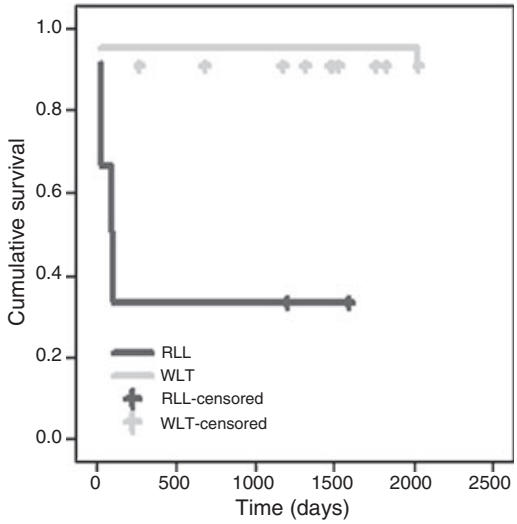

Figure 3 Patient survival after ERL and WLT transplantation in patients hyponatraemic pretransplantation.

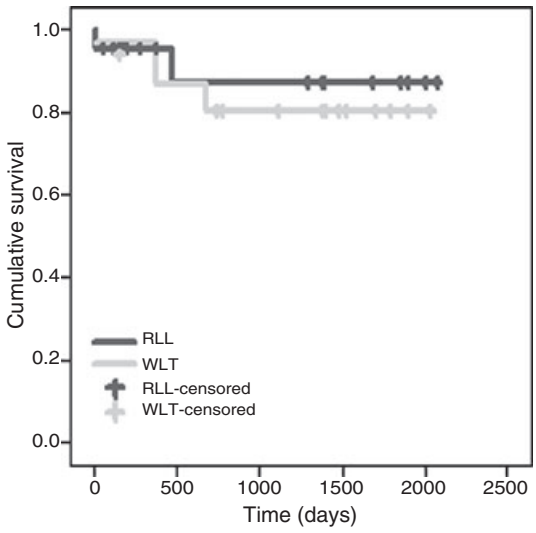

Figure 4 Patient survival after ERL and WLT transplantation in patients normonatraemic pretransplantation.

Discussion

Though favourable single centre reports following SLT were published [9,10], there were initially concerns regarding outcomes in the adult recipient leading some authors to surmise that 'one plus one does not always equate to two' [11].

Some large series have published excellent outcomes in ERL graft transplantation. One of the earliest of these, looking at European Split Liver Registry, showed a 6-month graft and patient survival of 72% and 80%, respectively, for elective adult recipients [12]. An early experience in the UK described a 95% patient and graft survival at 12 months for adult right lobe recipients [13]. More recently, there have been numerous studies comparing SLT and WLT outcomes with encouraging results (Table 5). A view frequently cited is that the favourable outcomes following SLT are because of better donor/recipient selection, resulting in a selection bias when comparing SLT to WLT.

In a bid to overcome this, studies have compared SLT to WLT with similar donor recipient characteristics, with two previous matched pair analysis from one centre [6,7]. These results, from one of the largest series of SLTs in the world, by the Hamburg group, are indeed commendable. Of note, they have demonstrated an improvement in survival in the SLT group with a good long-term survival (Table 5). However, they did not use MELD as a matching criteria. In addition, the difference in techniques of splitting, selection criteria for splitting and possibly better donor/recipient selection could have accounted for these better results.

Here, we performed a comparison of outcome using matching of ERL and WLT recipients using the MELD score. The MELD score has been shown to be a good measure of urgency of transplantation and has been used as part of the UNOS prioritization of patients on the liver transplantation waiting list [8]. By matching ERL and WLT recipients, according to recipient age, indication of transplantation and MELD score, we aimed in this study to compare recipients of similar urgency of transplantation and age.

Although not statistically different, there was a trend to a poorer patient and graft survival in the ERL group (ERL = 77.8 and 88.9%; WLT = 85.2% and 96.3%).

The inferior performance of the split graft has resulted in recent studies agreeing that the ERL graft is a marginal one. A number of algorithms predicting outcomes following liver transplantation have been published which have shown that split grafts are associated with an increased risk to the adult recipient. The two largest of these are the European Liver Transplant Registry [14] score and the Donor Risk Index score [15]. The former study, a multicentre European Study describing a predictive model of mortality following liver transplantation in 21 605 patients assigned an odds ratio of 3-month mortality of split recipients of 1.96 over that of WLT recipients.

Table 5. Summary of comparative studies of SLT and WLT.

Study	Type of study	Technical complications (% SLT versus WLT)		Survival (% SLT versus WLT)		Notes on SLT and WLT groups
		Biliary	Vascular	Patient	Graft	
Washburn *et al.* [2]	Series (SLT = 65, WLT = 210)	10	9	87	85	No statistical comparison between SLT and WLT cohorts
Cardillo *et al.* [3]	Series (SLT = 154, WLT = 1126)	NA	10 vs. 8	75 vs. 82	68 vs. 77	Younger donors in SLT group
Sebagh *et al.* [4]	Series (SLT = 20, WLT = 38)	40 vs. 8	10 vs. 3	95 vs. 92	95 vs. 92	Significantly younger donors in SLT group, different cause of liver failure between groups, longer total ischaemic time in SLT
Broering *et al.* [6]	Matched pair (SLT = 40, WLT = 40)	5 vs. 2.5	5 vs. 0	77 vs. 87	74 vs. 77	Matched recipient and donor characteristics (used Child's Pugh)
Yersiz *et al.* [5]	Series (SLT = 71, WLT = 1086)	10	7	78 (no significant difference)	69 (no significant difference)	No statistical comparison between SLT and WLT cohorts
Wilms *et al.* [7]	Matched pair (SLT = 70, WLT = 70)	11 vs. 10	3 vs. 0	89 vs. 84 (3 months) 67 vs. 76 (5 years)	84 vs. 76 (3 months) 74 vs. 83 (5 years)	Matched on recipient and donor characteristics (UNOS status)

The vascular complication rate was marginally higher in ERL group compared with that in the WLT group (7.4% vs. 3.7% respectively). There was also a significantly greater biliary leak rate in the ERL group with five patients developing biliary leaks, one requiring a reoperation for an anastamotic leak. The higher incidence of biliary complications in SLT is thought to be because of devascularization of the bile duct from the hilar dissection, the presence of the transected parenchymal surface and a failure to recognize biliary anomalies. Despite, the use of routine cholangiograms, methylene blue injections into the biliary tree and T-tube decompression, Wojcicki *et al.* [16] still demonstrated a biliary complication rate of 44%. However, the authors found a higher rate of cut surface and anastamotic leaks associated with Duct to Duct anastamosis without a T-tube compared with an anastamosis without a T-tube.

Another hypothesis frequently sighted as contributing to a poorer outcome following SLT is the longer CIT associated with *ex vivo* splitting. All splitting procedures in this study were performed *ex vivo*. Though not statistically significant, the splitting procedure has resulted in a longer CIT in the ERL group compared with the WLT group in this study (675 vs. 602 min respectively). Currently in the UK, facilities at donor hospitals do not allow for consistent practise of *in situ* splitting at the time of the donor operation. Although Washburn *et al.* [2] showed that *in situ* splitting resulted in better survival when compared with the *ex vivo* technique, the authors did identify an increased CIT associated with the *ex vivo* splitting. Therefore, including CIT and splitting method (*ex vivo* versus *in situ*) resulted in confounding variables.

We have previously shown that hyponatraemia independently predicts patients on the waiting list who would not proceed to transplantation because of deterioration of clinical disease or death [17]. When we performed a subset analysis of the patients with pretransplant hyponatraemia, we found a trend to a poorer outcome in the ERL recipient over that of the whole graft recipient. Hyponatraemia has been shown to have a negative impact on the survival in the setting of cirrhosis and liver transplantation [18–20]. Whether the prognostic value of hyponatraemia is directly attributed to a more advance liver disease is not known and continues to be investigated. Specifically in post-transplant survival, a recent study showed that pretransplant hyponatraemia independently predicted a poorer survival 3 months post-transplantation [21]. This was attributed to the higher occurrence of infectious complications and organ failure (neurological and renal). No comment on the type of donor, i.e. SLT versus WLT was made. However, longer term survival in this cohort plateaued and was similar to

those without hyponatraemia. This trend in fall in survival in the early period of post-transplantation in hyponatraemic patients is reflected in the SLT recipients in the current study (Fig. 3). Put together, it is apparent that pretransplant hyponatraemia is a negative prognostic indicator of post-transplant outcome. These patients may be better served by WLT grafts.

Despite the poorer outcome in the adult SLT recipient, there remains a utilitarian advantage in this technique. In a unique study, Merrion *et al.* showed that lifetime gained by a transplant recipient, 2 years after SLT or WLT, compared with a patient remaining on the waiting list, is 5.2 (SLT) and 5.8 (WLT) months in the adult recipient respectively [22]. The authors found that for 100 potentially splitable donor livers, 76 could be split for 152 recipients and 24 would be required for re-transplants whereas whole organ graft could be provided for 93 adult recipients, seven of whom would require a re-transplant. When the lifetime gained was applied to the SLT and WLT groups, the authors concluded that for 100 donor livers, the aggregate lifetime gained by transplant recipients 2 years post-transplantation for SLT was 56 years compared to 45 years in the WLT group, with 59 additional patients transplanted in the SLT group.

In the UK, a recent study, with a similar aim, showed the gain from SLT from paediatric recipients should be balanced by the loss caused by the inferior survival in the adult recipient [23]. Though designed with a number of assumptions, the authors showed that at 5 years post-transplantation, a gain of 25 life-years for the paediatric recipient balances a loss of 30 life-years for adult recipients. Though not significant, this trend in inferior survival in adult recipients of ERLs was reflected in the data presented here. However, this should be viewed in the light of the sustained rise in the adult and paediatric waiting list.

In summary, in the face of a rising number of patients on the waiting list and a falling number of liver donors [24], SLT is an effective way of increasing the number of available organs for transplantation. Though resulting in a poorer patient and graft survival and higher complication rate, the utilitarian advantage of ERL graft transplantation has been demonstrated. Therefore, in deciding to convert a normal graft into a marginal one, a careful balance between the supply and demand of organs specific to the transplant unit, region and country have to be weighted in balance.

Authorship

RP, PAL, GJT and SGP: designed study, edited paper. GKB, MA and AA: performed study. GKB: collected data. GKB and AA: analysed data. GKB and RP: wrote paper.

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