Futility Versus Acceptability of the Use of Grafts Taken From End of Line in the National Organ-Sharing Network

V. Soyer[a,*], S. Koc[a], A. Onur[a], B. Sarıcı[a], C. Kayaalp[a], B. Isık[a], B. Unal[a], S. Yologlu[b], and S. Yilmaz[a]

[a]Department of General Surgery, Liver Transplantation Institute, Inonu University, Malatya, Turkey; and [b]Department of Biostatistics and Medical Information, Inonu University, Malatya, Turkey

ABSTRACT

Background. The number of suitable donors for organ transplantation is limited in many countries. This limitation can be overcome with the use of organs removed from marginal donors (expanded-criteria donors [ECDs]). We examined the long-term results of 187 patients who underwent marginal cadaveric liver transplantation in our institution.

Methods. The data of patients who underwent cadaveric liver transplantation from January 2007 to April 2014 were retrospectively reviewed. ECDs were evaluated by considering 19 internationally accepted criteria. The clinical data of recipients including age, clinical status, and Model for End-Stage Liver Disease (MELD) score were also assessed.

Results. A total of 287 patients underwent cadaveric liver transplantation. A graft from an ECD was used in 181 (63.06%) patients. The mean MELD score was 18.8. In all, 45 patients (24.86%) underwent transplantations for fulminant liver failure and 136 patients (75.14%) underwent transplantations for other chronic conditions. The majority of donors died of cerebrovascular disease and trauma. Only hypotension requiring inotropic drugs and obesity significantly affected survival. The 90-day and 12-month survival rates of the recipients who received a graft from an ECD were 51.93% and 46.2%, respectively.

Conclusions. The use of ECD allografts immediately and significantly expands the existing donor pool. Because of persistent organ scarcity, pressure to use a greater proportion of the existing donor pool will continue to increase.

LIVER transplantation is the most effective treatment method for end-stage liver failure [1,2]. Although the number of patients awaiting liver transplantation has steadily increased, there has been no corresponding increase in the organs available for transplantation. Accordingly, multiple strategies for expansion of the donor pool are being pursued. The most commonly used strategy for organ allocation is the use of expanded-criteria donors (ECDs) to overcome the organ shortage [3]. Donors are generally considered to be ECDs if there is a risk of initial poor function or primary non-function (PNF), although those with a risk of late graft loss are also included [4]. Although the organs from ECDs may not be optimal, they can be a viable alternative to death while awaiting transplantation. An accepted description of ECDs has not been definitively established within the liver transplantation community. Among the most prominent donor characteristics that may contribute to the development of initial poor function or PNF in the recipient are increasing age, obesity, prolonged ischemia, hypotension requiring inotropic support, steatosis, malignancy, viral hepatitis, hypernatremia, anatomical variation, prolonged intensive care unit (ICU) hospitalization, infection, and split-liver transplantation. In this study, we evaluated the donor risk factors associated with liver graft dysfunction and how the use of ECDs affects patient and graft survival.

MATERIALS AND METHODS

In a retrospective review of 287 deceased-donor liver transplantations (DDLTs) performed from January 2007 to April 2014 at our institution,

*Address correspondence to Vural Soyer, Department of General Surgery, Liver Transplantation Institute, Inonu University, 44315, Malatya, Turkey. E-mail: hvuralsoyer@yahoo.com

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360 Park Avenue South, New York, NY 10010-1710

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Table 1. Recipient-dependent Factors and Statistical Results

Criteria	Alive n (%)	Dead n (%)	OR (95% CI)	*P*
Administration				
Hospital	20 (44.4)	25 (55.6)	0.95 (0.48–1.88)	.89
Home	60 (44.1)	76 (55.9)		
MELD score				
<33	3 (27.3)	8 (72.7)	2.29 (0.58–8.99)	.22
≥33	68 (46.3)	79 (53.7)		
Status				
Fulminant	20 (44.4)	25 (55.6)	0.95 (0.48–1.88)	.89
Chronic	60 (44.1)	76 (55.9)		

we identified 181 procedures involving ECDs. All records of the 181 ECDs were obtained from the respective organ procurement organizations and reviewed. The ECD effects and recipient survival data were retrospectively evaluated. ECDs were defined as donors with obesity (body mass index [BMI] >30 kg/cm^2), increased age (>75 years), hepatosteatosis (at least grade I), 5 or more days in the ICU, prolonged hypotension requiring inotropic drugs, prolonged cold ischemia time (>10 h), a peak serum sodium level >172 mEq/L, sepsis and viral infections (HBV, HCV), increased ALT and AST levels (minimally 3-fold), split-liver transplantation, trauma, anatomical damage or variation requiring back-table graft reconstruction, and extra-hepatic neoplasia (such as a central nervous system [CNS] tumor). Cadaveric grafts that were included in the study were obtained from donors with at least 1 and a maximum of 7 of the ECD criteria listed above. Recipient data that were analyzed included age, clinical status (fulminant or chronic), and Model for End-Stage Liver Disease (MELD) score (Table 1). After exclusion of hospital deaths in the first 90 days, the median follow-up time was approximately 27 months (range, 3–80 months). Statistical analysis and calculation of odds ratios were performed through the use of univariate logistic regression, and a value of $P < .05$ was considered statistically significant.

RESULTS

The 181 recipients included 110 male and 71 female patients. Their mean age was 32.8 years (range, 4 months to 70 years) and their mean MELD score was 18.8 (range, 7–60). In all, 45 patients (24.86%) underwent transplantations for fulminant liver failure and 136 patients (75.14%) underwent transplantations for other chronic conditions. The most common cause of chronic liver failure in recipients was hepatitis B (n = 58, 31.1%), followed by cryptogenic cirrhosis (n = 33, 17.1%), and hepatitis C (n = 17, 8.5%). The average total ischemia time was about 9 h, and all of the grafts were from the National Organ-Sharing Network. The majority (65%) of donors died of cerebrovascular disease and trauma; 112 of these 181 ECD grafts were taken from the end line of the national organ-sharing system. These grafts were rejected by other transplant centers; if we did not accept these grafts, they would not have been used. In total, 102 of the 181 (56.35%) patients who underwent DDLT with ECDs died, and their mean follow-up time was 1.8 months (range, 1 day to 40 months); in addition 79 (43.64%) are still alive, and their mean follow-up time was 34.8 months (range, 1–80 months). Fifty-three patients died of primary non-function within the first week after the transplantation. The PNF ratio was 28.34%.

Each ECD graft that would potentially affect survival of the recipient was examined individually (Table 2). Only hypotension requiring inotropic drugs (CI = 0.52, $P = .039$) and obesity (CI = 4.02, $P = .023$) significantly affected survival ($P < .05$). In total, 56 of 111 donors who received inotropic agents died, and 55 are still alive. Seventeen of the cadaver donors were obese (BMI, 30–42 kg/cm^2). Fourteen of these donors died in the post-transplant period, and 3 are still alive. Notably, however, the exact degree of graft steatosis among the donors with a BMI >30 kg/cm^2 was unknown. In these donors, the grafts were macroscopically evaluated during harvesting. The presence of 30% to 50% macrosteatosis was identified through histological examination in only 5 donors. All of the other parameters that were dependent on donor or recipient characteristics had no statistically significant effects on graft survival ($P > .05$). In total, 11 of 23 patients who received grafts from donors ≥75 years of age are still living ($P = .66$, CI = 0.82). Liver biopsy performed during harvesting in these older donors showed that 12 donors had grade ≥1 steatosis.

In our institute, one of the most common ECD characteristics was the split transplantation technique. Split-liver transplantation affected morbidity more than it affected mortality. The split technique was performed in 71 patients; 26 of these 71 patients who received a transplantation with a split graft died, and 45 are still alive ($P = .128$, OR = 1.85).

In total, 51 (48.1%) of the 106 patients who underwent transplantation with the use of non-marginal deceased-donor grafts died, and 55 (51.9%) are still alive. The indication for transplantation was fulminant hepatic failure in 12 of these 55 patients (22%). However, 20 patients who underwent transplantation with non-ECD grafts died of neurological complications of acute fulminant failure. The high mortality rate in patients in the non-ECD group probably is due to neurological complications of acute fulminant failure.

A total of 106 patients (36.2%) received non-ECD grafts, 181 (61.7%) were recipients from donors with at least 1 ECD factor, 25 (13.36%) were recipients from donors with 2 ECD factors, 39 (20.82%) were recipients from donors with 3 ECD factors, 53 (28.33%) were recipients from donors with 4 ECD factors, 45 (24.06%) were recipients from donors with 5 ECD factors, and 19 (10.16%) were recipients from donors with more than 5 ECD factors.

Accordingly, the 90-day and 12-month survival rates of the patients who received ECD grafts were 51.93% and 46.2%, respectively.

DISCUSSION

A shortage of donor organs has led transplant centers to consider the increased use of organs from marginal donors. An accepted precise definition of what constitutes an ECD for liver transplantation remains elusive. Conceptually, grafts from such donors are at increased risk of early failure (ie, PNF or delayed graft function) or may increase the risk

Table 2. Graft-dependent Factors and Statistical Results

ECD	Alive n (%)	Dead n (%)	OR (95% CI)	*P*
Age, years				
<75	69 (43.6)	89 (56.4)	0.82 (0.34–1.97)	.66
≥75	11 (47.8)	12 (52.2)		
Steatosis				
Lower than grade I	4 (33.3)	8 (66.7)	1.59 (0.46–5.49)	.45
None	76 (44.9)	93 (55.1)		
Obesity				
BMI >30 kg/cm^2	3 (17.6)	14 (82.4)	4.02 (1.11–14.5)	.023
BMI <30 kg/cm^2	77 (46.9)	87 (53.1)		
Split				
Yes	26 (36.6)	45 (63.4)	1.60 (0.87–2.96)	.128
No	54 (49.1)	56 (50.9)		
Hypotension and inotropic support				
Yes	55 (49.5)	56 (50.5)	0.52 (0.27–0.97)	.039
No	25 (35.7)	45 (64.3)		
Hypernatremia				
Na ≥172	8 (38.1)	13 (61.9)	1.29 (0.50–3.29)	.59
Na <172	72 (45.0)	88 (55.0)		
Cardiac arrest				
≥1 event	23 (46.5)	26 (53.1)	0.82 (0.42–1.6)	.57
None	57 (43.1)	75 (56.9)		
Cold ischemia time				
≥10 h	69 (43.6)	89 (56.4)	1.32 (0.54–3.2)	.53
<10 h	11 (50.0)	11 (50.0)		
ICU hospitalization				
≥5 days	38 (40.4)	56 (59.6)	1.34 (0.74–2.42)	.33
<5 days	43 (49.4)	44 (50.6)		
Graft injury				
Yes	9 (64.3)	5 (35.7)	0.39 (0.12–0.24)	.10
No	71 (42.5)	96 (57.5)		
Cystic graft				
Yes	2 (100.0)	0 (0.0)	6.46 (0.30–136.6)	.18
No	78 (43.6)	101 (56.4)		
HBV				
Yes	2 (16.7)	5 (83.3)	4.01 (0.45–35.0)	.17
No	78 (44.8)	96 (55.2)		
HCV				
Yes	1 (50)	1 (50)	0.77 (0.04–12.5)	1.0
No	79 (44.1)	100 (55.9)		
Infections				
Yes	11 (42.3)	15 (57.7)	1.06 (0.45–2.46)	.88
No	69 (44.5)	86 (55.5)		
CNS malignancy				
Yes	6 (46.2)	7 (53.8)	0.89 (0.28–2.77)	.84
No	74 (44.1)	94 (55.9)		
İncreased AST/ALT				
Yes	9 (36.0)	16 (64.0)	1.44 (0.60–3.46)	.41
No	71 (45.5)	85 (54.5)		

Abbreviations: OR, odd ratio; CI, confidence interval; ICU, intensive care unit; CNS, central nervous system.

of inferior graft or patient survival outcomes. Despite the absence of an international consensus regarding marginal donor criteria, factors that predict graft dysfunction after surgery include a donor age >70 years, BMI >30 kg/m^2, hepatic macrosteatosis >30%, systemic or intra-abdominal infection, an ICU stay >5 days, cold ischemia time >14 h, serum sodium level >160 mEq/L, positive hepatitis B or C titer, hypotension (<60 mm Hg) >4 h, high-dose inotropic support, previous cardiac arrest, graft reuse, AST level >150 IU/L, total bilirubin >3 mg/dL, ABO mismatch graft, and CNS malignancy [5].

There are 2 categories of marginal grafts: those that carry a high risk of technical complications and impaired function (eg, steatotic livers, non–heart-beating donors, elderly donors, split livers, and donors with high inotrope requirements or long ischemia times) and those that carry a risk of transmission of infection or malignancy to the recipient [4,6–10]. The increased use of marginal grafts has been primarily driven by 2 factors: the critical shortage of donor organs for transplantation and data demonstrating that marginal grafts may be used with acceptable outcomes [11,12]. Several recent studies have shown that recipient factors, especially the MELD score in association with ECD criteria, also adversely affect recipient outcomes [13–16]. Thus, the importance of simultaneous analysis of both donor and recipient factors has been emphasized when matching donors and recipients to compensate for their risks. Marginal grafts should not be used in high-risk recipients [17].

In contrast to other organs, the liver may be more immune to senescence, particularly in otherwise healthy persons. Older donor livers tend to be smaller and darker-colored and may have developed fibrous thickening of the capsule [18]. Older donors also have an increased incidence of steatosis [14,19], which may potentiate cold preservation injury [15]. Therefore, short ischemia times may be important in elderly donors. In our experience, the use of donors ≥70 years old has achieved results similar to those obtained when using younger donors. No PNF was observed, and the incidence of vascular complications was not increased.

Another important issue is prolonged cold ischemia time, which is an independent risk factor for liver preservation injury, even more so than donor age [20]. A cold ischemia time >14 h has been associated with a 2-fold increase in graft preservation damage resulting in a prolonged postoperative course, biliary stricture, and decreased graft survival [20–23]. Our cold ischemia time ranged from 9 h to 14 h. However, this period was reduced more through increased logistics facilities.

Hypernatremia is a common finding in brain-dead donors and may be caused by central diabetes insipidus. Donor hypernatremia can affect graft function and increase the risk of graft loss. This may be related to the increased osmolality that occurs with cellular injury, which becomes significant at the time of reperfusion. In our institute, we performed 21 DDLT procedures in which the donor sodium level was >172 mEq/L and encountered no signs of liver dysfunction in the postoperative period. Thus, cadaveric organ donors with high serum sodium levels can be safely transplanted. However, we often perfuse sodium-free hypotonic fluid through the inferior mesenteric vein during harvesting [24].

With the increase in donor age, a higher incidence of malignancy is expected [25]. Donors with CNS tumors are commonly overlooked because of concerns about the transmission of malignancies to immunosuppressed recipients. Transplant surgeons have been reluctant to accept organs from donors with a history of CNS malignancy. There is an absence of substantive data defining the true risk of tumor transmission.

Another important issue with CNS tumor grafts is the follow-up time during the post-transplantation period. In our experience, the first recipient who underwent DDLT with a CNS tumor graft was a 14-year-old male patient. The follow-up time was approximately 3 years and 8 months after transplantation, and no evidence of transmission was observed. Fourteen patients underwent transplantation with the use of CNS tumor grafts in our institute. Seven of these patients died and 7 are still alive. Recurrence is uncommon, even in patients with high-grade CNS tumors that violate the blood-brain barrier [26]. Recurrence of CNS tumor did not occur in any of our patients, and the cause of death was not the tumor.

Livers that are damaged by trauma or have anatomical variation should not necessarily be excluded from transplantation. The most common anatomical liver variation involves the hepatic artery and is observed in 30% of patients [27–30]. Recognition of these variations is very important during procurement. These variations require additional arterial anastomosis during back-table or transplantation.

Seven patients underwent DDLT with HBsAg+ grafts in our institute, and 4 of these grafts were used for HBsAg+ recipients. All of these patients were treated with the hepatitis B hyper-immunoglobulin during the intra-operative and postoperative periods. Five of them died in the early post-transplantation period. DDLT from an anti-HCV+ donor to an anti-HCV+ recipient does not appear to be associated with increased morbidity or mortality in the liver recipient. The graft and patient actual survival rates were identical to the graft survival rates from anti-HCV−donors. We transplanted livers from 2 anti-HCV+ donors to 3 anti-HCV+ recipients. One of them is still alive and 1 died.

Choosing the optimal recipients for ECD transplantation is extremely important. ECD grafts should not be used for high-risk recipients [31]. Marginal grafts should be transplanted in recipients with low risk (ie, those with a low MELD score, few comorbidities [such as those of young age], and few additional health problems) for better outcomes. In our institute, 46 recipients who underwent DDLT were >55 years of age, and 28 of them died. Patient and graft survival are significantly lower when ECD grafts are used in high-risk recipients [32]. The incidence of PNF after transplantation for fulminant hepatic failure is higher than that observed for other indications [33]. Forty-four patients with fulminant liver failure underwent DDLT with ECD grafts, and their outcomes were similar to those of patients with fulminant failure who used ideal grafts. Notably, there was a high ratio of neurological complications secondary to acute fulminant failure among patients who underwent transplantation with non-ECD grafts.

At least 1 and up to 7 ECD factors were present in all of the patients. Death in patients who underwent liver transplantation with an ECD graft was not due to only a single factor. As a result, the criteria do not affect recipient or graft survival alone. As can be seen from our results; when grafts from marginal donors are used under appropriate indications and in suitable recipients, the outcomes are comparable to those of normal cadavers in terms of morbidity and mortality.

In conclusion, ECD allografts immediately and significantly expand the existing donor pool. Because of persistent organ scarcity, pressure to use a greater proportion of the existing donor pool will continue to increase.

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