

Extended-Donor Criteria Liver Allografts

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ABSTRACT

Extended-donor criteria liver allografts do not meet traditional criteria for transplantation. Although these organs offer immediate expansion of the donor pool, transplantation of extended-donor criteria liver allografts increases potential short- and long-term risk to the recipient. This risk may manifest as impaired allograft function or donor-transmitted disease. Guidelines defining this category of donor, level of acceptable risk, principles of consent, and post-transplantation surveillance have not been defined. This article reviews the utilization, ethical considerations, and outcomes of extended-donor criteria liver allografts.

KEYWORDS: Liver transplantation, extended-donor criteria

Advances in immunosuppressive therapy, medical management, surgical technique, and identification of appropriate indications for liver transplantation (LTX) have resulted in significant improvements in patients' survival and universal recognition of the procedure as preferred therapy for patients suffering from hepatic failure. In North America, this recognition has resulted in logarithmically increasing demand within the last decade.¹ Increasing demand for LTX has not been paralleled by supply, with annual donor growth linear at less than 10%. Application of LTX is fundamentally limited by the existing donor pool. This discrepancy between supply and demand has been accentuated by an allocation policy that does not uniformly distribute supply throughout the United States, thereby creating areas of particular need.²

Increasing organ scarcity has motivated select transplant centers to relax customary restrictions to donation, creating the term "extended-donor criteria" (EDC) or "marginal" donor. However, precise definitions of these terms have not been widely accepted. Traditional restrictions to donor selection focused upon potential

recipient risk.³⁻⁸ This risk can be broadly categorized as impaired allograft function, donor-transmitted disease, or, in the case of adult-to-adult living-donor liver transplantation (aLDLT), living-donor morbidity.

Impaired allograft function is principally an immediate risk, manifest as delayed graft function or primary nonfunction (PNF). This complication prolongs recovery and may require retransplantation. Impaired allograft function is the result of ischemia-reperfusion injury that predisposes to long-term morbidity secondary to biliary complications.^{9,10} It is the consequence of a donor clinical event associated with hepatic parenchyma injury (ischemia, hypernatremia), an underlying physiologic property of the donor (age, steatosis), or an alternative recovery technique (donation after cardiac death [DCD], reduced-liver transplantation [RLT], split-liver transplantation [SLT]).¹¹

Donor-transmitted disease can be a virus or pathologic disorder and is principally a long-term risk.¹²⁻¹⁵ In these situations, immediate hepatic function is expected. Potential transmission of a virus may mandate prophylactic therapy (hepatitis B) or

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Immunosuppression, Organ Allocation, and Other Issues in Liver Transplantation; Guest Editor, Marion Peters, M.D.

Semin Liver Dis 2006;26:221-233. Copyright © 2006 by Thieme Medical Publishers, Inc., 333 Seventh Avenue, New York, NY 10001, USA. Tel: +1(212) 584-4662.

DOI 10.1055/s-2006-947292. ISSN 0272-8087.

surveillance monitoring (human T cell lymphotropic virus) and exposes the recipient to significant morbidity if viral disease arises.^{12,15} Transmission of a donor-derived pathologic disorder, such as hemophilia or cancer, is usually associated with significant morbidity or mortality.^{14,16}

aLDLT involves short- as well as long-term risks.^{17,18} Early complications in the recipient from surgical technique or insufficient hepatic mass increase the risk for impaired allograft function. Recipient risk is compounded by short- and long-term risks incurred by the donor who undergoes major hepatic resection.¹⁹ Current outcomes include aLDLT within the sphere of EDC.^{20,21}

ALLOCATION

Hepatic allograft allocation is dependent upon a calculated disease severity score, termed the model for end-stage liver disease (MELD) score,²² and geographic location with the United States separated into 10 regions. This has contributed to significant discrepancies in waiting times for LTX and disease severity at LTX (Fig. 1). Regions with short candidate wait times or low MELD at LTX enjoy a relative excess of donors and may practice selective donor utilization. EDC allografts become available for export out of the region of donor origin after being declined by all transplant centers within geographic proximity to the donor. They may be exported to other regions for patients prioritized for urgent transplantation (United Network for Organ Sharing [UNOS] status 1A) or as an “open offer” for allocation by the accepting transplant center in a region of donor scarcity.

EDC allocation is distinctly different from the allocation of optimal organs that remain locally and are distributed by MELD score according to a match list. The hypothesis supporting EDC utilization is that the benefit of earlier access to transplantation afforded by an

EDC allograft outweighs the combined risk associated with the specific allograft *and* the risk of additional waiting for LTX. This risk may be initial poor function or the presence of a disease within the donor that may be transmitted to the recipient. EDC recipients are typically *selected* by the transplant center rather than *allocated* according to regional wait list priority. Literature to date reflects this operational paradigm with significant increases in access to transplantation, wait-list mortality, and survival results that approach those observed utilizing optimal allografts.^{6,8,20,23-29} However, no data exist on utilizing EDC allografts in an allocation scheme that mirrors the allocation of optimal hepatic allografts.

INDICATORS OF IMPAIRED ALLOGRAFT FUNCTION

Expansion of donor criteria to include allografts with an additional risk of delayed function has been advocated for over a decade.^{6,8,23,30} During this period, numerous single-center reports have identified predictors of potentially poor allograft function. Donor characteristics demonstrated to yield an increased risk of delayed graft function or primary nonfunction include age older than 60 years,^{3,12,25,29,31-38} hypernatremia exceeding 155 meq/L,^{29,39} macrovesicular steatosis exceeding 40%,^{3,12,29,32,40-45} cold ischemia time exceeding 12 hours,^{3,12,29,30,39} partial-liver allografts (SLT, RLT, aLDLT),^{3,33} and DCD.^{12,33,46,47}

Acceptable donor age has been progressively expanding in response to population demographics, donor demographics, and increasing organ scarcity. In fact, donor age 65 years and older represents the largest expanding component of the current donor pool (Fig. 2). Recognition of unique physiologic and anatomic characteristics associated with older liver allografts is prerequisite to their successful utilization. Older liver allografts have a lower tolerance for preservation.¹² Endothelial injury from cold ischemia occurs earlier in older allografts; increasing the risk of inflammation, thrombosis, and T cell-mediated rejection.^{12,48} This may impede synthetic function and regenerative capacity.^{12,48,49} Characteristic anatomic features of older liver allografts include capsular fibrosis, smaller size, darker texture, increased steatosis, and arterial atherosclerosis.¹²

Elderly-donor procurements require a recovery physician experienced in physiologic and anatomic assessment of older liver allografts as well as advanced donor management and surgical recovery techniques. Elderly-donor management is complicated by decreased physiologic reserves and frequent comorbidities. As a result, optimal donor management includes the organ recovery surgeon participating in concert with procurement and hospital staff. This may delay the procurement to achieve improved donor physiology

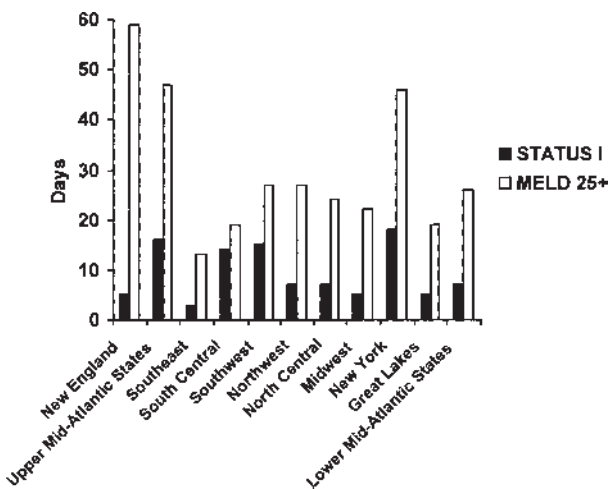


Figure 1 Median wait time for liver transplantation by region.

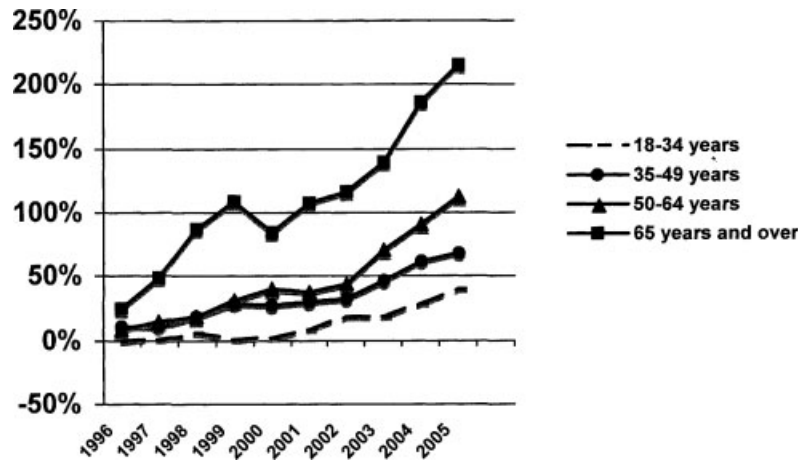


Figure 2 Donor pool age demographics.

and organ preservation. Comorbidities may also affect surgical recovery. Extensive vascular disease, aneurismal disease, abdominal operations, and previous cardiothoracic procedures significantly affect the recovery procedure and require advanced recovery techniques to yield allografts of optimum quality for transplantation.⁵⁰

Although recruitment of older donors offers the largest potential for immediate expansion of the donor pool, mounting data clearly indicate decreased overall performance from these allografts. Allografts from older donors demonstrate increased delayed graft function and prolonged cholestasis consistent with significant ischemia-reperfusion injury.²⁰ Wall et al initially reported the effect of donor age upon recipient survival in 1990.⁵¹ In an analysis of 184 consecutive orthotopic liver transplantations involving 23 allografts from donors older than 50 years, no difference was observed in actual 30-day patient or graft survival and overall graft performance. Alexander et al subsequently reported a Cox regression analysis of 3634 LTX procedures from the UNOS Transplant Registry between October 1987 and December 1989. In this study, 1-year actuarial patient survival was significantly decreased among recipients of allografts from donors older than 45 years. The difference in survival was ~10% and the authors noted the utilization of older donors in higher risk or older recipients, or both. This led the authors to conclude that donor age in itself should not preclude donation; rather, older liver allografts should be carefully assessed for satisfactory function within the donor and absence of underlying pathology associated with advanced age.^{35,52} Detre et al examined 6-month graft survival of 7988 initial adult LTX recipients from the UNOS Transplant Registry between October 1987 and December 1992. They also identified progressively decreasing graft survival for each decade after donors 20 years of age; however, the increased incidence of graft failure was consistently less than 5% and was offset by concurrent advances in medical and surgical management resulting

in improved overall recipient survival.³¹ Multiple single-center reports throughout the following decade confirmed acceptable allograft performance of donors in their seventh, eighth, and ninth decades, with a typical incidence of PNF of less than 10%.^{30,37,38,53–63}

Donor age limits allograft function. Busquets et al found that donor age older than 70 years was associated with decreased graft and patient survival.³⁴ Feng et al performed an elegant study of donor age correlation with graft failure from UNOS Transplant Registry data of 20,023 LTXs performed from 1998 to 2002.³³ Cox regression analysis of 1896 donors 60 to 69 years of age and 856 donors aged 70 years and older demonstrated a significant increase in graft failure with increasing donor age. Increased risk of graft failure was significantly higher among donors older than 60 years (relative risk of 1.53) and 70 years (relative risk of 1.65) compared with donors younger than 40 years. This mirrors previous data and suggests that the functional threshold for impaired allograft function, solely as a result of donor age, lies between 60 and 70 years.²⁵

An important caveat to the utilization of elderly donors is in the setting of hepatitis C virus (HCV). Convincing data from single centers as well as the UNOS Transplant Registry demonstrate earlier HCV recurrence and decreased survival of patients among HCV recipients of donor allografts older than 60 years.^{28,64–70} It is our current practice to avoid utilization of elderly donors in the setting of HCV whenever possible; however, this algorithm is relaxed when concomitant hepatocellular carcinoma is diagnosed as these patients are generally healthier at LTX and able to tolerate early introduction of interferon-based antiviral therapy.

Hypertatremia is a frequent clinical finding within the donor population that has a negative impact upon function of hepatic as well as extrahepatic allografts.⁷⁰ Hypertatremia may result from aggressive treatment of cerebral edema, decreased antidiuretic hormone

secretion secondary to cerebral ischemia, or inadequate donor fluid management. Allograft function has been postulated to be impaired secondary to a process whereby hepatocytes increase their intracellular osmolality to minimize cellular damage associated with the extracellular hypertonic state. This occurs through the influx of sodium and cytoplasmic osmoles, principally amino acids, methylamines, and polyols. During normalization of hypernatremia, intracellular water may rapidly accumulate, resulting in cell swelling and injury.^{12,70}

Donor hypernatremia is an independent predictor of post-LTX graft dysfunction. Avolio et al were the first to report a direct correlation between donor serum sodium concentration and peak serum aminotransferase following LTX.⁷¹ Gonzalez et al derived a similar conclusion from a study of 168 consecutive LTXs between November 1989 and October 1992 in which multivariate analysis revealed donor hypernatremia to be the strongest predictor of early graft dysfunction.⁷⁰ In an analysis of 649 LTX procedures performed among 11 Spanish transplant centers, donor plasma sodium exceeding 155 mmol/L at procurement ($n = 103$) was independently associated with an increased rate of retransplantation and decreased actuarial graft survival in a Kaplan-Meier analysis.¹⁰ Markmann et al analyzed 1393 consecutive LTXs performed at the University of California Los Angeles from June 1992 through January 1998 and determined that donor serum sodium ≥ 170 mEq/dL had independent prognostic value in predicting graft survival after primary LTX.⁷² One-year graft survival for donor serum sodium < 170 mEq/dL was 75% versus 61% for donor serum sodium ≥ 170 mEq/dL ($p = .008$) with a relative graft failure risk of 1.96 ($p = 0.003$).⁷²

Whenever possible, appropriate resuscitation to correct donor hypernatremia in the setting of the intensive care unit should be optimized prior to recovery. Hypernatremia is a clear indication to slow down the donation process as current data suggest that correction of serum hypernatremia prior to recovery abrogates its negative effect upon organ function. In circumstances where hypernatremia cannot be corrected prior to organ recovery, our protocol is to perform precool perfusion with 1 L of 5% dextrose in water for donor serum sodium levels above 160 meq/dL.^{12,50}

Donor hepatic steatosis is a frequent discovery. The etiology of hepatic steatosis is multifactorial and includes endemic obesity and diabetes within the general population as well as increasing donor age.^{12,43} Cellular physiology, energy synthesis, and regenerative capacity are all decreased in steatotic liver allografts.^{73,74}

Steatosis is categorized as microvesicular and macrovesicular on the basis of histologic appearance. Microvesicular steatosis is diffuse, intracellular lipid vacuolization associated with altered hepatic physiology from sepsis, prolonged hospitalization, enteral starva-

tion, or total parenteral nutrition.^{12,75} Microvesicular steatosis is reversible and is frequently absent in functional allografts within 1 week after LTX. Consistent data examining the effect of microvesicular steatosis on hepatic allograft function have not emerged.^{76,77} We regard microvesicular steatosis as an indication for additional inquiry into the potential clinical etiologies responsible for this condition with ultimate acceptance or declination of the allograft based upon those findings.

Macrovesicular steatosis is a combination of intracellular lipid vacuolization and extracellular lipid depots associated with underlying obesity, inflammation, and cellular injury. Lipoperoxidation and cellular dropout are replaced by adipocytes that disrupt the histologic architecture of hepatic sinusoids.⁴² Macrovesicular steatosis is subcategorized by histologic volume percent as mild (10 to 30%), moderate (30 to 60%), and severe ($> 60\%$). Precise grading of steatosis is difficult, and significant interobserver variability has been reported.^{42,78,79} Pathologic estimation should be attempted only by an experienced pathologist in cooperation with a seasoned recovery physician and should include only macrovesicular steatosis as the presence of microvesicular steatosis has not correlated with allograft function.

Substantial data have correlated the presence of macrovesicular fat with an increased incidence of delayed graft function and primary nonfunction. Transplantation of hepatic allografts with mild steatosis and no other negative prognostic indicators should yield results similar to those for nonsteatotic allografts when cold ischemia is minimized.^{42,43} Transplantation of allografts with severe steatosis should be avoided as post-transplantation function is unpredictable with reported incidences of PNF as high as 60%.^{40,41,75,80}

The transplantation of allografts with moderate steatosis is the current clinical challenge.⁴² The reported incidence of delayed early graft function approaches 35% as evidenced by peak transaminases, bile production, and increased transfusion requirements.^{76,80,81} Recipient age and status at LTX, in addition to HCV as the indication for LTX, correlated with donor steatosis to affect allograft survival negatively.⁴³ In this setting, procurement by an experienced recovery physician is invaluable as this individual can provide histologic verification of the biopsy as well as interrogation of the donor medical record for compounding variables and accurate assessment of the allograft with respect to texture and appearance.⁴³ The most common cause of death among recipients of allografts with moderate or severe steatotic was sepsis. The ultimate outcome of an allograft with moderate steatosis results from a combination of biopsy findings, visual inspection by an experienced procurement physician, minimum cold ischemia time, the presence of additional donor risk factors, and appropriate recipient matching, preferably in younger candidates without HCV.^{42,43}

The negative effect of cold ischemia time upon organ function is intuitive. Cold preservation increases anaerobic metabolism and cellular acidosis. Metabolic activity is reduced with mitochondrial energy uncoupling. Energy stores are depleted with an accumulation of hypoxanthine, a substrate for the generation of toxic, reactive oxygen species during reperfusion.¹² Reperfusion following prolonged cold ischemia in human and animal models is associated with inflammatory changes within the allograft that include sinusoidal cell damage, complement activation, small vessel hypercoagulability, and increased circulating levels of interleukin 6 (IL-6) and IL-8.^{12,82,83}

Prolonged cold ischemia time is an independent risk factor for the development of preservation injury and delayed graft function. Prolonged cold ischemia not only increases the incidence of short-term complications from allograft function but also increases the incidence of long-term biliary complications.^{9,10} The precise threshold for significant cold preservation injury varies with the individual allograft; however, general guidelines have emerged from the literature. In allografts from otherwise healthy donors who are not older than 60 years, the threshold for reduced allograft function secondary to prolonged cold ischemia lies between 14 and 16 hours. In a report of 315 LTX procedures from a European multicenter study group, Porte et al found that cold ischemia time greater than 16 hours was associated with increased PNF and reduced long-term graft survival.⁸⁴ Additional reports concur that cold ischemia times exceeding 14 to 16 hours are associated with a roughly twofold increase in complications related to allograft function.^{80,85-87} Totsuka et al correlated linear travel distance with cold ischemia time and demonstrated significantly decreased allograft function when travel distance exceeded 600 miles.⁸⁸ Hepatic allografts from older donors (age > 60 years) are much more sensitive to preservation injury and demonstrate optimal function when cold ischemia is under 8 hours.⁸⁹ Several authors have implicated a synergistic effect of prolonged cold and warm ischemia time on postoperative graft outcome.^{87,90}

Partial-liver allografts from cadaver or living donors are associated with decreased allograft function and increased recipient morbidity. Recognition that partial-liver allografts predispose to unique complications resulting from anatomic variations as well as donor and recipient physiology is prerequisite to successful application of these techniques. Technical challenges include the creation of sufficient liver volume to meet the metabolic demands of the recipient, graft positioning to optimize vascular flow and biliary drainage, and an appreciation of anatomic variations that necessitate complex biliary or vascular reconstruction. Frequent complications among partial-liver allograft recipients include parenchyma bile leak, hepatic arterial thrombosis, hepatic venous outflow obstruction, infection from

remnant necrotic tissue, and poor graft function secondary to insufficient hepatic volume.

Reduced-liver transplantation is the surgical reduction of a whole cadaver allograft to yield a single cadaver allograft of smaller size. This technique was initially reported by Bismuth⁹¹ and Broelsch⁹² as a mechanism to create allografts for children from adult cadaver donors. Early efforts were plagued by technical difficulties; however, later series demonstrated satisfactory outcomes in children.⁹³⁻⁹⁵ Although improved outcomes were achieved, the shortcomings of RLT, namely the discarding of a right hemiliver⁹⁶ and the increased competition between adult and pediatric candidates for the same donor pool,⁹⁷⁻⁹⁹ rendered the procedure impractical. Currently, RLT is rarely performed in adults. Sparse data exists on RLT outcomes because of the tremendous heterogeneity in allograft creation. Surgical reduction may be anatomic or non-anatomic resection, depending upon the necessity of the circumstances. This creates no practical way to classify or compare outcomes.

Split-liver transplantation, a procedure in which one cadaver liver is divided to provide for two recipients, has existed for over a decade.¹⁰⁰ Despite the potential for expanding the cadaver-donor pool and decreasing reliance upon living donation, SLT is seldom performed.¹⁰¹ Historically, the principal beneficiaries of SLT have been adult-pediatric recipient pairs; however, the current scarcity of cadaver organs has renewed interest in expanding these techniques to include two adult recipients for one adult cadaver donor.¹⁰²⁻¹¹³

Preliminary data from the UNOS Transplant Registry are available on SLT for adult-child pairs.^{101,114,115} A data request from the Organ Procurement and Transplant Network Liver and Intestinal Transplantation Committee was submitted to provide outcomes of SLT right lobe allografts in adults.¹⁰¹ As graft-specific coding does not exist in the database, a data search was performed for allografts classified as "partial right liver segments" that had corresponding left segments also transplanted or right "split liver segments" prepared either *ex vivo* or *in situ*. Assuming that SLT is restricted to optimal donors, partial right allograft outcomes were compared with two groups: a comparable group of whole-organ cadaver donors between 18 and 40 years of age and a surrogate EDC group consisting of cadaver whole-organ donors older than 60 years. Between 1994 and 2001, 215 SLT right allografts were identified. These included 33 partial, 42 *in situ*, and 140 *ex vivo* allografts that were compared with 2901 allografts procured from donors older than 60 years and 9802 allografts procured from donors 18 to 40 years old. Outcomes, measured by graft failure and recipient death, were stratified by medical urgency status and adjusted for body mass index, year of transplantation, cause of death, ABO blood compatibility, history of

previous liver transplantation, indication for transplantation, cold ischemic time, creatinine greater than 2 mg/dL, medical condition, and donor and recipient age, gender, and ethnicity. Graft failure and death occurred in 32% and 26% of right SLT recipients, respectively, with outcomes comparable to those for whole-organ allografts from donors older than 60 years and inferior to those for cadaver whole-organ donors 18 to 40 years old. SLT allografts demonstrated a significantly increased relative risk of graft failure and death compared with cadaver donors 18 to 40 years old. When stratified by recipient status, UNOS status I SLT recipients also demonstrated a significantly increased risk of graft failure and death compared with cadaver whole-organ donors 18 to 40 years of age. Significantly increased graft failure of SLT recipients versus cadaver donors age 18 to 40 years was observed in UNOS status IIB and III as well but did not translate into significantly increased death. SLT allograft data were comparable to those of the EDC group with overall graft failure and death not statistically different. Thus, SLT of optimal donors yielded adult allografts that functioned similarly to cadaver EDC whole organs. Individual centers have reported improved outcomes; however, no data conclusively support the performance of SLT in adults with preservation of optimum allograft function.¹⁰¹

Data are slowly emerging on SLT between two adults as these techniques have been cautiously implemented among select transplant centers. The University of Minnesota has reported the largest recent series on SLT for two adults. In 2001, Humar et al reported on 12 SLT allografts with patient and graft survival of 83% at a mean follow-up of 9 months.¹¹⁶ Ten of the 12 recipients, all of whom had nonurgent status at SLT, were alive and well. A later abstract by the same group reported nine procedures yielding 18 allografts with a mean follow-up of 18 months.¹¹⁷ Seventeen of the 18 recipients had nonurgent UNOS status and one had urgent UNOS status. Patient and graft survival was 89% for right lobe versus 78% for left lobe grafts. Biliary complications were most frequent (27%), followed by an 11% incidence of vascular complications that resulted in two deaths. There was one PNF in an unspecified graft.

Adult-to-adult LDLT should be considered EDC as outcomes do not meet expectations of optimal cadaver donors.¹¹⁸ Specifically, the incidence of technical complications is higher among aLDLT recipients, and outcomes, when applied to patients in urgent medical need of LTX, are inferior (Table 1). As this is a highly select group of recipients with relatively low MELD scores at LTX, the most frequent complication leading to aLDLT recipient mortality is allograft dysfunction. Limited application and a higher observed frequency of technical complications create a higher assumed risk for the aLDLT recipient compared with standard-criteria cadaver allografts; however, allocation of standard-

Table 1 Outcome of Living-Donor Liver Transplantation in the United States Utilizing Right Lobe

Center	Author	Year	n	Recip	Graft	Comp
New York ¹³⁸	Miller	2003	99	92%	88%	38%
Los Angeles ¹³⁹	Ghobrial	2002	20	95%	85%	39%
New York ¹⁴⁰	Fishbein	2001	50	87%	80%	32%
Denver ¹⁴¹	Bak	2001	41	93%	88%	> 34%
New York ¹⁴²	Goldstein	2001	20	75%	55%	30%
Chapel Hill ¹⁴³	Fair	2001	14	93%	78%	N/A
Memphis ¹⁴⁴	Grewal	2001	11	91%	88%	63%
Rochester ¹⁴⁵	Marcos	2000	40	88%	85%	47%
Richmond ¹⁴⁶	Marcos	1999	25	88%	88%	52%

Recip, recipient 1-year survival; Graft, graft 1-year survival; Comp, incidence of complications.

criteria allografts to potential aLDLT recipients is unlikely. Additional risk is also transferred to the donor. Adult-to-adult LDLT recipients and donors assume increased risk earlier to avoid the morbidity and mortality associated with waiting, a rationale identical to that for the utilization of EDC.¹¹⁹⁻¹²⁴

Donation after cardiac death is a rapidly expanding component of the donor pool that has received increased emphasis as part of the Health Resources Service Administration-sponsored Organ Transplant Breakthrough Collaborative.¹²⁵ DCD is a fundamentally different recovery technique based upon cardiopulmonary criteria for death rather than neurologic criteria for death. Consequently, potential donors must undergo circulatory arrest, pronouncement of death, and a period of observation to rule out spontaneous resuscitation before the procurement can begin. Unlike donor procurements based upon neurologic brain death criteria that proceed with cardiopulmonary circulation to the point of induced circulatory arrest and cold preservation, DCD allografts experience a significantly longer time frame of warm ischemic injury that begins with terminal extubation resulting in hypoxia, cardiopulmonary collapse, circulatory arrest and concludes with absent blood flow at body temperature for a period of time until the procurement can be performed and cold perfusion initiated. The potential negative effect of neurohumoral events associated with cardiopulmonary collapse upon hepatic parenchyma quality is unknown.

Cohesive single-center outcomes data in addition to UNOS Transplant Registry data¹²⁶ on hepatic allograft function procured by DCD techniques are just beginning to emerge to the point where broad recommendations on utilization are possible (Table 2). DCD should be performed by personnel with significant experience in assessment of donor allograft quality and DCD techniques. Precise definitions of the terminology, technique, incorporation of vasodilatory drugs, antioxidants, preservation solutions, and necessity for

Table 2 Incidence of Primary Nonfunction with Donation-after-Cardiac-Death Donors

Author/Reference	Date	n	PNF (%)
Muiesan ¹⁴⁷	2005	31	6.45
Foley ⁴⁶	2005	36	5.56
Manzarbeitia ¹⁴⁸	2004	19	5
Abt ⁴⁷	2004	144	11.8
Otero ¹⁴⁹	2003	20	25
Fukumori ¹⁵⁰	2003	25	NR
D'Alessandro ¹⁵¹	2000	19	10.5
Reich ¹⁵²	2000	8	0
Casavilla ¹⁵³	1995	12	17

PNF, primary nonfunction.

anticoagulation in DCD have not been standardized.¹²⁶ Available data indicate that the time from terminal extubation to initiation of cold preservation is optimally under 30 minutes¹²⁶ and the incidence of biliary complications increases significantly with extended warm ischemic times.¹²⁷ Every effort should be made to limit cold ischemia to less than 8 hours if possible.¹²⁶ Furthermore, the upper age limit for optimal outcomes utilizing current preservation technology is probably in the sixth decade. Even under these circumstances, detailed interpretation of the donor hospitalization and expert assessment of allograft quality by the procurement physician are essential. Physiologic, functional, and procurement insults typically of trivial significance during procurement of neurologic-death cadavers assume much greater significance in attempting to predict the outcome of hepatic allografts procured by DCD.

DONOR-TRANSMITTED DISEASE

Donors with an increased risk of disease transmission include those with positive serologic data (HCV, hepatitis B virus [HBV], human T cell lymphotropic virus [HTLV I/II], carcinoma outside the liver, and Centers for Disease Control [CDC] high-risk behavior). Guidelines on utilization of these EDC allografts and post-transplantation screening for donor-disease transmission have not been established.

The utilization of HCV (+) allografts for HCV (-) recipients or HCV (+) recipients with an undetectable viral load should be reserved for extreme necessity. In contrast, utilization of HCV (+) allografts among HCV (+) recipients who are active viral replicators of genotype 1 or 4 should be encouraged and, in the current era of donor scarcity, these situations should not be considered EDC. Current data clearly indicate no difference in HCV recurrence graft, or patient survival with utilization of HCV (+) allografts.¹²⁸⁻¹³¹ Recent data from our center evaluating 125 HCV-positive recipients of HCV (+) EDC allografts showed that histologic HCV recurrence was not significantly differ-

ent from that of recipients of a MELD-allocated or living-donor HCV (-) allograft. Furthermore, histologic recurrence did not correlate with survival within either group. Our current practice includes genotype and monitoring viral load among all HCV (+) LTX candidates with routine allocation of HCV (+) allografts to HCV genotype 1 or 4 candidates with active viral replication.²⁰

Liver transplantation is a highly efficient mechanism for transmission of HBV from an HBV-core antibody donor¹³²; however, HBV immune globulin and lamivudine (Epivir, GlaxoSmithKline, Middlesex, England) provide effective prophylaxis for advocating HBV-core antibody allografts to naïve candidates.¹³³⁻¹³⁷ In a study of over 350 LTX recipients, Saab et al reviewed HBV viral recurrence when utilizing dual prophylaxis, single prophylaxis, and no prophylaxis.¹³¹ Dual prophylaxis significantly lowered HBV recurrence with an observed 1- and 3-year recurrence incidence of 5% and 8%, respectively. In light of excellent antiviral therapy, we advocate HBV-core antibody allografts across the entire spectrum of recipients. Substantial data exist demonstrating effective long-term prophylaxis against HBV activation with lamivudine.

HTLV I/II (+) allografts are usable for select recipients. Angelis et al reported UNOS data for nine LTX recipients indicating no HTLV I/II-related disease with a median follow-up of 11.9 months.¹⁵ Donor serology positive for HTLV I/II should be confirmed by Western blot analysis. The authors' experience includes transplantation from five HTLV I/II donors: three represented false positives, one true positive was allocated to an HIV/HCV recipient who expired at 12 months from recurrent HCV, and one HIV/HBV-coinfected recipient is healthy 18 months after LTX.

Recipients of an allograft with an increased risk of donor-transmitted disease should receive additional screening after LTX. CDC high-risk allograft recipients should be tested at an appropriate time for HBV, HCV, HTLV, and human immunodeficiency virus (HIV). HBV core antibody-positive allograft recipients should be treated indefinitely with lamivudine; however, no specific screening for recipients of HCV or HBV core antibody donors is clinically indicated in the presence of normal liver function. Lastly, recipients of an allograft from a donor with a history of extrahepatic carcinoma do not receive specific screening unless clinically indicated.

CONSENT

Participation in EDC allocation should be voluntary for all individuals listed for LTX. Upon completion of a standard evaluation to determine candidacy and listing for LTX, recipient candidates typically receive a separate surgical consultation to discuss EDC utilization, including living donation. This should be supported by a

specific consent that documents patients' understanding of the risks and benefits of participation.^{2,20,28}

At our center, EDC candidates are reviewed weekly during a multidisciplinary conference to discuss each individual and that person's immediate need for LTX. Candidates are advocated and prioritized by their clinical condition. When a cadaver EDC organ becomes available, the candidate is given specific donor information as well as pertinent literature detailing the risk assumed prior to surgical consent. A copy of the information provided is retained in the medical record and the category of EDC detailed in the operative note.

CONCLUSIONS

The increasing discrepancy between organ supply and demand resulting from the successful application of LTX has motivated select centers in areas of particular scarcity to adopt strategies for the utilization of these organs with overall satisfactory results. As organ scarcity intensifies, there will be further emphasis on expanding donor criteria. Guidelines defining this category of donor, level of acceptable risk, principles of consent, and post-transplantation surveillance have not been defined.

Incumbent upon expansion of the donor pool is the establishment of guidelines that distinguish standard- from extended-donor criteria. To date, this has not been achieved. Although predictors of early graft dysfunction from cadaver donors have been identified, there has not been an emergence of well-defined guidelines to distinguish extended-criteria from standard-criteria donors. Current opinion defines extended-donor criteria on the basis of assessment of the risk incurred by the recipient. Utilizing such an approach, increased risk incurred by a recipient could include a recognized higher risk of early graft failure or delayed graft function; alternatively, the recipient may be assuming an added risk of known or potential donor-transmitted disease. Although all cadaver organ recipients assume a theoretical risk associated with the process of organ transplantation, the transplantation of an allograft with positive serologic analysis or an extrahepatic carcinoma significantly elevates the risk profile.

Accepting potentially increased risk must be accompanied by a process of informed consent that specifically addresses the concerns of the patient with respect to the particular donor as well as the transplant procedure. Informed consent must be based upon estimates in this newly emerging category of organ and aggregate historical data provided to the candidate.

Inclusion of aLDLT as an EDC allograft is supported through data on allocation, probability of a complication, and risk associated with immediate graft function. Living-donor allocation occurs at the transplant center and is ideal among candidates who do not

suffer from acute decompensation of chronic liver disease or fulminant hepatic failure. Outcome data on the application of aLDLT in the setting of advanced liver failure do not equal outcome data from cadaver whole-organ transplantation. In addition, the incidence of technical complications is higher among aLDLT recipients. These factors contribute to a higher assumed risk for the aLDLT recipient when compared with the expectations of LTX utilizing standard-criteria, whole-organ cadaver allografts; however, allocation of a standard-criteria cadaver whole organ is unlikely. Therefore, the clinical paradox that motivates patients to participate in EDC is identical for aLDLT as patients assume an earlier increased risk to avoid the morbidity and mortality associated with waiting. Because most families do not have a living donor, participation in cadaver EDC is the only option to avoid wait-list morbidity and potential mortality. The difference is that cadaver EDC recipients assume the additional risk whereas in aLDLT that risk is transferred to the donor.

The deployment of surgeons experienced in medical resuscitation, assessment, and efficient donor recovery utilizing advanced techniques such as thoracic aorta cannulation, SLT, or DCD is central to successful application of EDC. Experienced recovery teams rarely require a biopsy to determine utilization and facilitate timing of the recipient operation to coincide with arrival of the allograft as to minimize cold ischemia time.

The routine implementation of an EDC program for liver transplantation significantly increases transplant center volume and patients' access to transplantation. Aggressive EDC utilization significantly lowers median wait time for transplantation, MELD score at transplantation, and wait-list deaths in areas of extreme donor scarcity. Fundamental to further progress in the utilization of EDC allografts is prospective, multicenter data collection to define clearly the risk, mechanism of consent, and recognized guidelines for standard- and extended-criteria donors. Such data could broaden the existing cadaver-donor pool by encouraging the utilization of donors that are currently deemed unsuitable for transplantation.

ABBREVIATIONS

aLDLT	adult-to-adult living-donor liver transplantation
CDC	Centers for Disease Control
DCD	donation after cardiac death
EDC	extended-donor criteria
HBV	hepatitis B virus
HCV	hepatitis C virus
HTLV	human T cell lymphotropic virus
IL-6	interleukin 6
LTX	liver transplantation
MELD	model for end-stage liver disease

PNF	primary nonfunction
RLT	reduced-liver transplantation
SLT	split-liver transplantation
UNOS	United Network for Organ Sharing

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