Review Article

Liver transplant donation

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Abstract: Orthotopic liver transplantation provides definitive management of end-stage liver disease. While short and long-term outcomes for graft survival and patient survival are excellent, a limiting factor has been persistent mismatch of the number of available donors to the number of recipients in need of organs. Strategies to address these donor short falls include: utilization of living related donors, split liver transplantation, donation by cardiac death, hepatitis serology positive donors, and marginal liver donors. With careful recipient selection, the overall outcomes do not appear to differ between the use of standard neurologic death donors and these extended criteria donors. As indications for liver transplantation continue to expand, innovative strategies to increase the donor pool are necessary to mitigate patient mortality while on liver transplant wait lists and morbidity of end-stage liver disease.

Keywords: Liver transplantation; extended criteria donor; neurological death donors (NDD); donation after cardiac death (DCD); living related donors (LRD)

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Introduction

Liver transplantation has become the standard of care for end-stage liver disease in patients who qualify for such a procedure (1,2). Since its introduction in the 1960's, improvements in surgical technique, organ procurement/preservation, and immunosuppression have resulted in recipient survival rates exceeding 85% and 70% at 1-year and 5-year post-transplantation, respectively (1,3). Although the procedure is resource-intensive, long-term costs are similar to that of recurrent hospitalization for decompensated cirrhosis and chronic medical therapies to manage end-stage liver disease (1,3). Inadequate supply of donor livers remains a perplexing issue in liver transplantation, with potential recipients exceeding the pool of eligible donors world-wide (1,2). In the United States, there were 11,352 new patients awaiting liver transplantation and only 6,291 patients who underwent transplantation in 2010 (1). As a result, living related donors (LRDs), expanded criteria cadaveric donors, and split liver donation have been introduced to address this shortage of organ donors.

Neurological death donors (NDD)

The concept of brain death was first introduced in 1968 and led to the harvest of organs in donor patients who were neurologically deceased but with preserved cardiorespiratory function (1). The United Network for Organ Sharing (UNOS) provides criteria in evaluating potential donors by local Organ Procurement Organizations (4). NDD must meet criteria for brain death, consent to organ donation by next of kin, and are ideally young, otherwise healthy individuals who have suffered irreversible cerebral insult (4). Contraindications exist for NDD organ procurement such as: extracranial malignancy (except for basal or squamous cell cancer of the skin), overwhelming sepsis, hepatic cirrhosis, or hepatic macrosteatosis greater than 60%/microsteatosis greater than 30% (4). In practice, advanced donor age is also a contraindication to deceased organ donation with several transplant centers declining a donor with age greater than 70 years as unsuitable for organ donation (4). The typical work-up for these donors

includes: (I) assessment of compatibility for a potential recipient such as ABO blood typing, height, weight; (II) evaluation of organ health via basic blood work to include liver function studies, possible ultrasound and/or biopsy of the liver; (III) testing for transmissible diseases by way of blood/urine cultures, viral hepatitis screen, venereal disease screen, cytomegalovirus screen, and nucleic acid testing for human immune deficiency virus (4). NDD livers comprise approximately 95% of all livers used for transplantation in the United States (4,5).

LRDs

In certain countries, there are cultural barriers that preclude cadaveric organ donation for which living related organ donation remains the only acceptable procedure (6). For instance, Japan has performed thousands of LRD liver transplantations as a result of their paucity of cadaveric donors (6). Their technical expertise and success in this field have resulted in healthy donors undergoing donor hepatectomy with acceptably low rates of peri-operative morbidity and mortality at 10% and 0.5%, respectively (6).

A shortage of cadaveric donors is a world-wide issue with 10–20% of patients on liver transplant wait lists who die before receiving a graft (3). As a result of these initial successes with LRD liver transplantation, there are increasing centers that have adopted this technique to addresses disparities in supply of cadaveric organs and demand from patients awaiting liver transplantation (3,6). Evaluation of potential donors is extensive and includes medical, psychosocial, and anatomic assessment for suitability (3,6). Donors must accept the potential risks of surgery without coercion and in certain European countries, LRD must be first-degree relatives of the potential recipient as a precaution against commercial transplantation (3,6). With this said, only 15–20% of potential LRD are deemed suitable candidates as ABO blood group incompatibility, major anatomical variations, psychosocial history, uncovered medical comorbidity prohibiting safe donor hepatectomy, obesity, hepatic steatosis, or excessive alcohol intake precluding LRD organ donation (3,6).

LRD liver transplantation necessitates split liver donation from the donor to the recipient. In pediatric recipients, the left lateral section (segments 2–3) is generally donated by the LRD, whereas in adult recipients, a formal left lobe (segments 2–4) or right lobe (segments 5–8) are donated by the LRD (3). LRD liver transplantation is appealing as it allows for optimization of the health of the recipient, shortens wait time and progression of liver disease, potentially avoids mortality while awaiting a cadaveric graft, and shortens cold ischemia time of the liver graft (3,4). While there has been growing interest in harvesting LRD hepatectomy laparoscopically, the risk to an otherwise healthy LRD cannot be overstated (3,7). The magnitude of donor risk is highly dependent on extent of hepatic resection with formal hepatic lobectomies conferring greater risks than left lateral section resections (8). In the literature, post-operative donor mortality rates range from 0.1–1% with morbidity rates of 15–30% (3,8).

LRD liver transplantation from adult donor to pediatric recipient has become well-accepted and standardized in centers that offer pediatric liver transplantation (3,9). For pediatric patients, an additional advantage of LRD transplant is expansion of the donor pool given relatively low pediatric organ donors (9). LRD harvest of the liver is generally performed via left lateral section hepatectomy from the donor and implanted to the pediatric recipient (9). In a single institution case series of 50 patients at King's College, recipient and graft survival was 98% at 1 year and at 5 years, recipient survival was 96% and graft survival was 93% (9). Recipient complications included hepatic artery thrombosis at 6%, portal vein thrombosis at 4%, and biliary complications at 14% (9). Donor peri-operative mortality was 0% and major morbidity from bleeding requiring re-operation was 2% (9).

Over the past decade, there has been a trend towards improved graft survival with LRD liver transplantation (10). Peri-operative complications for LRD recipients include biliary (cholestasis 7%, bile leak/biloma 6%, biliary strictures at 1%) and vascular (hepatic artery/portal vein thrombosis 2–6%) complications, the vast majority of which are managed conservatively or radiologically without need for re-operation (3). Long-term outcomes from European centers suggest a 75% graft survival rate at 3 years (3). In Japan, 5-year graft survival rates are 70% for adult recipients (3).

A recent study examined 10-year outcomes of 1,427 liver recipients undergoing deceased and LRD liver transplants between 1998–2014 at 12 North American Centers (11). Patient survival at 10 years was 70% for LRD transplant and 64% for deceased donor liver transplant (11). As recipients of LRD transplant had lower model for end-stage liver disease (MELD) score and were less likely to be receiving grafts while being a hospital inpatient, admitted to intensive care unit (ICU), dialysis-dependent, or ventilator-dependent, an adjusted analysis of 10-year survival between LRD and

deceased donor liver transplant recipients demonstrated no significant differences with a hazard ratio of 0.98 (11). As a result of LRD transplant recipients being healthier than deceased donor transplant recipients, LRD transplant recipients spent fewer days in the ICU than deceased donor transplant recipients (11). Predictors of long-term outcome were evaluated: recipient female sex and primary sclerosing cholangitis were associated with improved long-term survival whereas dialysis, recipient age >55 years, and donor age >50 years was associated with worse long-term survival (11). Predictors of long-term graft failure were evaluated as well: autoimmune hepatitis and primary sclerosing cholangitis were protective whereas hepatocellular carcinoma, recipient dialysis at time of transplant, recipient age >55 years, donor age >50 years, and high MELD score were harmful (11). The question of LRD donor age is controversial, though, as a prospective case series from Toronto General Hospital did not demonstrate any differences in recipient or donor outcomes with right lobe LRD liver transplant when comparing donors greater than 50 years old versus donors less than 50 years old (12). There are no long-term differences in patient or graft survival depending on right versus left LRD liver transplant (11), which has also been demonstrated in a prospective case series comparing right versus left LRD liver transplant from Columbia University Medical Center (13).

Extended criteria cadaveric donors

Adult to adult LRD liver transplants place otherwise healthy donors at risk for serious complications and death (3,6). Moreover, the majority of donors who are evaluated are eventually deemed unsuitable for donor hepatectomy after a resource and time intensive work-up (3,6). Thus, while LRD transplantation in the adult population exists, the reality is that it has not significantly contributed to the overall pool of potential liver donors in western nations (5). Extended criteria cadaveric donors were introduced to further address donor organ shortages for potential liver transplant recipients.

Donation after cardiac death (DCD) donors were introduced in patients with severe neurologic injury without chance of meaningful recovery who did not meet strict criteria of brain death (14). Evaluation of DCD donors proceeds similarly to NDD donors and controlled withdrawal of life support is performed in the operating theater until patient death is declared by a clinician who is not a part of the procurement or transplant team (15). An additional waiting period of up to 5 minutes is then observed following cardiorespiratory death for which organ retrieval is performed (15).

There has been steady increase in the use of DCD livers in the United States over the past decade (5). Outcomes of DCD liver transplant recipients have been compared with NDD liver transplant recipients (2,16,17). Notably, recipient survival is lower in the DCD versus NDD liver transplant recipients: at 1 year, DCD survival was 84% compared to NDD survival at 91%; at 5 years, DCD survival was 68% versus NDD survival at 81%; at 10 years, DCD survival was 54% versus NDD survival at 67% (2). Graft survival is also lower in the DCD versus NDD liver transplant recipients: at 1 year, DCD graft survival ranges from 69–71% versus NDD graft survival at 80–86% (2,16). At 3 years, DCD graft survival was 60–61% versus NDD graft survival at 72–75% (5,16). At 5 years, DCD graft survival was 56% versus NDD graft survival at 76%; at 10 years, DCD graft survival was 43% versus NDD graft survival at 60% (2).

Biliary complications, particularly ischemic cholangiopathy, have been implicated as the primary reason behind these poorer outcomes in DCD versus NDD liver transplants (2,16,17). Risk of ischemic cholangiopathy in DCD recipients was 13–34% versus 1% in NDD recipients (2,17). Predictors of developing ischemic cholangiopathy following DCD liver transplant include: longer cold ischemic time (greater than 8–9 hours), older donor age (greater than 40–50 years), and donor weight >100 kg (2,17). Indeed, when defining low-risk DCD livers by warm ischemia time <30 minutes and cold ischemia time <10 hours, graft survival rates do not significantly differ between DCD and NDD allografts: graft survival at 1 year for DCD is 81% versus NDD at 80% and at 3 years for DCD is 67% versus NDD at 72% (16). Recipient risk factors have been implicated in predicting graft failure which include: recipient age >60 years, hospital inpatient or ICU status at time of transplant, previous liver transplant, and dialysis dependence or renal dysfunction (16). Thus, comparable outcomes to that of NDD liver transplants may be achieved in DCD liver transplants depending upon careful selection of both donor and recipient.

Deceased donors with transmissible viral diseases such as Hepatitis C (HCV), Hepatitis B (HBV), and human immune-deficiency virus (HIV) may also be considered extended criteria donors. Approximately 43% of patients awaiting liver transplantation in the United States are HCV positive and the use of HCV positive donors addresses donor shortages (18). For HCV positive liver transplant recipients,

there are no differences in 1-year and 5-year patient or graft survival when comparing HCV positive donors versus HCV negative donors (19,20). Recent utilization of direct-acting antivirals against HCV, such as sofosbuvir and simeprevir, have improved sustained virologic response in the treatment of HCV infection, which has more than doubled the use of HCV-positive donors to HCV-positive recipients from 7% in 2010 to 17% in 2015 (18). Use of HBV-positive donors may also be considered in certain circumstances: HBV core antibody positive donor livers may be offered to HBV surface antigen positive recipients although recipients who lack HBV antibodies may receive such livers provided they receive effective prophylaxis with HBV vaccination, immunoglobulin, and/or oral antiviral agents such as lamivudine (21,22). It is also possible to transplant HIV positive donor livers to HIV positive recipients without reported risk of super-infection or resistance (23).

Overall outcomes of extended criteria cadaveric donors have been evaluated in numerous studies (24-27). The definitions of these extended criteria among studies is variable but generally includes factors thought to adversely affect liver transplant outcomes such as: advanced donor age, moderate-severe hepatic steatosis, hypernatremia, hemodynamic instability, and prolonged cold ischemia time (24,26). In one single-center American study, extended criteria donors were defined as: age ≥60 years, body mass index ≥35 kg/m^2, serum sodium ≥170 mEq/L, total bilirubin ≥2.0 mg/dL, maximum aspartate amino transferase ≥500 units/L, maximum alanine amino transferase ≥500 units/L, HBV/HCV positive serology, DCD donor, cold ischemia time >12 hours, more than two vasopressors at any time, ICU stay >5 days, alcohol use >30 g/day for more than 10 years, current central nervous system tumor, current meningitis, any history of non-skin cancer, and/or liver trauma > grade I injury (24). Patient and graft survival between standard donors versus extended criteria donors did not differ significantly at 90 days (patient survival 93% versus 90%, graft survival 91% versus 88%), 1 year (patient survival 87% versus 82%, graft survival 84% versus 80%), and 2 years (patient survival 83% versus 79%, graft survival 78% versus 77%) (24).

Another single-center study from Europe has corroborated findings that extended criteria donors have similar recipient and graft survival (25). Extended criteria donors were rejected by other transplant center and transplanted into appropriate recipients for the following reasons: HCV/HBV positive serology, hepatic steatosis ≥30%, neoplastic risk, infective risk, advanced age, current drug use, obesity, factor XI deficiency, or a combination of these causes (25). There were no significant differences between patient or graft survival at 1, 3, and 5 years when comparing recipients of standard donors versus extended criteria donors who were rejected by other transplant centers (25).

The concept of "marginal livers" has evolved from extended criteria donors (26). In a single-center study from New York of more than 2,000 liver transplants, marginal livers were defined as: discarded livers by other transplant centers, donor age >70 years, HCV-positive donor, split liver, cold ischemia time >12 hours, DCD livers, macrosteatosis >30%, or a combination of these factors (26). Recipients of marginal livers tended to have less risk factors than recipients of standard livers such as: lower MELD scores (16 versus 21) hepatocellular carcinoma (27% versus 21%), current ICU admission at time of transplant (9% versus 22%), and dialysis dependence (5% versus 15%) (26). There were no significant differences in patient or graft survival when comparing 5-year outcomes between recipients of marginal versus standard livers (26). Moreover, when this center compared survival outcomes with the national average, there was significantly improved 5-year survival despite an aggressive policy of marginal liver utilization (26). In addressing the impact of using marginal livers on donor organ supply and recipient need disparities, there was significantly decreased waitlist deaths at this center compared to the national average (26).

Split-liver transplantation

Split-liver transplantation has been previously discussed with LRD liver transplantation where a portion of the live donor liver is passed onto the recipient. Liver splitting is feasible due to the inherent ability of healthy liver to regenerate and hypertrophy (8). Generally, a right trisectionectomy (segments 4–8 with caudate) is given to an adult recipient while a left lateral sectionectomy (segments 2–3) is given to a pediatric patient (28-30). Occasionally, a formal right lobe hepatectomy (segments 5–8) and left lobe hepatectomy (segments 2–4 with caudate) are split for two adult recipients or one adult recipient and one larger pediatric recipient (30). When specifically evaluating left graft recipients, the overall patient survival is 91% at 1 year, 90% at 5 years, and 89% at 10 years and graft survival is 90% at 1 year, 87% at 5 years, and 86% at 10 years (30). Overall patient survival for right graft recipients is 87% at 1

year, 82% at 5 years, and 81% at 10 years and overall graft survival is 82% at 1 year, 81% at 5 years, and 79% at 10 years (30). Peri-operative outcomes suggest a primary non-function rate of 1%, hepatic artery thrombosis rate of 7–8%, portal vein complication rate (stenosis or thrombosis) of 3–4%, and biliary complication rate (bile leak or stricture) of 21% (30). Given the potential to optimize the use of a single cadaveric liver for more than one recipient, the American Society of Transplant Surgeons has proposed policies for donor and recipient criteria for split liver transplantation (28).

Conclusions

Liver transplantation has evolved into the standard of care for definitive management of end stage liver disease. Short and long-term outcomes are excellent and as result of these successes, the available pool of standard cadaveric donors is far exceeded by the number of recipients in need of such livers. Innovative strategies exist to address these donor short falls, such as increasing utilization of: LRDs, split liver transplantation, donation by cardiac death, hepatitis serology positive donors, and marginal liver donors. Overall outcomes do not appear to differ between the use of standard neurologic death donors and these other types of donors; however, careful selection of recipients who are healthier than those receiving standard livers may explain such findings. With this said, the indications for liver transplantation continue to expand without parallel increases in the standard pool, necessitating the use of other donors to mitigate patient mortality while on liver transplant wait lists and morbidity of end stage liver disease.

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