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The use of marginal grafts in liver transplantation

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Abstract
Because of the shortage of organ supplies, more transplant programs have begun to use marginal grafts in liver transplantation. A number of single-center experiences with marginal grafts have yielded encouraging results, but recent analyses using nationwide databases show that outcomes are inferior to results with normal whole-liver grafts. Use of marginal grafts is still acceptable, however, and plays an important role in expanding the donor pool and decreasing mortality on the waiting list. In the broadest terms, national data and single-center experiences show that: (1) there is no limit in donor age for liver transplantation, (2) appropriate selection of steatotic livers improves outcomes, (3) prolonged graft ischemia is a preventable factor, (4) livers from donors with hepatitis B or C virus can be safely transplanted, and (5) adequate prophylaxis prevents recurrence of hepatitis B without significant graft loss. In addition, grafts procured after cardiac death are another growing source of marginal grafts. Transmission of malignancy from donors is rare but life-threatening. Reduced-size grafts from living-donor or split-liver transplantation have shown similar outcomes to whole-liver transplantation. In this review, we will discuss the current status of the utility of these marginal grafts in liver transplantation.

Key words Liver transplantation · Marginal grafts · Extended-criteria donors

Introduction

Critical to the evolution of liver transplantation into the standard of care for end-stage liver diseases has been

the optimization of patient selection, surgical techniques, immunosuppression, and patient management.[1] Despite these advances, the shortage of donor organs continues to be a major obstacle to providing this life-saving procedure to all who need it. According to data from the United Network for Organ Sharing (UNOS), 6650 liver transplants were performed in the United States in 2006, but more than 17 000 patients were on the waiting list.[2]

Faced with this severe organ shortage, many transplant centers are selectively accepting livers from so-called extended-criteria donors or marginal donors.[3] Yet while the use of marginal grafts helps to increase the donor pool and decrease waiting list mortality,[4] the quality of these livers is suboptimal, and recipients may face higher risks of graft dysfunction or nonfunction.[3] In this article, we will review the use of marginal grafts in liver transplantation.

Donor age

Advanced age was once considered a contraindication to liver donation because it was feared to increase the risk of poor graft function.[5] In fact, however, the outcome of transplantation using aged donors without any other risk factors has been shown to be similar to that of using younger donors.[6,7] Accordingly, UNOS data show that the upper age limit for liver donation has increased over the past decade (Fig. 1). In 1996, 25% of all transplanted livers ($n = 1024$) were from cadaveric donors aged more than 50 years. Ten years later, in 2006, cadaveric liver donors aged more than 50 years accounted for 34% ($n = 2397$). A similar trend is observed in cadaveric donors aged more than 65 years: 6% in 1996 vs 10% in 2006.[2]

Whereas advanced donor age is not by itself a contraindication, careful assessment must be made on a case-by-case basis. Older livers tend to be smaller and
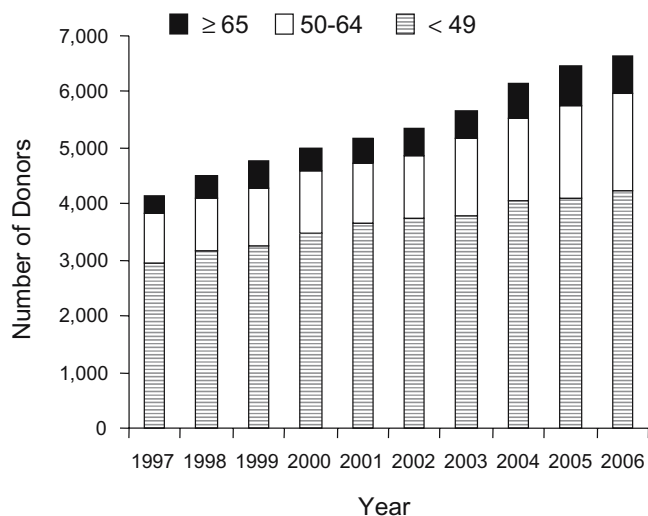
Fig. 1. Changes in the number of donors for liver transplantation in the United States. The total number of donors aged greater than 50 years has been steadily increasing over the past decade. A similar trend is observed in donors aged greater than 65 years

more fibrotic than younger livers, but these morphologic changes might not impair functional hepatic capacity. Possible explanations of the relatively good results with aged livers include great functional reserve, regenerative capacity, and dual blood supply, which far exceeds their metabolic needs.[8,9]

However, older donors in general have a higher incidence of severe atherosclerosis and fatty infiltration in the liver. Careful attention should be paid to the possible effects of atherosclerosis on arterial vessels. Calcified plaques on the hepatic artery might result in severe complications.[7] In addition, the combination of older donor age and moderate to severe steatosis adversely impacts early allograft survival.[10] Transmission of malignancy is another consideration with aged donors because of the higher incidence of unrecognized malignancies in the elderly.

Advanced donor age may also be associated with early severe recurrent liver disease in hepatitis C virus (HCV)-positive (HCV+) recipients.[11,12] In a review of UNOS data from 1994 to 2002, Russo et al.[11] found that 1-year graft survival in HCV+ recipients was 84% when donors were less than 40 years old, vs 73% when donors were aged 60 years or more ($P = 0.003$). Rayhill et al.[12] reported that donor age more than 60 years put recipients at high risk for deleterious histologic outcomes and graft failure due to early, aggressive disease recurrence. Because chronic HCV infection is the most common indication for liver transplantation and recurrent HCV infection is a major problem after transplantation, donor age should be used to guide clinical decisions for HCV+ recipients.

Finally, older donors also have a higher prevalence of long-standing medical conditions such as hypertension and diabetes mellitus, but while these diseases impair kidney transplant outcomes,[13] liver transplant outcomes are not affected.[14]

In summary, when other risk factors are controlled for, the risk of death due to age is reduced in well-selected recipients. Age per se should not be used to limit liver transplantation.

Steatosis

The prevalence of steatosis in liver donors ranges from 13% to 26%,[15] with two histologic patterns of fatty infiltration typically observed: microvesicular steatosis, in which the cytoplasm contains diffuse small-droplet vacuolization, and macrovesicular steatosis, in which large vacuole deposits displace the nuclei. The outcome of transplantation is not affected by microsteatosis in the donor liver, regardless of the severity.[16,17] In addition, grafts with mild macrosteatosis (<30%) can be safely used, because these livers show similar results to nonsteatotic grafts.[18] Donor livers with severe macrosteatosis (>60% of hepatocytes have large fat deposits within the cytoplasm) do have a significant risk of graft failure and should not be used for transplantation. The use of grafts with moderate steatosis (>30% and <60%) is controversial, because these may impose a relative risk on posttransplant outcomes. Previous reports have shown an increased incidence of primary nonfunction (PNF) after liver transplantation from donors with moderate steatosis compared with nonsteatotic livers (13% vs 3%).[19] The use of grafts with moderate steatosis should be considered in conjunction with other donor and recipient factors.

The mechanisms of poor graft function in steatotic livers have been investigated. There is a general consensus that steatosis compromises hepatic microcirculation. Fat accumulation in the hepatocytes is associated with an increase in cell volume that reduces the size of the hepatic sinusoidal space by 50% compared with normal livers; this effect may partially or completely obstruct the hepatic sinusoidal space.[20] As a result of impaired hepatic microcirculation, steatotic livers have reduced tolerance against ischemia-reperfusion (I/R) injury.

Prolonged ischemia

Prolonged ischemia remains one of the major causes of early graft dysfunction, with clear evidence that preservation times affect the incidence of PNF in liver transplantation, as well as overall outcomes. Prolonged cold ischemic time (CIT) increases the risk of PNF and is an

independent risk factor for hepatic I/R injury.[21,22] Prolonged ischemia is also a risk factor for intrahepatic biliary stricture.[23,24] In addition, Wiesner et al.[25] reported that livers preserved for more than 15 h were more likely to have early rejection. Furthermore, donor brain death per se can promote organ injury that alters the immunological and inflammatory status of the graft, leading to increased sensitivity to I/R injury and consequently to an increased rate of PNF and acute rejection.[26,27]

The vulnerability of individual grafts to CIT varies, however. Total ischemic times of less than 12 to 16 h are well tolerated by donor livers without any risk factors, but not by marginal grafts. In the modern era of liver preservation with University of Wisconsin solution,[28] the incidence of I/R injury and PNF is quite low if recipients are transplanted with nonmarginal grafts. In marginal grafts, however, with such risk factors as steatosis, donor age more than 50 years, donation after cardiac death (DCD) donor, and reduced size, it is essential that CIT be minimized.

Hepatitis B and C infection

Donor seropositivity for hepatitis B virus (HBV) or HCV had long been considered a contraindication to liver transplantation. In an early study, researchers in Pittsburgh reported that no HBV-naive recipient who received allografts from a donor positive only for hepatitis B surface antibody (anti-HBsAb+) developed HBV infection after liver transplantation, while 72% of HBV-naive recipients of a hepatic allograft from a hepatitis B core antibody-positive (anti-HBcAb+) donor developed HBV infection. In contrast, in recipients positive for anti-HBsAb, this incidence decreased to 13%.[29] In that report, recipients had no prophylaxis, which is now given routinely to prevent HBV infection after liver transplantation. Prieto et al.[30] also reported that posttransplant HBV infection developed in 15 of 30 recipients of livers from anti-HBcAb+ donors, compared with 3 of 181 (2%) livers from anti-HBcAb-donors ($P < 0.001$). Recipients of livers from anti-HBc+ donors are at high risk for acquiring HBV infection, whereas recipients of livers from anti-HBs+ donors are significantly less likely to acquire HBV infection.

Combined prophylaxis with hepatitis B immune globulin and lamivudine has proved effective not only against HBV recurrence but also against de-novo HBV infection or transmission in recipients of anti-HBcAb+ livers.[31–37] Nery et al.[36] reported that of 62 recipients of anti-HBc+ livers, 60 were serologically free of HBV infection under combined or lamivudine monotherapy at a mean follow-up of 23.5 months.

It is quite reasonable that anti-HBcAb+ organs be allocated to patients with HBV-related liver diseases, because these organs do not affect graft or patient survival in recipients with HBV-related cirrhosis. Saab et al.[38] reported that patient and graft survival at 5 years after liver transplantation was similar between anti-HBcAb+ grafts (73% and 71%) and anti-HBcAb- grafts (81% and 75%). On the other hand, many transplant programs have accepted anti-HBc+ donors for HBV-naive recipients because of organ shortage.[39]

The effect of HCV+ grafts has also been well studied. In HCV+ recipients, no effect has been observed on either patient or graft survival. In an interesting report by Marroquin et al.,[40] UNOS data showed patient survival at 2 years to be significantly higher in HCV+ recipients of HCV+ grafts ($n = 96$) than in HCV+ recipients of HCV− grafts ($n = 2827$) (90% vs 77%; $P = 0.01$). In contrast, in a high-volume series of patients with HCV-related liver disease from a single institution, there was no significant patient survival difference between the 59 patients who received HCV+ grafts and the 419 who received HCV− grafts.[41]

Khapra et al.[42] evaluated the clinical outcome and impact of histological features in HCV+ recipients of HCV+ livers and found no significant difference in survival between recipients of HCV+ livers ($n = 39$) and HCV− livers ($n = 580$). Importantly, however, recipients of HCV+ livers from older donors (age ≥ 50 years) had higher rates of graft failure (hazard ratio, 2.74) and death (hazard ratio, 2.63) compared to recipients receiving HCV− livers from the same age group. Further, recipients of HCV+ livers had more severe fibrosis after liver transplantation than recipients of HCV− livers ($P = 0.008$). More advanced fibrosis was observed in HCV+ grafts from older donors compared to HCV+ grafts from younger donors ($P = 0.012$).

Saab et al.[38] recently reported on 22 patients transplanted with livers positive for both anti-HBc and HCV. Patient survival was 91%, 81%, and 74% at 1, 3, and 5 years, respectively. There were no significant differences in patient and graft survival when comparing patients with HBV or HCV-related cirrhosis transplanted with anti-HBc+ or HCV+ livers.

Donation after cardiac death (DCD)

Recently, a number of transplant programs have begun to use livers from DCD, or nonheart-beating donors (Fig. 2).[2] DCD can be divided into two categories; uncontrolled and controlled donation. In uncontrolled DCD donors, death has occurred without life-support equipment in place. Because of prolonged warm ischemia before cold perfusion, the organs suffer severe ischemic insult. Liver transplantation using uncontrolled
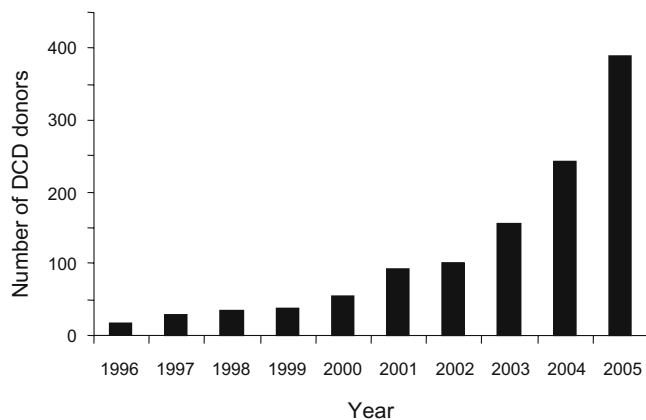
Fig. 2. Changes in the number of donation after cardiac death (DCD) donors for liver transplantation in the United States. The number of DCD donors has been steadily increasing over the past decade

DCD donors has resulted in inferior outcomes. In an early study from Pittsburgh in 1995, three of six allografts from uncontrolled DCD donors did not function and 1-year graft survival was 17%.[43] Otero et al.[44] reported that the incidence of PNF was 25% in uncontrolled DCD donors ($n = 20$), with graft and patient survivals of 55% and 80%, respectively.

In contrast, in controlled DCD donors, life-support is carefully withdrawn in the operating room, when donor surgeons are available, with minimal hypotension and warm ischemia. In these circumstances, the outcomes of liver transplantation are acceptable. In the report from Pittsburgh, although 1-year graft and patient survival was 50% ($n = 6$), there was no incidence of PNF.[43] D'Alessandro et al.[45] reported that the rate of PNF was 10.5% in controlled DCD donors. Graft survival in recipients from DCD donors was lower than that from donation after brain death (DBD; 53.8% vs 80.9%; $P = 0.007$) despite no difference being seen in patient survival.[45] In a series of eight controlled DCD cases, Reich et al.[46] had no PNF and 100% graft and patient survival at 18 months. The rejection rate, however, was 50%.

Abt et al.[47] reported that controlled DCD livers had a higher incidence of intrahepatic ischemic-type biliary strictures compared to DBD livers (33.3% vs 9.5%; $P < 0.01$), but the two types of livers had similar graft and patient survival.

More recently, the University of Wisconsin group reported the updated outcome of controlled DCD donors ($n = 36$). Mean warm ischemic time (WIT) at organ recovery in DCD donors (from the time of extubation of the donor to cold perfusion) was 17.8 min. The incidence of PNF was similar in DCD and DBD livers, but the overall incidence of biliary strictures at 3 years was greater in the DCD livers (37% vs 12%; $P = 0.0001$). In addition, hepatic artery stenosis, hepatic abscess, and biloma were more frequent in DCD livers. Both 3-year

patient and graft survival were inferior in DCD donors (68% vs 84%; $P = 0.002$ and 56% vs 80%; $P = 0.0001$).[48] Muiesan et al.,[49] from King's College Hospital, recently reported on 31 controlled DCD donors. Mean WIT was 14.7 min (range, 7–40 min). All grafts had good early function except for one right-lobe split graft, which developed PNF after prolonged CIT (14.3 h). Overall patient and graft survivals were 87% and 84%, respectively, at a median follow-up of 15 months. In a study by Fujita et al.,[50] of 1209 DBD donors and 24 controlled DCD donors at the University of Florida, 1- and 3-year patient survivals were similar (86.8% and 81.7% in DCD vs 84.0% and 76.0% in DBD, respectively), but graft survival appeared inferior in the DCD group at 1 year (69.1% vs 78.7%) and 3 years (58.6% vs 70.2%; $P = 0.082$). There were no significant differences in the incidence of PNF or biliary stricture. In the DCD group, however, all cases of biliary stricture led to graft loss and retransplantation.

On the other hand, nationwide data have shown inferior outcomes. UNOS data between 1993 and 2001 characterize 117 DCD grafts as controlled, 11 as uncontrolled, and 16 as unknown or not identified. When the controlled DCD and DBD livers were compared, graft survival at 1 year was lower in controlled DCD (72.3% vs 80.4%; $P = 0.056$). DCD recipients had a higher incidence of PNF (11.8 vs 6.4%; $P = 0.008$) and retransplantation (13.9% vs 8.3%; $P = 0.04$) compared with DBD recipients. However, patient survival was similar in both. Predictors of early graft failure within 60 days after transplantation were prolonged CIT and use of recipient life support at time of transplantation (e.g., pressors).[51] Merion et al.[52] examined a national cohort of DCD ($n = 472$) and DBD ($n = 23\,598$) liver transplants between 2000 and 2004 using the Scientific Registry of Transplant Recipients database. There was no categorization of DCD donation such as controlled/ uncontrolled status in their analysis. Graft survival at 3 months, 1 year, and 3 years after liver transplantation was worse in DCD recipients (83.0%, 70.1%, and 60.5%) compared with that in DBD recipients (89.2%, 83.0%, and 75.0%; $P < 0.001$). The adjusted relative risk of DCD graft failure was 85% higher than that for DBD grafts.

Mateo et al.[53] reported the importance of risk evaluation to improve graft survival in a DCD setting. They analyzed the UNOS database between 1996 and 2003. They identified six significant risk factors in recipients for graft loss, based on multivariate Cox regression analysis (relative risk > 1.5): a history of a previous liver transplant, being on life-support, being hospitalized or in an intensive care unit, having received dialysis, serum creatinine value more than 2.0 mg/dl at time of transplant, and age more than 60 years. Graft survivals at 1 year and 3 years with DCD donors (71% and 60%;

$n = 367$) were significantly inferior to those with DBD donors (80% and 72%; $P < 0.001$). However, low-risk recipients with low-risk DCD livers (WIT < 30 min and CIT < 10 h; $n = 226$) achieved graft survival rates at 1 and 3 years (81% and 67%) not significantly different from those of recipients with DBD livers ($n = 33\,111$). Similar results were reported by Lee et al.[54] Graft survival from the low-risk DCD donors (donor age ≤ 45 years, WIT ≤ 15 min, and CIT ≤ 10 h) was comparable to that from DBD donors. In contrast, increasing donor age was more highly predictive of poor outcomes in DCD, especially in recipients in poor preoperative condition.

Another analysis of UNOS data encouraged the use of DCD livers as a reasonable alternative to the increasing use of marginal livers. Three-year patient and graft survival in 345 DCD donors were inferior to those in 20 289 DBD donors aged less than 60 years (77% vs 80% and 65% vs 75%; $P = 0.016$ and $P < 0.0001$, respectively). However, the outcome of DCD donors was comparable to that of current alternatives, such as DBD livers from those aged 60 years or more ($n = 3604$) and split livers ($n = 450$).[55]

Malignancies

As described above, the use of aged donors has increased in the face of the organ shortage. Given that the incidence of malignancy increases with age, the probability of an incidental tumor is higher in these donors.

According to UNOS, 2.7% of deceased donors have a history of cancer. Between 2000 and 2005, grafts from donors with a history of malignancy were used in 891 liver transplants. The most common cancers were non-melanoma skin cancer ($n = 306$) followed by central nervous system (CNS) malignancies ($n = 179$) and carcinoma of the uterine cervix ($n = 108$). Forty-five donors had a history of melanoma.[56] Presumably, none of the donors had any evidence of active malignancy, with the exception of nonmelanoma skin cancers such as basal cell carcinoma and squamous cell carcinoma and CNS malignancy. During the study period, only two donors transmitted a fatal malignancy to recipients. One had an active glioblastoma multiforme at the time of donation (liver, kidney, and lung), and the other had been treated for melanoma 32 years earlier.[56] Given earlier reports of the fatal transmission of disease from donors with glioblastoma,[57–59] organs from these donors should not be used. Furthermore, livers from donors with a history of melanoma should not be used for transplantation, even if the melanoma was treated years earlier. Previously, Penn[60] had reported a case of fatal transmission of melanoma from a donor treated 10 years earlier. In the donor treated 32 years previously, the lungs,

liver, heart, and two kidneys were transplanted. Over a 24-month follow-up, the lung recipient developed melanoma.[56]

Buell et al.[61] have reported an overall transmission rate of CNS tumors of 23%. If donors have high-grade malignancies and/or risk factors, recipients face an increased incidence of tumor transmission of 53%. Risk factors include surgical shunts, previous craniotomy, or previous prolonged chemotherapy. These high-risk donors also should be avoided. In contrast, donors with a low-grade malignancy in the absence of any known risk factors carry a 7% risk of tumor transmission.

What about recipients of organs from donors with incidental early cancers? Should the organs be removed, or should special therapies be employed? Serralta et al.[62] reported on six livers from donors (mean age, 65 years) found to have incidental genitourinary carcinomas (four renal, two prostate). All tumors were early-stage, and all were detected after the livers had been implanted. Over a mean follow-up of 51 months, there was no evidence of tumor transmission in any of the six recipients. In recipients of livers from donors with early genitourinary carcinoma, therefore, it may be not always necessary to perform transplantectomy or special treatments.

Living-donor liver transplantation

Living-donor liver transplantation (LDLT), while an established treatment for end-stage liver disease, is nevertheless considered to involve the use of marginal grafts because of the higher risk of complications in the recipient.[63] LDLT has some well-documented advantages, including the use of a graft from a healthy donor with minimal ischemic time, the ability to schedule surgery electively, a reduced risk of the recipient dying on the waiting list, and allowing the recipient to be medically stabilized.[64] LDLT has disadvantages as well: a higher rate of surgical complications for both the donor and recipient, and a potential risk of small-for-size syndrome. Furthermore, LDLT carries inherent risks for the healthy donor.[65–68] Therefore, careful selection of the donor and recipient is crucial to minimize risks and complications and to obtain acceptable outcomes in LDLT.

Favorable candidates for LDLT include patients with biliary cirrhosis with severe pruritus, primary sclerosing cholangitis with recurrent life-threatening cholangitis, metabolic liver diseases with normal liver function, acute liver failure without UNOS status 1 criteria, and unresectable hepatocellular carcinoma (HCC) beyond the Milan criteria.[64] Although these patients have an urgent need for transplantation, they have low Model for End-Stage Liver Disease (MELD) scores and poor

chances for timely deceased-donor liver transplantation (DDLT). In general, patients undergoing LDLT have lower MELD scores than those undergoing DDLT (mean MELD scores, 15.6 vs 22).[69]

The Adult-to-Adult Living Donor Liver Transplantation Cohort Study (A2ALL) is a consortium of United States liver transplant centers with the primary goal of comparing outcomes of adult-to-adult LDLT vs DDLT. In its first detailed report on 385 cases, 90-day and 1-year graft survivals were 87% and 81%, respectively. The outcomes were characterized by frequent biliary complications (30% early, 11% late) and 13% graft failure because of vascular complication, PNF, and sepsis.[69] Foster et al.[70] compared the outcomes after adult-to-adult LDLT to those after DDLT using nationwide databases. The 1- and 3-year patient survival rates after LDLT were similar to those after DDLT (89.1% and 80.3% vs 85.7% and 77.7%, respectively). Graft survival rates at 1 and 3 years were also similar (79.3% and 70.1% vs 80.7% and 71.1%, respectively). However, the severity of illness was substantially lower in LDLT recipients than in DDLT recipients.

It has been suggested that HCV replication might be increased in reduced-size LDLT grafts, but the data are controversial.[71-75] Schmeding et al.[74] reported that fibrosis progression and viral load were similar in LDLT and DDLT recipients, and they concluded, therefore, that the intensity of HCV recurrence was not increased in LDLT. Recently, the A2ALL study group retrospectively analyzed the outcomes of HCV-infected patients who underwent either LDLT ($n = 181$) or DDLT ($n = 94$). Graft survival at 3 years was lower in LDLT recipients than in DDLT recipients (68% vs 80%; $P = 0.02$), but patient survival was not significantly different (74% vs 82%). The A2ALL study highlighted the importance of surgical experience with LDLT on outcomes: graft and patient survivals among the first 20 LDLTs were inferior to those in later recipients and DDLT recipients, whereas graft and patient survivals in later LDLTs and DDLTs were not significantly different.[75]

The A2ALL study group also reported discouraging outcomes of LDLT for HCC. Although there was no difference in mortality, LDLT recipients ($n = 58$) had a shorter time from listing to transplant (160 vs 469 days; $P < 0.0001$) and a higher rate of HCC recurrence (29% vs 0%; $P = 0.002$) within 3 years than DDLT recipients ($n = 34$). Enthusiasm for LDLT as HCC treatment is dampened by higher HCC recurrence compared to that with DDLT.[76]

The major concern in adult-to-adult LDLT is the adequacy of graft size. Although harvesting a larger graft carries a higher risk for the donor, a residual liver volume of 30% can be tolerated by the donor in the absence of steatosis,[77] and right-lobe grafts have become standard for adult LDLT. Recently, Soejima et al.[78] reported acceptable outcomes with left-lobe grafts in adult-to-adult LDLT. However, the incidence of small-for-size syndrome was 25% in left-lobe recipients vs 6% in right-lobe recipients ($P < 0.01$). To increase the margin of safety in grafts at risk of small-for-size syndrome, any donor and recipient risk factors should be avoided.[79]

Split-liver transplantation

Split-liver transplantation (SLT), in which two allografts are created from a single cadaver liver, is a well-established technique for addressing the organ shortage, but because of technical and logistic issues in both donors and recipients, SLT accounts for only 4% of liver transplantations.[80,81] While splitting was originally performed as an ex vivo bench procedure, in situ liver splitting was introduced to decrease CIT and prevent blood loss after reperfusion.[82] It had been feared that prolonged surgical time and increased blood loss associated with in situ splitting of livers might negatively affect the function of other solid organs procured from the same donor, but in fact, in stable donors, in situ splitting can be accomplished without significant negative effects on other organs.[83-85] If a donor becomes unstable, splitting should be aborted, with rapid progression to cross-clamping.[86]

Left-lateral-segment (LLS) or left-split grafts have mainly been transplanted into children,[87-90] and right split or right trisegment (RTS) grafts into adults, with excellent outcomes.[91-95] Yersiz et al.[93] from the University of California, Los Angeles, reported on 100 livers that were split in situ, yielding 190 grafts for transplantation. LLS grafts were transplanted to pediatric recipients and RTS grafts were transplanted to older children and adults. Patient and graft survivals were equal to those in 1086 recipients of cadaver whole-organ grafts during the same time period. Wilms et al.[95] compared the outcome of 70 RTS grafts and 70 whole-liver grafts in adults. At a mean of 36 months, 2-year patient and graft survivals were similar between SLT and whole-liver transplantation (86.3% and 78.4% for patient survival, 77.3% and 71.9% for graft survival). The only notable observation was a higher transaminase level within the first 7 postoperative days in SLT patients. There was, however, no increased incidence of graft dysfunction secondary to small-for-size syndrome, because the RTS grafts contained approximately 80% of the standard liver volume. Wilms et al.[95] concluded that SLT did not put adult recipients at increased risk of morbidity or mortality.

Successful SLT in two adults has also been reported.[96-98] Humar et al.[96] observed good outcomes, with no PNF, in 10 of 12 adult in situ split-liver recipients. Azoulay et al.[98] also reported acceptable results in 34 adult recipients of grafts split either ex situ ($n = 30$) or

in situ (n = 4). PNF occurred in 3 of 17 left split-liver grafts, but in none of the 17 right split-liver grafts. Graft survival of left split-liver grafts at 2 years was inferior to whole-liver grafts (43% vs 85%, P = 0.003) and was adversely affected by graft steatosis and a graft-to-recipient body weight ratio of less than 1%. In that study, SLT for two adults increased the number of recipients by 62% compared with whole-liver transplantation.

Recently, the American Society of Transplant Surgeons surveyed 83 transplant programs in the United States and Canada to gather preliminary data on SLT application and outcomes. The surveyed centers provided data on 387 SLT grafts (207 LLS, 152 RTS, 15 left lobe, 13 right lobe). In 46% of the donors, the split procedure was performed ex vivo. Biliary complications were more frequent among in situ split grafts (17% vs 5%). While the majority of RTS grafts were used in nonurgent recipients, morbidity and mortality were concentrated among urgent recipients. Overall mortality among RTS recipients was 15%, with more than 50% of deaths attributed to graft-related complications. The overall incidence of PNF was 4%.[99] A multicenter study from Italy reported the outcomes of 323 split grafts (147 LLS, 154 RTS, and 22 left/right splits for adults) with a median follow-up of 22 months. Multivariate analysis revealed that donor age more than 60 years, the use of RTS grafts, low center volume (<50 transplants annually), urgent transplantation (UNOS status I and IIA), prolonged CIT (>7 h), and retransplantation were independent predictors of graft failure and poor patient survival. SLT decreased the adult patient dropout rate on the waiting list from 27% to 16%.[100]

Summary

With the persistent shortage of organs for transplantation, the use of marginal grafts has been increasing in liver transplantation. While outcomes are inferior to results with optimal whole-liver grafts, the continued and increasing use of marginal grafts has led to decreased mortality on the waiting list. Careful use of selected marginal liver grafts is a viable option for expanding the donor pool. Recent analyses using nationwide databases help to shed light on the current status of the use of marginal donors in liver transplantation and the outcome of this use.

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