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REVIEW

The marginal liver donor – an update

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Abstract

The number of patients awaiting liver transplantation keeps steadily rising with no corresponding rise in suitable grafts for transplantation. There also is an increasing trend of patients dying or being taken off waiting lists because of deterioration while waiting for a transplant. Over the preceding years the use of marginal grafts in liver transplantation has been driven by the critical shortage of donor organs and by emerging data that their use has resulted in a favourable outcome. This review revisits the factors defining marginality of a graft, and the issues faced by transplant units in making the decision to use such a graft. It also looks at the innovations in transplantation geared towards increasing the donor pool and the resulting issues of matching marginal grafts to suitable recipients.

Introduction

Orthotopic liver transplantation is the only effective treatment for end-stage liver disease [1,2]. While the number of patients awaiting liver transplantation has shown a steady rise over the last decade, there has been no corresponding increase in the organs available for transplantation. In the UK there is currently a mortality of about 6% of patients on the waiting list for liver transplantation while another 6% are removed from the waiting list because they become too sick to withstand the process of a transplant (UK Transplant data). Based on encouraging results from many centres around the world, the use of marginal grafts has become common place, in an attempt to keep up with the growing need for donor grafts.

A marginal graft could be defined as an organ with an increased risk for poor function or failure that may subject the recipient to greater risks of morbidity or mortality. There is no consensus however about the specific factors that define a graft as marginal or about which factors or combinations thereof should exclude the graft from use because of unacceptable risk to the recipient. The decision to transplant a specific organ therefore depends on the judgement of the transplant surgeon and consideration of the specific recipient.

Broadly there are two categories of marginal grafts. Firstly there are grafts which carry a high risk of technical complications and impaired function, examples of which are steatotic livers, nonheart beating donors (NHBD), elderly donors, split livers, donors with high inotrope requirement or long ischaemia times. Secondly, grafts will be considered marginal if they carry a risk of transmission infection or malignancy to the recipient (Table 1). This increased use of marginal grafts has been driven primarily by two factors: the critical shortage of donor organs for transplantation and data demonstrating that marginal grafts may be used with favourable outcomes.

All grafts undergoing transplantation are subject to preservation and ischaemia-reperfusion (IR) injury, a multifactorial process that affects graft function after liver transplantation [3,4]. It represents a continuum of events that are triggered when the liver is deprived of oxygen and then reoxygenated, culminating in hepatocellular injury [3,4]. The severity of the resulting liver dysfunction is also determined in part by the degree of hepatic injury that occurs as a consequence of local and systemic

Table 1. Types of marginal grafts.

Risk of impaired graft function	Risk of disease transmission
Steatotic livers	Donors with +ve serology
Donor obesity	Elderly donors
Elderly donors	Unexplained cause of death
NHBD	Donors with malignancy
Split grafts	High risk life style
Inotropic support	Active bacterial infections
High serum Na	
Cardiac arrest	
Long ischaemia	
Long ICU stay	

haemodynamic changes in response to brain death, organ retrieval and implantation. These factors crucially influence graft viability before the process of rejection [5].

Some marginal grafts have a lower tolerance of hypoxia and a greater susceptibility to reperfusion injury [6–8]. The functional derangement that results has varying degrees, the severest is the irreversible state of primary nonfunction (PNF), with less severe forms exhibiting reversible graft dysfunction termed initial poor function (IPF) [9,8]. In the longer term, nonanastomotic biliary strictures and an increased incidence of acute and chronic rejection have been attributed to the consequences of IR injury.

Steatotic livers

Hepatic steatosis is frequently observed in potential donors, and is considered an important risk factor for preservation injury with a higher incidence of postoperative graft dysfunction [10]. Severely fatty livers are more susceptible to preservation and IR that could lead to IPF and PNF [11,12]. Livers that are greater than 30% fat have a 25% chance of developing PNF [13]. Steatotic livers have an increased sensitivity to endotoxin, endothelial damage, decreased ATP stores, sinusoidal swelling and congestion following preservation and IR [14,15].

Several mechanisms produce early hepatic dysfunction in steatotic livers. Fat droplets have been seen to expand during cold preservation altering the infrastructure of the cell itself by displacing the surrounding organelles [10]. With the expansion of these droplets and the increase in girth of the hepatocytes secondary to swelling, the microcirculation of the liver tends to deteriorate. Sinusoidal congestion occurs, eventually causing a decrease in blood flow when compared with nonsteatotic livers [16]. Free radical formation by Kupffer cells following cold preservation compromise graft function by mediating lipogenesis through the inhibition of beta-oxidation [10,17]. During reperfusion Kupffer cells are further activated in response to endotoxin insult [18]. Additionally, liver mitochondrial function and plasma membrane fluidity are altered during the process of preservation and IR [15].

There are two forms of steatosis encountered in liver grafts. Macrovesicular steatosis; in which the fat vacuoles occupy most of the hepatocytes cytoplasm and displaces the nucleus peripherally and this is commonly associated with excessive alcohol, obesity, diabetes and hyperlipidaemia [19]. Microvesicular steatosis, where the vacuoles are smaller and have a centrilobular distribution and is commonly found in pathological conditions associated with mitochondrial injury such as acute viral or drug induced injury, sepsis and some metabolic disorders.

Graft steatosis is a common finding at cadaveric organ retrievals and this is also a not infrequent finding with live donors [20]. It is estimated that moderate to severe steatosis is encountered in approximately 20% of potential live donors [21,22]. Given the steady increase in the mean age of cadaver donors and the overall increase in the prevalence of obesity it is expected that a further increase in the prevalence of steatosis in both cadaveric and live liver donors [19].

Severe graft steatosis is associated with higher rates of PNF or dysfunction [13,14,23,24]. Some early studies have shown that graft steatosis is the most important variable in multivariate analysis of factors determining graft function after transplantation [25]. However, steatotic livers can be transplanted safely with good results for long-term organ survival especially if other contraindications for their use are absent [19].

Assessment of graft steatosis maroscopically is very subjective and is a wide range of inter-observer variation that is experience related [19,26]. Microscopic assessment remains the 'gold standard' despite being relatively subjective and can vary between individual observers. Frozen section is the preferred method because of time constraints between graft retrieval and transplantation [19,26]. Severity of steatosis is traditionally graded as mild <30%, moderate 30–60%, and severe >60%. It has been shown that a scoring system that includes degree of steatosis and donor age correlates well with the outcome of fatty livers [27].

More importantly, it is essential to distinguish between macrovesiular and microvesicular steatosis, as grafts with microvesicular steatosis even when severe, in contrast to macrovesiular steatosis, are safe to use, with graft and patient survival rates are similar to those using nonsteatotic grafts [28,29]. However, livers with moderate to severe degree of macrovesicular steatosis are associated with high degree of PNF [24,30]. This is more profound if other factors including prolonged ischaemia time (>12 h) and elderly donors are used [31]. It may be possible to selectively use liver with moderate degrees of

Table 2. Summary of studies related to graft steatosis.

>25–30% macrosteatosis increase risk of PNF	Urena 1999	Zamboni 2001	Salizzoni 2003	Angelico 2005	Verran 2005		
Microvesicular is safe	Fishbein 1997	Romero 1999	Crowley 2000	Zamboni 2001			
Graft steatosis in live donors	Monsour 1994	Rinella 2001	Soejima 2003	Cho 2005	Kwon 2006	Cho 2006	Halon 2006

steatosis if there is no other risk factor, short ischaemia time and in selected recipients under certain circumstances [8,19] (Table 2).

In live donors, assessment for possible steatosis by body mass index (BMI), CT/MRI scan and histopathology are readily available and give good correlation with outcome [32–34]. Donors with mild to moderate degrees of steatosis can be used and it was observed that steatosis disappeared immediately after transplantation and hepatic regeneration power was not impaired in grafts with <30% of macrovesicular steatosis [32–34]. Furthermore, a mildly steatotic graft did not increase the risk of graft dysfunction or morbidity in LDLT [32–34]. However, a degree of hyperbilirubinaemia and transient intrahepatic cholestasis is expected if the liver has 5–30% macrosteatosis compared to livers with <5% macrosteatosis [35].

Elderly donors

Although no hepatic disorders are known to be restricted to old age, there are some changes that are now been found to affect the liver with aging. Liver weight and volume as well as blood flow are reduced with aging [36]. As alluded to earlier, the shortage of available organs for transplantation coupled with increase in the average age of the population has led to extended use of livers from donors above the age of 60. Results were initially conflicting; The UNOS data base showed that liver donors above the age of 50 years increased from 2% to 17% during 1987 to 1992 with an associated adverse effect on 6-month graft survival [37]. There were however reports from the same era, which concluded that donors above the age of 50 years could be transplanted with the same success as younger donors [38].

A significant number of liver donors now are above the age of 60 years. A stepwise expansion was noted and gradually the donor age was increased from 50 to 80 years [39,40]. Donors >70 years showed no significant difference in patient and graft survival compared with donors <70 years [41,42]. There are reports of liver grafts from donors over 80 years being transplanted with good results, especially if into a recipient with malignancy and otherwise stable liver function [43].

Caution must be taken when using grafts from elderly donors because any additional risk factor in the donor such as steatosis or prolonged ischaemia may increase the incidence of organ dysfunction [44]. Recipient selection is also paramount as very sick recipients do not benefit from these marginal grafts and careful selection is mandatory to optimise the results [45]. Studies have shown that patients with HCV cirrhosis has increased risk of recurrence and reduced patient and graft survival [45–48]. Also donor age may be important in recipients with primary biliary cirrhosis as this can adversely affect their outcome [49].

Nonheart beating donors

The last few years has seen a considerable renewal of interest in nonheart beating donors (NHBD) or donation after cardiac death as a potential to increase the pool of available organs. This has followed the good results of kidney transplantation from NHBD [50]. Organ retrieval from NHBD can be controlled or uncontrolled based on Maastricht classification [51].

Controlled heart beating donors undergo circulatory arrest following planned withdrawal of life support with the donor team ready in theatre to start the procurement process within a time frame that is slightly variable between different countries [52]. Uncontrolled NHBD are donors who had unplanned cardiac arrest with failed cardiopulmonary resuscitation, or dead on arrival to hospital. Organs from controlled NHBD suffer less damage and have better chance of recovery compared with uncontrolled ones [53].

Several studies have shown that controlled NHBD are safe to use and the long-term outcome was not different from brain dead donors. In a recent study, 33 livers were transplanted with overall patient and graft survival of 87% and 84%, respectively, at a median follow up of 15 months. In this study, one PNF was reported and 9.4% biliary complications were recorded with few vascular complications [54].

In another study, the patient and graft survival up to 2 years was not different from heart-beating cadaveric donors. In this study the rate of PNF was 10%, However, the incidence of postoperative cholestasis and acute cellular rejection was higher and the rate of vascular complications in this series was 15.6%, a figure that is three times higher than what should be expected after cadavaric donor liver transplantation [55].

Ischaemia time has been shown to be extremely important when NHBD are considered [56]. If warm ischaemia

time (WIT) is restricted to below 30 min and cold ischaemia time (CIT) less than 10 h, graft survival rate in the NHBD group has been found to be 81% and 67% at 1 and 3 years respectively, which is not significantly different from recipients of brain dead donors [57]. Results from uncontrolled NHBD were less good and actuarial graft survival at 2 years was 55%. The uses of uncontrolled NHBD livers was also associated with significantly higher incidence of PNF, IPF and biliary complications compared with livers from heart-beating cadaveric donors [55]. It is recommended that a maximum duration of 130 min of warm ischaemia during cardiopulmonary resuscitation or cardiopulmonary support be used as a 'cut off' if these organs were to be used in transplantation [55]. NHBD livers have also been used in the paediatric setting with similar results [54].

In summary, controlled NHBD can be a significant source of grafts for transplantation, however, there are certain criteria that should be fulfilled in order to achieve good patient and graft survival. Criteria used at our centre presently include a restriction of organ procurement should the patient continue to breathe for more than 3 h after the withdrawal of treatment with the maintenance of a systolic BP >50 mmHg. Warm ischaemia is defined as the interval of hypotension (systolic blood pressure <50 mmHg) to aortic perfusion. The procurement should be swift and perfusion should be started within 15 min from cardiac arrest with immediate venting of the cava to avoid organ congestion. CIT should be kept to a minimum. Any additional risk factor such as advanced donor age should be carefully considered before a decision is made on the organ being used.

Donors with positive virology

Potential donors with positive serology should not be completely ruled out from the donor pool. Donors with past exposure to Hepatitis B infection can be used selectively in some recipients. Hepatitis B core antibody (anti-HBc) positive donors were initially thought to carry a small risk of *de novo* HBV infection to the recipient. However in patients who are immune to HBV (previous vaccination) it has been found to be safe to use these organs [58]. In recipients with active HBV infection or in desperate circumstances these organs have been used safely in combination with antiviral prophylaxis and immunnoglobulins [59–61]. Additionally, donors with positive hepatitis B surface antibody (anti-HBs) do not appear to transmit HBV infection after liver transplantation [59,62].

About 5% of all potential organ donors in the United States and some parts of Europe are positive for antibody to HCV, and about half of these donors are HCV RNA positive by PCR [63]. Liver transplantation for recipients with HCV cirrhosis from HCV +ve donors were found to provide graft survival that is equivalent to HCV-ve grafts to HCV +ve recipients [64]. Studies found no difference in either patient survival, graft survival, the incidence, timing, or severity of recurrent HCV disease following use of such grafts [65]. There has also been no consistent pattern of viral repopulation found [64,65]. Viral genotype is only predictive of response to interferon treatment and not of disease severity, therefore genotype should not be an important consideration in the decision to use a liver from HCV +ve donor into HCV +ve recipients [64,65].

It is obvious that livers from donors with active on going hepatitis and/or fibrosis should not be used for transplantation. In donors with a history of such infection, there have been recommendations for a routine liver biopsy before use of a graft for transplantation [66] A scoring system has been derived in order to aid the decision of whether a graft should be used for transplantation in this setting [66].

Donors with malignancy

With the rise in the donor age, it is inevitable that the incidence of malignancy is expected to be higher [67]. It has been routine to use organs from donors with a history of nonmelanoma skin cancer (NMSC) and selected cancers of the CNS as the risk of cancer transmission appears to be low [67]. CNS tumours like astrocytomas or glioblastomas or medulloblastomas grade III or IV, as well as tumours that have breached the blood brain barrier following ventriculoperitoneal shunts or surgery along with cerebellar tumours and previous prolonged chemotherapy for such tumours should be excluded as they present an unacceptable risk of tumour transmission to the recipient [68,69]. A study using UNOS database, identified 397 donors with past history of CNS tumours and a total of 1220 organs transplanted from these donors. It was found that patient survival of organs from CNS tumour donors was comparable to donors with no CNS tumours. A total of 39 patients reported to have developed malignancy following transplantation but none of these tumours were donor-derived [70].

In a previous report by the same authors using UNOS data identifying 257 donors with a history of cancer; no donor derived malignancy was observed with a mean follow up period of 45 months [71]. However, there are reports which have demonstrated tumour recurrence in cases of colon and breast cancer following apparent cancer-free survival [72–74].

It has been estimated from data off a population-based cancer registry that the risk of having a donor with undetected malignancy was 1.3% and risk of transmitting a

cancer from such a donor was 0.2% [75]. A review on this subject using UNOS data showed a total of 21 donor related malignancies in 108 062 transplant recipients over 8 years giving an incidence of tumour transmission to be 0.02% [76].

The current thinking on this form of marginal donors are that NMSC, most of CNS tumours and *in situ* carcinoma seem to be safe source of solid organs for transplantation [76]. A history of melanoma, choriocarcinoma, lymphoma, carcinoma of the breast, lung, kidney and colon seem to possess a high rate of cancer transmission, even after long apparent cancer-free survival [76]. It is left to the judgement of the transplanting team that determine the use of these organs under certain circumstances.

Technical variant grafts

Conventional split grafts

Split liver transplantation was developed as a strategy to increase the donor pool. In a study, which analysed data from 34 664 first adult liver transplants using the European Liver Transplant Registry to identify factors associated the risk of mortality at 3 and 12 months, split liver transplantation was found to carry a mortality risk of 1.96 [77]. Another study concluded that recipients of whole and left lateral segment grafts had significantly better patient and graft survival compared with right trisegmental lobe graft [78]. It was also found that right trisegment lobe graft had an outcome that is not different from marginal livers [78]. Due a possible graft volume and recipient requirement mismatch, split liver grafts have an added risk of small for size syndrome and careful selection of recipients is important [79]. It is also noted that biliary complications are higher in split grafts compared to whole grafts with an incidence up to 26% in some series [80,81].

However, overall many studies support the view that split grafts have an equivalent outcome to whole grafts [82,83]. Split liver transplants offer a significant advantage to the paediatric recipients with life years gained compared with remaining on the waiting list [84]. It was found that 11 extra life years and 59 incremental recipients accrued from each 100 livers used for split compared with whole organ transplants [84].

Full-right full-left splits

Full-right full-left splitting is safely possible and should be considered as a reasonable option for liver transplantation [85]. However, splitting for two adults requires high technical skills and profound knowledge of the anatomic variations and should be performed in centres with large split transplantation experience [86]. With rigid selection criteria, it is feasible to split livers between two adult recipients without an increase in technical complications, delay in allograft function or compromise in patient and graft survival [87,88]. Split liver transplantation for two adults can increase the number of recipients and is possible in about 15% of optimal cadaver donors [87,88]. Outcomes and complication rates can be improved by rigid selection criteria for donors and recipients, particularly for the smaller left graft, and possibly also by *in situ* splitting in cadaver donors [89,90].

Reduced-size grafts

Reduced size grafts are usually used for large children or small adults. In one study a total of 251 liver transplants were performed of which 138 were reduced-size grafts and 30 were split grafts. One-year patient and graft survivals were comparable at 73% and 67%, respectively, in both groups [80]. There was no difference in the incidence of vascular complications between groups. Biliary complications were significantly more common after split grafts when compared with reduced-size grafts (21% vs. 4%, $P < 0.0001$)[80]. This however did not affect patient or graft survival [80].

Live related liver transplantation

Live donor grafts could be considered nonmarginal with patient and graft survival that is equivalent or superior to cadaveric grafts [91, 92]. This is the only form of liver transplantation in some countries, especially in the Far East [93]. Following initial concerns regarding donor safety and the possibility of small for size syndrome, live donor liver transplantation is today considered a safe option [92,94]. Technical advances required to overcome initial problems encountered with live donor transplantation has led to the use of techniques like middle hepatic vein inclusion or reconstruction [95], hemi-portocaval shunts [96], splenic artery ligation or dual grafts [97].

Other suboptimal donors

There are other categories of donors who could be considered suboptimal. Donors with high-risk life style run the risks of disease transmission (e.g. HIV) to recipients and should also be considered marginal. Donor obesity caries a risk, and high body mass index (BMI >30) is associated with poor 90 day survival following transplantation [49].

Hypernatraemia

A number of studies have suggested that donor hypernatraemia can affect graft function and increase the risk of

graft loss [98,99]. This is possibly related to the increased osmolality with cellular injury which becomes significant at reperfusion. The cause of hypernatraemia could be related to derangement of fluid balance and diabetes insipidus in potential donors [98,99]. In a study investigating the peak donor sodium level and the corrected sodium level at the time of retrieval, it was found that hypernatraemia (sodium >155 mEq/l) was associated with 18.5% rate of primary nonfunction compared with 3.4% in the normal sodium group. With the correction of hypernatraemia before procurement, this rise in the primary nonfunction was no longer found [99].

Hypotension and inotropic support

Prolonged hypotension or haemodynamic instability may add to the risk of graft dysfunction. The use of inotropic support could be used as a surrogate marker of this [100,101]. The use of norepinephrine in the donor has been therefore in this setting shown to be associated with better outcome [99,102].

Infections

Bacterial or fungal infections in donors are common, and mainly affect the respiratory and urinary tracts. Transmission of bacterial and fungal infection to recipients has been previously documented [103]. Adequate antibacterial cover for both donor and recipient will reduce the infection risk in the recipient and should result in good graft function and survival [104]. This also include donors with bacterial meningitis [105].

Trauma

Livers that are damaged by trauma should not necessarily be excluded from transplantation. There is anecdotal evidence that parenchymal damage even when associated with transient hypotension caused by severe bleeding that requires surgical interventions are not contraindications for liver retrieval [106,107]. This has also been reported in the NHBD setting as well [107].

Research

Research tools may be valuable to predict the outcome of marginal livers by monitor metabolic changes in the liver graft. At our centre we have used microdialysis in the setting of human cadavaric liver transplantation to monitor metabolic changes that occur during organ harvest, backtable preparation of the graft, and following implantation in the recipient for 48 h [108–112]. Using microdialysis with analytical plateforms like HPLC with electrochemical detection, we have been able to study the effects preservation, ischaemia and reperfusion has on glucose and amino acid metabolism. Early results show that factors like interstitial lactic acidosis in the donor allograft was associated with significant reperfusion injury on implantation [111]. Studies are currently underway to assess a greater part of the metabolome during transplantation with a view to identifying factors that would indicate poor graft function post-transplant while still in the donor setting.

Analysis of multiple donor variables

Several studies have investigated the effect of multiple donor factors on graft survival (Table 3). A Spanish study looked at 52 donor variables from 5150 liver transplants performed between 1994 and 2001 using a univariate analysis [102]. A Cox regression model was used for the factors that were found statistically significant in relation to graft survival. It concluded that several donor factors had a negative impact on graft survival including; donor age >50 years (RR = 1.27 and if >70 years; RR = 1.4), stroke as a cause of death, body mass index >25, use of inotropes (Dopamine infusion more than 15 μg/kg/min), ICU stay >6 days (RR = 1.21), increase liver enzymes levels (ALT, AST or GGT >200 U/l), low bicarbonate level <18 mEq/l (RR = 1.27) and history of hypertension >3 years and associated antihypertensive treatment (RR = 1.16) [102].

In another study the long-term outcome in 3200 liver transplantation over 20 years in one centre were analysed [113]. A number of donor factors were examined. This study found that donor inotropic requirement, serum sodium level and history of cardiac arrest prior to donation have no impact on long-term survival. In contrast, survival was significantly less when donor hospital stay was longer than 6 days and interestingly recipients of livers from donors older than 60 years had a lower mortality than donors between ages of 55–60 years of age. Multivariate analysis of factors concluded that extended CIT and WIT were significant independent risk factors for mortality. Warm ischaemia beyond 55 min doubled the risk, while cold ischaemia greater than 10 h substantially increased the risk of death (mortality risk ratio of 2.14 and 1.43 respectively) [113].

Another study based on data from the European Liver Transplant Registry looked at 3 and 12 months mortality in patients following liver transplantation [77]. The 3 months survival data were based on 31 094 transplants and 12 months data was based on 27 165 transplants. Donor factors of significance were; Donor age >60 years with odds ratio for mortality; 1.16 and 1.21 at 3 and 12 months respectively, split or reduced grafts (odds ratio

Table 3. Summary of studies that identified donor risk factors.

Statistically significant factors	Mirza 1994	Agnes 1996	De Carlis 1999	Tekin 2004	Cuende 2005	Busuttil 2005	Cameron 2006	Feng 2006	Burroughs 2006
Age	>55	>55	>55	>60	>60		>55	>60	>60
Afroamerican									Yes
Inotropes	Yes		Yes						
Hypotension	Less than 90 mmHg for 15 min or more	Less than 50 for more than 60 min	More than 60 min						
Long ICU stay	>3 days	>7 days	>5 days		>6 days	>6 days	>5 days		
CVA as cause of death					Yes			Yes	
NHBD								Yes	
Obesity	>100 kg				BMI>25				
Metabolic acidosis					Bicarbonate <18 meq/l				
Liver enzymes	AST >150 ALT >100	AST >150 ALT >150	AST		>200 IU/l				
Split grafts								Yes	Yes
Cold ischaemia				>12 h		>10 h	>10 h	Yes	>13 h
Warm ischaemia						>55 min	>40 min		

CVA, cerebrovascular accidents; LRD, living-related donors; NMSC, nonmelanoma skin cancer; PNF, primary nonfunction.

of 1.96 and 1.57), total ischaemia time >13 h (1.38 and 1.27) [77].

In a study carried out at our centre, we performed an analysis on data collected prospectively of 397 cadaveric liver transplants [27]. Both univariate and multivariate analyses were performed on donor, recipient, and perioperative factors with relation to early allograft dysfunction. A score was developed that classified donors into marginal and nonmarginal populations, and the influence of cold ischaemia was determined for each group. Multivariate analysis-determined donor age and steatosis (moderate to severe) were independent predictors of deranged function. This enabled us to produce a scoring system to differentiate marginal donors with respect to risk of early allograft dysfunction, using the following: formula = (20.06 × steatosis) + (0.44 × donor age), cutoff 23.1. In the marginal group, the cut off value of cold ischaemia time was 12.6 h. This scoring system classified an organ as marginal or nonmarginal depending on the donor age and degree of steatosis [27].

The donor risk index

The donor risk index (DRI) is a concept that was developed initially in the kidney transplant population [114]. Data from the Scientific Registry of Transplant Recipients which included 20 023 liver transplants from deceased donors were used [115]. Seven risk factors were identified as significantly associated with graft failure. A donor age of more than 60 years was the strongest risk factor of graft failure. Livers from African–American donors had 19% higher risk of graft failure compared with those from white donors (RR 1.19; $P < 0.001$), reduced donor height, CVA as a cause of death, NHBD and split grafts were also significant negative factors. Each additional hour of CIT was associated with a 1% increased risk of graft loss. A DRI was derived following analysis of this data and a DRI of 1 or less was associated with 87.7% 1-year survival compared with 79.9% if DRI was 1.5–1.6 and 76.9% if DRI was 1.6–1.8 [115].

At our centre over an 18-month period, livers used in 30 of 213 consecutive transplantations were from marginal donors. These donors had either abnormal liver function tests, a history of alcohol abuse, drug overdose (including paracetamol), cardiovascular disease, sepsis, prolonged hypotension (systolic blood pressure <80 mmHg for >1 h), or high-dose inotrope useage. Sixteen of these grafts had been turned down by other UK liver transplant centres because of their marginal nature. The outcome of these transplants was compared with the 183 nonmarginal grafts transplanted during this period. The marginal grafts showed satisfactory early function but had higher first 24 h ($P = 0.0004$) and peak serum aspartate aminotransferase

($P = 0.0008$) values compared with the nonmarginal grafts. Graft and patient survival at 1 year in the two groups was similar (72% vs. 73% and 80% vs. 82% respectively) [116]. In a more recent study, 68% of recipients ($n = 388$) received marginal livers. Here too graft and overall patient survival were found to be similar in both groups at 90 days and 1 year post-transplant [117].

Recipient selection

Choosing recipients for marginal grafts is extremely important. Marginal grafts should not be used for marginal or high risk recipients [92]. Marginal grafts should be transplanted in recipients with low risk who have a low MELD score, with fewer co-morbodities. These grafts perform better in patients who can tolerate a bigger insult immediately following transplantation when compared with high risk recipients [118]. Patient and graft survival have been found to be significantly lower when marginal grafts were used in high risk recipients [119]. This is well demonstrated by a study which showed a favourable outcome in low-risk recipients (MELD ≤ 9) following transplantation with steatotic livers [120]. Survival functions in moderate-risk recipients (MELD 10–19) were moderately affected with <30% steatosis and severely with those with >30%. In this study grafts with 30–60% steatosis worked poorly in high-risk recipients (MELD ≥ 20), and very poorly if steatosis was >60% [120].

In conclusion, marginal grafts are now encountered in about 50% of livers that are available for liver transplantation in the climate of increased requirement for liver grafts coupled with the rising mortality on transplant waiting lists. It has been shown repeatedly that the use of marginal grafts is safe. However, donor and recipient selection is paramount in this setting. The appropriate use of these organs is a challenge we all face and the emergence of better markers of outcome and for graft assessment in the future will no doubt add to the armamentarium the transplant surgeon has at present.

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