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REVIEW

Report of the Paris Consensus Meeting on Expanded Criteria Donors in Liver Transplantation

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Because of organ shortage and a constant imbalance between available organs and candidates for liver transplantation, expanded criteria donors are needed. Experience shows that there are wide variations in the definitions, selection criteria, and use of expanded criteria donors according to different geographic areas and different centers. Overall, selection criteria for donors have tended to be relaxed in recent years. Consensus recommendations are needed. This article reports the conclusions of a consensus meeting held in Paris in March 2007 with the contribution of experts from Europe, the United States, and Asia. Definitions of expanded criteria donors with respect to donor variables (including age, liver function tests, steatosis, infections, malignancies, and heart-beating versus non–heart-beating, among others) are proposed. It is emphasized that donor quality represents a continuum of risk rather than "good or bad." A distinction is made between donor factors that generate increased risk of graft failure and factors independent of graft function, such as transmissible infectious disease or donor-derived malignancy, that may preclude a good outcome. Updated data concerning the risks associated with different donor variables in different recipient populations are given. Recommendations on how to safely expand donor selection criteria are proposed. ***Liver Transpl 14:1694-1707, 2008.*** © **2008 AASLD.**

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Major advances have been achieved over the last 2 decades, allowing significant improvements in both life expectancy and quality of life after liver transplantation.[1-3] In many patients with liver failure and/or hepatocellular carcinoma, there is no practical alternative to transplantation; however, the principal limitation of transplantation remains access to an allograft. The number of patients who could derive benefit from liver transplantation markedly exceeds the number of available deceased donors. This imbalance has led to relaxation of deceased donor selection criteria and the utilization of extended criteria allografts.[4-7] The issue is not whether extended criteria allografts should or should not be used in liver transplantation. Extended criteria donors are immediately needed even if using such allografts generates increased morbidity and mortality.

Abbreviations: BMI, body mass index; CIT, cold ischemia time; COD, cause of death; CVA, cerebrovascular accident; DCD, donation after cardiac death; FAP, familial amyloid polyneuropathy; GGT, gamma glutamyl transpeptidase; HCV, hepatitis C virus; LDLT, living donor liver transplantation; MELD, Model for End-Stage Liver Disease; UW, University of Wisconsin.

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What must be appreciated is that donor quality represents a continuum of risk rather than "good or bad." The terms *marginal* and *compromised* are inappropriate in a climate of scarcity. The definition of *extended criteria allograft* should apply only to variables affecting risk specific to the allograft and independent of other variables. The central concerns are how to safely expand the donor pool with respect to specific quantification of risk, how to optimally allocate extended criteria allografts, and what information should be provided as part of informed consent.

There is significant heterogeneity in the use of extended criteria allografts across different countries and different centers, depending on the impact of organ shortage on waiting list mortality, local or regional policies, and the presence of alternatives to deceased donor transplantation (ie, living donor transplantation). Data-driven guidelines supported by consensus are needed. To that end, the International Liver Transplantation Society organized a consensus conference on March 30-31, 2007 in Paris, France to clarify issues related to expanded criteria donors and propose guidelines. In this article, we report a summary of the topics discussed during the meeting and conclusions that could be drawn.

DEFINITIONS

An extended criteria donor implies higher risk in comparison with a reference donor. The risk may manifest as increased incidence of poor allograft function, allograft failure, or transmission of a donor-derived disease. In the past, a reference (or ideal) donor was defined according to the following criteria: age below 40 years, trauma as the cause of death, donation after brain death, hemodynamic stability at the time of procurement, no steatosis or any other underlying chronic liver lesion, and no transmissible disease.[8,9] A reference donor implies a very low risk of initial poor function or early allograft failure leading to death or requiring retransplantation. Additional factors such as transmissible disease, which do not directly affect the risk of graft failure, must also be considered in the definition of extended criteria. Factors that are not directly related to the donor, such as technical difficulties during the procedure, surgical complications, or disease recurrence, should not be included in the definition.

An ideal allograft is different from an ideal donor. The ideal allograft category may be influenced by variables that are introduced following procurement, such as the prolonged cold ischemia time (CIT), or technical variants, such as those occurring with allograft reduction (eg, split-liver allograft). These variables should not be included in the definition of *extended criteria donor* because the aim is to assess risk at procurement.

CURRENT TRENDS IN THE USE OF EXPANDED CRITERIA DONORS IN EUROPE, NORTH AMERICA, AND ASIA

Reported utilization of extended criteria donors in the United States, Europe, and Asia has varied widely as a result of clinical practices and definitions, allocation patterns, and demographic variations of indications for liver transplantation.[4,5,9-13] Although the scarcity of donation after brain death limits all deceased donor allograft utilization in Asia, European and North American data on extended donor criteria allografts are sporadic because of the absence of a clear definition of extended criteria, a database specifically designed to analyze donor-derived variables, and widespread variation in each center's ability to allocate these organs. An analysis of the Scientific Registry of Transplant Recipients of the United Network for Organ Sharing clearly indicates increased allograft utilization from elderly donors, donation after cardiac death (DCD), and donors with positive serologies for hepatitis B and hepatitis C.[14] However, the database cannot provide reliable information on biopsy data, steatosis, donor physiology, or follow-up serology. It is equally significant that these organs are allocated by widely variable methods and criteria. Extended criteria organs can be allocated by conventional algorithms or at the complete discretion of the transplant center. Thus, we are left only with center-specific reports of success with these allografts, and we are unable to transcend the data to larger multicenter inferences on donor and recipient selection.

ROLE OF TERMINAL ILLNESS AND BRAIN DEATH PRIOR TO PROCUREMENT

Brain death is associated with a number of circulatory, metabolic, and hormonal changes eventually leading to somatic death.[15] Circulatory changes are the leading cause of organ dysfunction.[16] There are no guidelines on the care of donors with respect to optimizing liver allograft function. Donor homeostasis, defined by a mean arterial pressure between 65 and 100 mm Hg, urine output between 1 and 1.5 mL/kg/hour, hemoglobin between 7 and 9 g/dL, normal arterial blood lactate, partial pressure of arterial oxygen over 80 mm Hg, temperature between 35.5°C and 38°C, and serum sodium below 150 mmol/L, should be the goal to optimize recovery and provide a period to assess solid organ function.[17] Accumulated data, both in animal models and in humans, have demonstrated dysfunction of the hypothalamic-pituitary-adrenal axis during brain death that leads to a decrease in circulating thyroid hormone and corticosteroids.[18] However, no clear evidence exists indicating that exogenous hormone therapy (thyroid hormones and/or corticosteroids) improves outcomes.[19,20] Additional areas of future research include the potential usefulness of nutritional support, glycine, and *N*-acetyl cysteine.[21-23]

COLD ISCHEMIC TIME

Prolonged CIT is an independent risk factor for the development of delayed graft function and primary nonfunction.[24] Recipient survival was shown to be adversely affected by CIT over 12 hours in a European survey and over 10 hours in a US survey.[3,25] Several reports have documented that CIT greater than 15

hours is associated with an increased risk of primary nonfunction and reduced long-term survival.[26] The European Liver Transplant Registry survey showed that 5-year recipient survival was 57% with CIT over 15 hours versus 64% with CIT between 12 and 15 hours and 67% with CIT below 12 hours.[27]

Liver grafts from elderly donors and/or donors with steatosis are even more affected by prolonged CIT and preservation injury. In this group, optimal liver function can be best achieved when CITs are kept less than 8 hours.[28] These results emphasize the need to shorten CIT as much as possible in the case of extended criteria donors. During the last decade, CIT has been reduced in European centers from 570 to 470 minutes on average.[3] A similar trend has been observed in the United States.[29] Therefore, there is growing evidence that, independent of any other risk factor, reducing CIT results in better outcomes.

PRESERVATION SOLUTIONS

Preservation solutions are designed to reduce cellular injury during cold ischemia and minimize reperfusion injury. The development of the University of Wisconsin (UW) preservation solution dramatically improved the quality of preserved allografts over then existing solutions.[30-33] UW has been used throughout the world for more than 20 years but is now challenged by 3 other solutions—Celsior, histidine tryptophan ketoglutarate, and IGL-1—which are less expensive and potentially superior for organ preservation.[34-36] No difference in short-term or long-term outcomes has been observed for each of these 3 solutions in comparison with UW.[35-37] However, the study populations in the trials that have been reported so far are relatively small and nonselect groups of donors. The lower viscosity of histidine tryptophan ketoglutarate and Celsior may prove to be of benefit in select cases such as older donors and non–heart-beating donors in whom the microcirculation may be compromised.[38] IGL-1 is a low-viscosity solution that may be superior to UW for the preservation of steatotic grafts.[36] Although UW remains the leading preservation solution for livers, "a la carte" use of preservation solutions in specific situations is an attractive option until further studies clarify the benefits of each preservation solution. However, no evidence for the superiority of this approach has been proven. This will be an important field of research with possible implications for procurement-specific practices.

DONORS WITH ABNORMAL LIVER FUNCTION TESTS

Abnormal liver function tests are common findings in donors as a result of hemodynamic instability, underlying conditions including steatosis, and sepsis. However, not all donor factors translate into abnormal liver function tests. The main issue is whether abnormal liver function tests will affect allograft function. There is no clear upper limit in serum transaminases that contraindicates use in transplantation. Liver procurement should not be excluded on the basis of liver function tests. However, normal or near normal liver function tests are not a guarantee that there are no significant parenchymal lesions. In cases of markedly increased serum transaminases, donor hemodynamics is an essential consideration. A rapid decrease in serum transaminases over time indicates resolving hepatocellular injury, which should promote consideration for transplantation. Donors should not be discarded solely on the basis of the gamma glutamyl transpeptidase (GGT) level. However, during the consensus meeting, it was agreed that a marked increase in the GGT level (over 200 UI/L) is a concern, further consideration for utilization should be carefully weighted in light of other donor factors, and liver biopsy is warranted. In the case of a marked increase in the GGT level, other donor factors, including a history of alcohol abuse and nonalcoholic steatohepatitis, should be carefully assessed before procurement is considered. In addition, if the liver is enlarged or there is hyperechogenicity on ultrasonography, there should be a high suspicion for significant steatosis.

A low prothrombin index and increased international normalized ratio are not contraindications for transplantation. In deceased donors with major brain trauma, these changes are more likely to be due to disseminated intravascular coagulation than to altered liver function.

FATTY LIVER GRAFTS

Steatosis is one of the most important factors affecting liver allograft function. Steatosis is common in several situations, including obesity, diabetes, and alcohol abuse. Although steatosis can regress within weeks after liver transplantation, early functional recovery and regenerative capacity are significantly impaired with steatotic allografts, mostly because of more severe ischemia-reperfusion injury.[39]

Steatosis can be categorized as microvesicular or macrovesicular. Microvesicular steatosis, which rarely occurs in an isolated form, apparently has less influence on ischemia-reperfusion injury and poor graft function than macrovesicular steatosis.[40,41] Macrovesicular steatosis is more commonly associated with poor graft outcome and should be taken into account only when the likelihood of graft function is being assessed.

Steatosis is generally suspected by inspection at the time of procurement. However, biopsy is the gold standard to obtain an objective assessment.[42] Macrovesicular steatosis can be subcategorized as mild (<30%), moderate (30%-60%), or severe (>60%). Substantial data have correlated the extent of macrovesicular steatosis with an increased incidence of graft dysfunction.[7,43-45] Mild steatosis (<30%) has minimal impact on liver function post-transplantation, provided that CIT is short.[46] When macrovesicular steatosis exceeds 60%, except in research protocols employing specific preservation solutions with very short CIT in highly selected recipients, there is a consensus for discarding

allografts because of a high rate of primary nonfunction.[47]

The use of grafts with moderate steatosis (30%-60%) remains a challenging issue. In this group, the incidence of primary nonfunction may reach 15%, and the rate of delayed graft function approaches 35%.[47-49] As a result, careful evaluation and measures aimed at avoiding other graft factors (short CIT in particular) are needed.[50] Practically, inspection at procurement helps detect steatosis. However, there is a poor correlation between surgical assessment and degree of steatosis when steatosis exceeds 35%. Biopsy should be systematically performed. Whatever the extent of steatosis is, the existence of any grade of fibrosis should lead to discarding the graft. Even though biopsy is needed, it may take additional time and, as a result, prolong CIT. Again, the procedure should be as rapid as possible because, in the case of steatosis, short CIT is a prerequisite. Except when procurement is performed by an experienced transplant surgeon, no graft should be rejected solely on the basis of inspection. Biopsy should be viewed as a means for transplanting more organs. Recipient selection and minimal CIT are paramount to the successful utilization of moderately steatotic allografts as a period of delayed allograft function is expected.

Liver biopsy quantification of degree of steatosis should be kept as one of the elements in databases in order to clearly answer this issue in future analysis.

TABLE 1. Donor Factors Associated with Liver Graft Failure

Donor Factor	Risk Ratio	*P* Value
Age		
<40	1.00	0.0002
40–49	1.17	<0.0001
50–59	1.32	<0.0001
60–69	1.53	<0.0001
>70	1.65	<0.0001
African American (versus white)	1.19	<0.0001
Donor height (by 10-cm decrease)	1.07	<0.0001
Cause of death, cerebrovascular accident	1.16	<0.0001
Cause of death, other*	1.20	0.018
Non–heart-beating	1.51	0.0006
Partial/split	1.52	<0.0001

NOTE: The data were taken from Feng et al.[8] Donor risk index = exp[(0.0154 if 40 ≤ age < 50) + (0.274 if 50 ≤ age < 60) + (0.424 if 60 ≤ age < 70) + (0.501 if 70 ≤ age) + (0.079 if COD = anoxia) + (0.145 if COD = CVA) + (0.184 if COD = other) + (0.176 if race = African American) + (0.126 if race = other) + (0.411 if non–heart-beating) + (0.422 if partial/split graft) + (0.066 ((170 − height)/10)) + (0.105 if regional share) + (0.244 if national share) + (0.010 × cold time)].

Abbreviations: COD, cause of death; CVA, cerebrovascular accident.

*The cause of death was not trauma, stroke, or anoxia.

ELDERLY DONORS

Advanced age is a nontechnical and nonmodifiable donor variable that has a significant impact on early allograft function. Advanced age impairs regenerative capacity[51] and significantly increases the severity of hepatitis C virus (HCV) recurrence.[52-54]

Over the years, the mean age of donors has increased in Europe and the United States. Donor risk related to age also represents a continuum (Table 1).[8] There is no absolute limit of donor age for liver transplantation. Reports have shown excellent graft survival with octogenarian donors, provided that there are no additional risk factors.[55,56] It is strongly recommended not to allocate elderly donors to HCV-infected recipients.

LIMITS FOR PEDIATRIC RECIPIENTS

In most countries, pediatric recipients receive a specific priority for organ allocation. As a result, waiting list mortality is markedly lower than in adult recipients, and there is less incentive to use extended criteria allografts, except for the smallest children. Because the smallest children have difficult access to transplantation, the use of split-liver grafts is more often considered. The influence of factors such as steatosis and advanced age is unknown in children. Nonetheless, even if limited, waiting list mortality in pediatrics is hardly acceptable for the community.

Recent reports suggest that technical variations including split-liver transplantation and living donor liver transplantation (LDLT) are associated with increased morbidity and a slight decrease in survival in comparison with whole liver transplantation.[57] However, donors meeting extended criteria because of age, steatosis, cause of death, or liver function abnormalities should not be considered for splitting. Donor age limits should be more restrictive for pediatric recipients.

DONORS WITH INFECTION

Donors with positive viral serologies where transmission to the recipient is possible (ie, hepatitis B core antibody positivity, hepatitis B surface antigen positivity, HCV antibody positivity, and other infections, eg, human T-lymphotropic virus 1) should be used only in certain circumstances (eg, if the recipient is already infected with the same agent or the recipient has a critical need and is fully informed of the risk of subsequent donor transmission).[58,59]

Bacterial infections in the donor do not represent by themselves a risk factor for liver graft failure. The risk of transmitting a bacterial infection in the case of bacteremia in the donor is low. Although there is no evidence that a positive culture of preservation solution requires systematic prescription of prophylactic antibiotics, early fever and positive blood cultures in the recipient as well the presence of yeast justify empirical therapy.[60-62]

Donors with documented bacterial meningitis do not

TABLE 2. Estimated Risk of Transmission of Malignancy from Donor to Recipient According to the Type of Malignancy and Recommendations Concerning the Use of Organs

Malignancy	Estimated Risk of Transmission	Recommendations
Central nervous system malignancy	0.37%	—
Grade I/II	0%	Use with caution
Grade III/IV	40%	Reject
Melanoma	81%	Reject
Lung cancer	39%	Reject
Colon cancer	19%	Reject
Renal cell carcinoma	61%	Use with caution*
Breast	29%	Reject

*Transmission has been frequently limited to the kidney graft.

preclude transplantation, provided that recipients receive prophylactic antibiotics during the early post-transplantation period.[63] Donors in whom brain death results from an undefined central nervous system infection are probably at risk of transmitting the infectious disease. In this group, further evaluation with newer nucleic acid testing techniques is warranted.

DONOR WITH MALIGNANCY

The incidence of cancer in donors is approximately 3%, and the risk of transmitting malignancy by transplantation of an organ is roughly 0.01%.[64-66] It can be reasonably assumed that the risk of malignancy increases with donor age, and this means that transplanting organs from elderly donors may increase the risk of transmitting defined and undefined malignancies. Independent of the organ transplanted, the most frequently transmitted malignancies originate from central nervous system tumors, melanoma, renal cell carcinoma, and lung carcinoma. The estimated risks of transmission of the most frequent donor malignancies and corresponding recommendations are summarized in Table 2.[64,66] The risk of transmission is increased in the case of a metastatic malignancy in the donor. In addition, tumor grade is an important risk factor, poor differentiation being associated with a higher risk of transmission.[66] Donors with a documented history of malignancy are not necessarily discarded. Donors with low-grade malignancies treated years ago (ie, skin cancers other than melanoma) or donors with low-grade central nervous system tumors and an especially low risk of transmission to the recipients may be considered. Guidelines and practices vary according to different countries.[14,67] However, any metastatic malignancy in the donor should exclude donation.

Recipients of donors with malignancies should have their immunosuppression modulated because overimmunosuppression reduces immune surveillance that can accelerate tumor growth. The potential benefit from mammalian target of rapamycin inhibitors, which have both immunosuppressive and antiangiogenic properties,[68] requires investigation.

SPLIT LIVER

Surveys in Western populations indicate that split-liver transplantation in adults is associated with significant increases (about 10%) in graft failure and recipient morbidity.[3,8,69-71] Results are notably better in children.[72] Even if split-liver allografts are procured from young donors with normal parenchyma and short CIT, they should be considered extended criteria grafts for the following reasons: (1) the graft volume is generally lower than the recipient's standard liver volume and may be insufficient to adequately meet the metabolic demand during the early postoperative course, and (2) there are higher technical requirements, and nonoptimal positioning of the partial graft may result in compromised venous outflow. As a result, biliary leakage, hepatic artery thrombosis, focal or global outflow obstruction, and poor early graft recovery are more frequent in comparison with whole organ transplantation.[73]

Split-liver transplantation for 2 adults has been performed in select transplant centers with better results for right allografts versus left allografts.[74,75] Adult transplantation with a left graft remains a challenging technical procedure with a high risk of primary nonfunction due to insufficient parenchymal volume and often complex biliary and vascular anastomosis.[73] Even if an optimal donor is selected, split-liver transplantation is hampered by logistical constraints requiring short CIT and recipient limitations.

Split-liver transplantation can be considered only in optimal donors and yields at least 1 extended criteria allograft. Unless significant technical advances are achieved, the use of left allografts cannot be widely applied to adults but are best suited for pediatric recipients in whom split-liver transplantation offers excellent results. In adults, split-liver transplantation using the right lobe slightly increases the rate of graft failure. This should not represent a disincentive for using split-liver transplantation as this technique expands the donor pool, particularly for pediatric recipients. Overall, split-liver transplantation provides more aggregate years of life than whole organ transplants.[76] Recent data demonstrate no significant difference between in

situ and ex vivo surgical techniques in experienced centers.[77]

LIVER DONOR LIVER TRANSPLANT

The results of LDLT differ according to whether the recipient is an adult or child, the location of the center, and the experience of the center. Accumulated experience with pediatric LDLT has proven that short-term and long-term survival rates are similar to or even better than those obtained with deceased donor organs in children.[27] In contrast, in Western countries, most reports suggest that the results of adult-to-adult LDLT are less favorable than those of whole grafts from deceased donor transplantation,[14,27] even though the most recent reports in the United States indicate similar patients survival when it is adjusted for several factors, including the Model for End-Stage Liver Disease (MELD).[78] The results of adult-to-adult LDLT in Western countries have not been as good as those in some Asian countries where the absence (or extreme scarcity) of deceased donors has mandated widespread utilization of living donation and improved the safety and efficacy of this technique.[79,80] This may partially explain the plateau in adult-to-adult LDLT in Western countries.

For Western adult recipients, almost all living donors must undergo right hepatectomy in order to transplant a sufficient parenchymal volume (while left lobe resection is generally sufficient for adult-to-child LDLT). On theoretical grounds, right grafts procured in living donors might be optimal grafts because the donor is highly selected, the liver parenchyma is normal, CIT is very short, and the whole procedure can be scheduled. However, in European registry reports, right lobe adult-to-adult LDLT carries higher mortality and morbidity risks in comparison with whole liver deceased donor transplantation.[27] In US reports, LDLT achieves similar results only after experience has accumulated in centers to overcome a learning curve.[78,81] Liver allografts originating from living donors should be considered extended criteria allografts even though, by definition, living donors are ideal donors. Paradoxically, minor technical differences between deceased donor split-liver transplantation and right lobe living donation can translate into a significant increase in posttransplant morbidity after living donation. This may be related to the absolute need to preserve sufficient liver parenchyma volume with its pedicles in the donor. Some studies have suggested that posttransplant regeneration of the partial graft can enhance recurrence of both malignancy and viral infection.[82,83] However, these results have not been confirmed by others,[84] so no particular caution should be recommended in these patients with respect to LDLT.

Overall, partial liver grafts from living donors should be considered extended criteria allografts with more technical complications and an increased risk of graft failure,[81,85-87] particularly where there is little experience with these more complex surgical techniques. After LDLT, the better outcome reported in Asian countries can probably be attributed to the maintenance of excellent technical skill with a great number of cases performed each year and to other factors such as the recipient size, etiology of liver diseases, and optimal timing of transplantation.[88-90] These results raised the minimum number of cases per year required for achieving adequate results. Selection criteria of right lobe living donors are extremely stringent and necessary to preserve donor safety.[91]

LEFT LOBES FOR TRANSPLANTING ADULT RECIPIENTS

On theoretical grounds, there are several justifications for considering left lobes for transplanting adult recipients. First, there are many more adult recipients than pediatric recipients. A large number of adult recipients could benefit from a left lobe graft originating from split-liver transplantation. Second, in the context of LDLT, the procurement of a left graft in a living donor carries significantly lower morbidity rates than the procurement of a right graft. Third, in contrast to a right graft, a left graft more frequently represents a true anatomical entity and is more likely to have a single arterial and portal supply, a single outflow vein, and a single bile duct. Finally, as a result of the huge regenerative capacities of the liver, a healthy individual undergoing right hepatectomy has a rapid recovery in liver function. A similar process might be expected in a recipient receiving a relatively small left graft.

Until now, except in series from highly specialized Asian centers[89,92,93] and in recipients weighing less than 50 kg, the results of adult-to-adult left lobe liver transplantation have been dismal, with a high rate of primary nonfunction. A low graft-to-recipient weight ratio (<0.8%) is considered to be the main cause of graft failure. However, several measures might help improve the results of left lobe transplantation in adults, including short CIT, optimal positioning of the graft (aimed at ensuring optimal venous outflow), and calibrated portal flow (in order to avoid overperfusion and the resulting parenchymal damage).[94] These innovative strategies need to be validated.

Dual left lobe LDLT, a technique consisting of transplanting 2 left lobes from 2 different living donors, represents another alternative. Early results have been encouraging.[89] Even though 2 living donors are involved in this procedure, mortality and morbidity risks for each donor are lower than those related to right lobe donation. However, this technique is complex and demanding on a logistical basis.

Dual left lobe transplantation using 1 graft from a living donor combined with 1 split graft from a deceased donor has been reported recently.[95]

DOMINO TRANSPLANTATION IN THE CONTEXT OF FAMILIAL AMYLOID POLYNEUROPATHY (FAP)

Apart from the genetic defect resulting in the production of variant transthyretin, a protein whose accumu-

lation eventually leads to polyneuropathy, the liver of a patient undergoing transplantation for FAP is normal. Transplant candidates with FAP are frequently younger than 50 years, and these patients' native livers, when excised at the time of transplant, have been used as allografts for other recipients.[96-98] Indeed, optimal results can be expected in domino transplantation as the CIT can be minimized. Transmission of the FAP metabolic defect to the recipient is constant. Recipients of domino allografts have detectable blood levels of variant transthyretin following transplantation.[99,100] However, the development of the amyloid disease is uncommon. According to an international registry, only 2 of 540 domino recipients developed manifestations of polyneuropathy; this occurred 7 and 8 years after transplantation, respectively.[101] Although procuring the FAP patient's liver most often requires preservation of the inferior vena cava, which may increase technical difficulties in implanting these livers into the second recipient, domino grafts from patients with FAP can be considered reference grafts rather than extended criteria allografts, particularly for candidates whose life expectancy is less than the time needed to develop amyloid disease, such as older candidates. In addition, novel methods of reconstruction may allow the transplantation of whole grafts without the retrohepatic inferior vena cava.[98] However, FAP is a rare disease, and domino transplantation is a modest contribution to the expansion of the donor pool.

NON–HEART-BEATING DONORS

Liver transplantation from non–heart-beating donors, now termed donation after cardiac death (DCD), is a promising way to increase the supply of organs.[102] In controlled circumstances, the organs are retrieved after a standoff period of 2 to 5 minutes after death is certified. In some countries, only uncontrolled DCD, including patient death on admission and/or unsuccessful resuscitation, is accepted because of ethical considerations.

In either controlled or uncontrolled DCD situations, the organs are subjected to a variable period of warm ischemia, which predisposes them to primary nonfunction, delayed graft function, or irreversible ischemic-like diffuse cholangiopathy.[103] In early reports, the prolonged period of warm ischemia resulted in markedly increased early graft dysfunction in comparison with donation after brain death donors. It has been possible to achieve good results with an incidence of primary nonfunction below 15% and a lower incidence of biliary complications with specific measures.[104,105] These measures include judicious donor selection, including donor age below 40 years and no steatosis, a specific resuscitation technique, including preservation of the organ with systemic heparin, the use of extracorporeal oxygenation, a short warm ischemia time (less than 15 minutes), and a short CIT (less than 10 hours)[106,107] (Table 3). Although this procedure is limited to selected centers with specific protocols, DCD has the potential to increase the donor pool by 10% to 20%.[102,105] Methods to address the microcirculation of the biliary system in DCD donors may improve the incidence of biliary strictures.[38]

TABLE 3. Selection Criteria for Non–Heart-Beating Donor Transplantation

Donor Factor	Selection Criteria
Donor age	<40 years
Intensive care unit stay	<5 days
Warm ischemia*	<15 minutes
Cold ischemia	<10 hours
Steatosis	Absent or minimal

*Warm ischemia is defined by a mean arterial pressure < 50 mm Hg and/or oxygen saturation < 70 mm Hg.

DONOR RISK SCORES

In parallel to recipient risk scores (eg, the MELD score), studies have focused on the identification of donor factors that are associated with graft failure after transplantation. The objectives are to quantify the risk associated with any donor and to identify important associations of donor variables.

A donor risk score has been proposed, based on a large series of deceased donors for adult recipients in the United States.[8] Factors entered in this score and the score itself are shown in Table 1. The risk score is derived from these factors in addition to regional sharing versus national sharing and CIT. CIT is not available at the time of offer because it depends on the duration of hepatectomy in the recipient. In the United States, the median donor risk index has steadily increased since the end of the 1990s. In general, the number of discarded donors increases with increasing donor risk score. Donor risk score obviously helps assess the risk for a given donor. However, it does not take into account important variables such as steatosis. No such score has been established in European or Asian populations. In these areas, some variables such as African American or regional sharing versus national sharing may not be relevant.

The issue of how donor risk score may help optimize donor and recipient matching remains open. An interesting finding in the United States is that the lower the MELD score is in the recipient, the higher the donor risk index liver that is used. However, as indicated previously, there is evidence that recipients with high MELD scores are those who derive the highest benefit from transplantation with a high donor risk index organ.[108]

ROLE OF BIOPSY

In a number of situations, liver biopsy is the reference for accepting or discarding any liver graft. Frozen section biopsy permits rapid assessment of liver architecture, fibrosis, steatosis, inflammation, and extent of hepatocyte necrosis. Biopsy is the only reliable method for assessing the extent of macrovesicular steatosis and

TABLE 4. Role of Liver Biopsy in the Selection of Extended Criteria Donors

Donor Variable	What Is Expected from Frozen Section Biopsy
Fatty liver (on the basis of donor BMI, liver function tests, ultrasound examination, and inspection at procurement)	Distinction between microvesicular and macrovesicular steatosis Quantification of macrovesicular steatosis Identification of superimposed lesions (ie, fibrosis and inflammatory infiltrates)
Candidate for LDLT with abnormal liver function tests and/or hyperechogenicity	Identification and quantification of macrovesicular steatosis
Anti-HCV positive donor	Identification of any grade of fibrosis
Donor with any risk factor for chronic liver disease (alcohol abuse in particular) and abnormal appearance at procurement	Identification of any grade of fibrosis, inflammation, or other parenchymal changes

Abbreviations: BMI, body mass index; HCV, hepatitis C virus; LDLT, living donor liver transplantation.

TABLE 5. Allocation Policies of Extended Criteria Donors for Low-Risk or High-Risk Recipients: Arguments Pro and Con

Policy	Arguments
Extended criteria graft to the healthiest recipients	Pro: The recipient can tolerate a difficult postoperative course. Con: The recipient can wait for a better graft.
Extended criteria graft to the sickest recipients	Pro: The recipient will die if he does not receive a donor rapidly. No synergistically adverse interactions of the donor risk index and Model for End-Stage Liver Disease score have been identified. Con: The recipient is unlikely to endure the difficult postoperative course.

addressing the issue of superimposed lesions, such as fibrosis and inflammatory infiltrates, which can represent contraindications to transplantation (Table 4). A single biopsy is sufficient for assessing steatosis.[42] Independent of steatosis and fibrosis, the usefulness of biopsy for allograft assessment in the context of elderly donors, unstable hemodynamics, and DCD requires clarification. Similarly, evidence that biopsy is useful in donors with a history of alcohol abuse when the appearance of the graft is normal at the time of organ procurement is lacking. An important goal in utilization of extended criteria allografts is minimal cold ischemia. Unfortunately, frozen section biopsy may prolong the selection process and increase cold ischemia. The benefits of biopsy must be balanced against its consequences in terms of CIT. In addition, difficulties can be anticipated with frozen section biopsies.

Because of insufficient data, liver biopsy has not been integrated into donor risk scores, although it can be anticipated that biopsy has a significant impact on the risk of graft failure.

MATCHING EXTENDED CRITERIA DONORS AND RECIPIENTS

The matching of donors and recipients is not random. Allocation policy is based on utility, equity, reduction of waiting list mortality, and transplant benefit. We have switched from the concept of low-risk organs (non–extended criteria donors) for high-risk patients to another concept, according to which the sickest patients may benefit from any organ (Table 5). This switch is supported by the finding that there is no significant interaction between donor risk index and MELD score in the recipient.[109] In other words, the donor risk index imposes the same amount of risk for graft failure, regardless of the severity of the recipient's disease. Recent data based on large cohort studies in the United States have confirmed that the benefit from transplantation is higher when extended criteria donors are transplanted into recipients with MELD scores over 20.[108] Thus, using grafts from extended criteria donors adds significantly more risk to stable patients than they already carry but increases the chance for long-term survival for patients at high risk of dying of their liver disease. Therefore, extended criteria donors should be proposed for patients with higher risks of dying such as those with MELD scores > 20.

There are no algorithms for the allocation of extended criteria donors to either high-risk or low-risk patients. In hepatocellular carcinoma patients, the allocation policy must take into account not only the MELD score but also the risk of tumor progression on the waiting list. General policies allow the transplant practitioner to make a decision.

REPERFUSION STRATEGIES AND SURGICAL TECHNIQUES

Reperfusion strategies and surgical technique can make a significant difference in extended criteria allografts. Any technique should be aimed at reducing CIT as much as possible and avoiding liver injury.

Specific reperfusion techniques have been proposed in order to limit injury in extended criteria allografts. In comparison with the standard procedure (end-to-end caval anastomosis), the piggyback technique decreases the operation time and shortens the anhepatic phase as well as the warm ischemia time. In addition, preservation of caval flow, sometimes associated with preservation of portal flow when associated with temporary portocaval anastomosis, maintains hemodynamic stability.[110] However, these potential advantages have not been clearly assessed yet for extended criteria grafts. Progressive rewarming of the graft by initial retrograde reperfusion through the caval anastomosis seems to improve early graft function.[111] It has been shown that initial arterial reperfusion and simultaneous arterial and portal reperfusion both decrease the rate of reperfusion syndrome and improve early graft function.[112,113] The initial high perfusion pressure with a maximum oxygen supply delivered by the arterial flow is balanced by a prolongation of the anhepatic period because arterial anastomosis takes more time. These variations in technique need to be assessed prospectively in detail.

POSTTRANSPLANT MANAGEMENT OF SMALL-FOR-SIZE GRAFTS

Small-for-size syndrome results from the transplantation of a liver parenchymal mass insufficient to meet the metabolic demands of the recipient in the early postoperative period. This situation, which occurs more frequently in recipients with cirrhosis and poor liver function, is attributed to the adverse effect of high portal flow in a small volume graft. Small-for-size syndrome is characterized by significant ascites associated with a high bilirubin level, a low prothrombin index, and a slight elevation of transaminase levels. Small-for-size syndrome has been associated with a high mortality rate.[114]

Specific interventions for the management of small-for-size syndrome are essentially preventive. A reduction of portal venous pressure and flow is considered the main objective. This objective can be achieved by splenic artery ligation and/or mesocaval shunt.[94,114] Therapies aimed at modulating vascular tone (nitric oxide donor and endothelin receptor A antagonist) in partial grafts during the early posttransplantation period could also help improve the outcome.[115] However, none of these agents have been validated. In this setting, the results of albumin dialysis have been dismal.[116] On the basis of the experience of LDLT, optimization of outflow with large caval anastomosis is strongly recommended when potential small-for-size grafts are used.

USE OF EXTENDED CRITERIA GRAFTS IN HCV-INFECTED PATIENTS

Donor factors are potentially involved in the outcome of HCV-infected recipients through the severity of and time to HCV recurrence. Advanced donor age is a donor variable that strongly correlates with HCV recurrence[52,117] and fibrosis rates, with these donor age–associated effects on HCV recurrence appearing for donors 40 years old and older.[53] Some have recommended that elderly donors be allocated to recipients without HCV infection.[52] However, HCV-infected patients represent a substantial proportion of all candidates waiting for liver transplantation in Western countries. Therefore, on a practical basis, not all HCV-infected patients can be transplanted with donors less than 40 years old. Allocation should be performed according to patient benefit. Although warm ischemia may affect the course of HCV recurrence,[118,119] there is no clear evidence that, independent of age, donor steatosis and prolonged cold ischemia have a deleterious impact on posttransplant HCV recurrence. Similarly, as discussed previously, there is no evidence that a reduced-size graft (split or living donor) impairs outcome.

Because HCV virus genotyping is typically unavailable at the time of procurement, it must be assumed that the viral genotype in the donor is one least sensitive to interferon therapy. Acceptable results have been reported from HCV-infected recipients of HCV-infected allografts.[58,120-122] HCV infection is not equally distributed throughout the world. In the United States and most of Europe, the contribution of HCV-infected donors to the expansion of the donor pool is modest.

CRITERIA FOR EMERGENCY RETRANSPLANTATION

Using expanded criteria donors increases the risk of primary nonfunction. Therefore, patients should be informed about the possibility of retransplantation.

In Europe, 47% of all retransplants are performed within 1 month after transplantation. Primary nonfunction is the main indication for emergency retransplantation during this early period. The survival rate after emergency retransplantation (about 50% at 1 year) is markedly inferior to that of initial transplantation.[123]

Criteria for emergency retransplantation in the context of extended criteria donors have not been clearly established. It can be anticipated that criteria for emergency transplantation in patients with acute liver failure are not relevant to this population because, apart from insufficient liver function, a number of additional risk factors are involved (ie, previous major surgery, underlying chronic liver disease, and sepsis). In general, a retransplantation decision should be made at an earlier stage in comparison with patients with acute liver failure.

The following definition for primary nonfunction has been proposed: serum aspartate aminotransferase over 5000 UI/L and either an international normalized ratio

over 3.0 (regardless of fresh frozen plasma) or acidosis (pH $<$ 7.3 or serum lactate $\geq$ 2 times normal) all within 10 days following transplantation.[14] Primary nonfunction represents by itself an indication for emergency retransplantation. The issues of delayed graft function and small-for-size syndrome are more complex. More studies are needed to define the criteria and optimal timing for retransplantation.

ETHICAL CONSIDERATIONS AND PATIENT INFORMATION

An ethical allocation practice is based on justice, equity, and utility. Candidates for transplantation must be informed about the possibility of allograft-specific risks. They need to understand early in the transplant process (ideally at listing and without an allograft available) that donor risk is a continuum. A distinction between the risk of graft failure and the risk of disease transmission should also be emphasized as part of the informed consent process.

The criteria for accepting and discarding extended criteria donors remain variable from country to country and from center to center. A prospective evaluation necessitates that the donor characteristics and the outcome be periodically reported in a standardized manner and centralized.

CONCLUSIONS AND PERSPECTIVES

It can be reasonably assumed that the issue of the chronic imbalance between the number of potential recipients of liver transplantation and available donors (the imbalance between supply and demand) will not be solved within the next decades. In the context of organ shortage, a number of patients with end-stage liver disease and/or liver malignancy are not considered for liver transplantation, although they could derive a significant benefit from this option. In the absence of an efficient alternative to transplantation, the expansion of the donor pool will continue to be a priority. Therefore, efforts should be made to better determine which expanded criteria donors can be considered for liver transplantation, how they have to be managed, and in which candidates they should be transplanted in order to optimize resource utilization.

Beyond the specific scope of liver transplantation, further studies focusing on the area of expanded criteria donors will continue to help us better understand many aspects of liver diseases, liver surgery, and, more generally, strategies for optimizing healthcare resources.

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