6 Recipient and Donor Selection and Transplant Logistics—The European Perspective

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The intermediate and long-term outcome following orthotopic liver transplantation (OLT) has improved significantly over the years, with 1- and 5-year patient survival rates of 90% and 75%, respectively. This success resulted in growing numbers of potential transplant recipients on waiting lists. The unchanged number of liver grafts during the last decades cannot meet the increasing demand for available organs (Fig. 6.1). Therefore regardless of various organ allocation policies adopted by transplant programs, waiting list mortality remains a major problem. This chapter will describe the current situation in Europe with special emphasis on efforts to increase the availability of liver grafts.

Recipient Prioritizing

In most transplant centers all over the world liver allocation is performed on the basis of the MELD score [1], which predicts waiting list survival at 3 months. For some underlying diseases severity of chronic liver failure is not reflected by laboratory MELD (lab MELD) score, such as hepatocellular carcinoma in mild cirrhosis, some metabolic diseases, and others. Therefore, standard exceptions were defined that receive usually 22 MELD points (15% 3-month mortality equivalent). Patients can be requested for a standard exception (SE) at any time after registration in the Eurotransplant area. Recipients must fulfill country- and disease-specific criteria before the exceptional MELD (match MELD) can be approved. If the exceptional MELD was approved, this status is granted for the duration of 90 days. Before the expiry of this 90-day period the SE status must be reconfirmed.

In Eurotransplant MELD allocation was introduced in 2006, but typically for the heterogeneity in Europe modalities are somewhat different between the countries. Germany, Belgium, and the Netherlands pursue a patient-based allocation system according to match MELD. In contrast, Austria, Croatia, and Slovenia use a center-oriented allocation system. The advantages of allocation based on the MELD score is the transparency and objectivity. Nevertheless, medical urgency is not always appropriately expressed by the MELD system and for several disease patterns standard exceptions have been defined to overcome this problem. Another significant disadvantage under strict patient-oriented allocation system (according to MELD) is the impossibility for donor and recipient matching. For example ECD organs may have a higher risk for initial dysfunction, fair even worse with prolonged cold ischemia time and may therefore not be suited for every candidate. Despite a number of models predicting outcome based on donor and recipient factors [2–4] the clinical judgment of the transplant team has the final decision.

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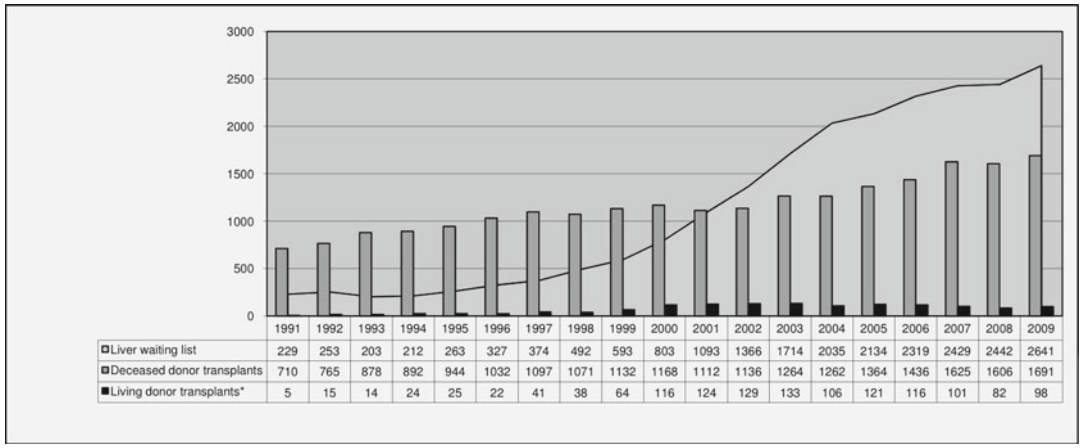

	1991	1992	1993	1994	1995	1996	1997	1998	1999	2000	2001	2002	2003	2004	2005	2006	2007	2008	2009
Liver waiting list	229	253	203	212	263	327	374	492	593	803	1093	1366	1714	2035	2134	2319	2429	2442	2641
Deceased donor transplants	710	765	878	892	944	1032	1097	1071	1132	1168	1112	1136	1264	1262	1364	1436	1625	1606	1691
Living donor transplants*	5	15	14	24	25	22	41	38	64	116	124	129	133	106	121	116	101	82	98

Fig. 6.1 Dynamics of the Eurotransplant liver waiting list and liver transplants between 1991 and 2009 [1]

Organ Distribution

Objectives of Organ Procurement Organizations (OPOs) are almost comparable all over the world and aim to achieve an optimal use of available donor organs and secure a transparent and objective allocation system. Furthermore, they assess the importance of factors that have the greatest influence on waiting list mortality and transplant results. OPOs also promote, support, and coordinate organ donation and transplantation. In Europe many different OPOs exist: national structured agencies like in Spain, France, or Italy as well as multinationally structured agencies. Within a multinational OPO legislation the national legislation is prioritized over international interests of the organization, for example, when it comes to issues such as presumed or informed consent for organ donation. The most important multinational OPOs in Europe are the following:

– Scandiatransplant [5] is the Scandinavian organ exchange organization and covers a population of 24.5 million in five countries (Denmark, Finland, Iceland, Norway, and Sweden). The most frequent exchanged organ between centers within Scandiatransplant is the liver followed by heart. The overall exchange rate of kidneys has stabilized around 12% during the last years. One third of kidney transplants are performed from living donors.
– NHS Blood and Transplant [6] combines the United Kingdom and the Republic of Ireland with a total population of 65.4 million. Donor livers are not allocated to patients but are center-specific according to the "Donor Organ Sharing Scheme" prepared by the Liver Advisory Group. Following these general principles donor/recipient matching should be provided, especially for livers derived from donors with extended criteria.
– Eurotransplant [7] is the central European OPO and covers a population of 124.6 million inhabitants in seven countries (Austria, Belgium, Croatia, Germany, Luxemburg, the Netherlands, Slovenia). The most frequently exchanged organs between centers are kidneys. In the setting of acute liver failure the next available appropriate organ within the ET area is offered to the requisitioning transplant center. Liver exchange thereafter follows a payback system, which means that the recipient center has to offer the next available donor liver of equal blood group to the previously donating center. Allocation priority is ranked from "high urgency" to "accepted combined transplantation" to "center" to "ET pool."
– The Spanish transplant system [8] is well known all over the world as (one of) the most successful in the world with more than 35 donors per one million inhabitants. The main principles of the Spanish Model of Organ Donation are an unrivaled transplant coordination network. In-house coordinators perform a continuous audit on brain deaths and

outcome after donation at intensive care units in transplant procurement hospitals. They are specially trained in communication with hospital staff as well as relatives. A central office as an agency in support of the process of organ donation has a great influence on medical training and maintains close relationships with the media and intensive care units.

Donor Selection

The disparity between organ demand and available grafts has increased over the past years. Since outcome of liver transplantation has improved transplant centers now face the problem of increasing numbers of patients listed for liver transplantation. On the other hand the number of available donors remained stable [7, 9, 10]. Therefore, several strategies have been developed to increase the donor pool (Fig. 6.2a). Most popular strategies are the use of extended criteria donors (ECDs), donation after cardiac death (DCD), and living donation (LD) (Fig. 6.2b).

Extended Criteria Donor

Several publications convincingly showed that donor factors such as age, gender, race, graft type, and ischemia time affect post-transplant survival [2]. Despite the definition of risk factors, their relative risk for post-transplant primary non-function or poor function is weighted differentially [3, 11] and an accepted definition of ECD livers with cut-off values has not been established yet. Age is one of the best-described extended donor factors. Several studies investigated a donor age older than 55 as significant factor for poorer graft survival [2, 3, 12]. Nevertheless due to changes of the donor demographics in the last decades donor age and age-related comorbidities have increased. Donor death from cardiovascular reason is now more common than trauma as the cause of death [13] and more than 60% of organs are harvested from donors who died due to cardiovascular disease.

Cold ischemic time is another very well-documented donor risk factor and an imprecise cutoff between 10 and 13 h has been investigated [2, 3, 14]. In an era of MELD-based allocation this is a very important aspect. Increased local donor utilization would therefore result in decreased transportation times and reduced cold ischemic times.

Donor graft quality is one of the main determinants of outcome in liver transplantation. It is difficult to classify the quality of organs based solely on laboratory values however some authors consider donor transaminases levels >150 U/l as risk factors [15, 16]. Increased donor gamma-glutamyl transpeptidase has also been identified as a risk factor for increased 3 months graft failure but not 1-year survival [17]. Biopsy-proven steatosis was responsible for primary non-function rates up to 25% and was highly correlated with increased donor age and obesity [18].

Direct osmolar damage caused by increased plasma sodium levels is responsible for hepatocellular swelling and dysfunction. Totsuka et al. [19] reported comparable outcomes between normonatremic and hypernatremic donors after correction of sodium levels below 155 mEq/ml. However we found that the peak sodium values during the intensive care unit stay was a significant factor for post-transplant outcome [17]. This supports the theory that a short duration of plasma sodium value deviations may cause long-lasting damage in hepatocytes due to changes of intracellular osmolarity even when sodium levels are rapidly and aggressively corrected.

Donation After Cardiac Death

DCD is the donation of organs shortly after cardiorespiratory support has been terminated and cardiac death ensued. Most DCD donors are patients who suffered severe irreversible cerebral injury but not brain death and the family/health care proxies wish to withdraw support. Minutes after death occurred the organs are harvested for transplantation.

The recent increase of DCD in some European countries has contributed to an increase in the number of transplants with outcomes comparable

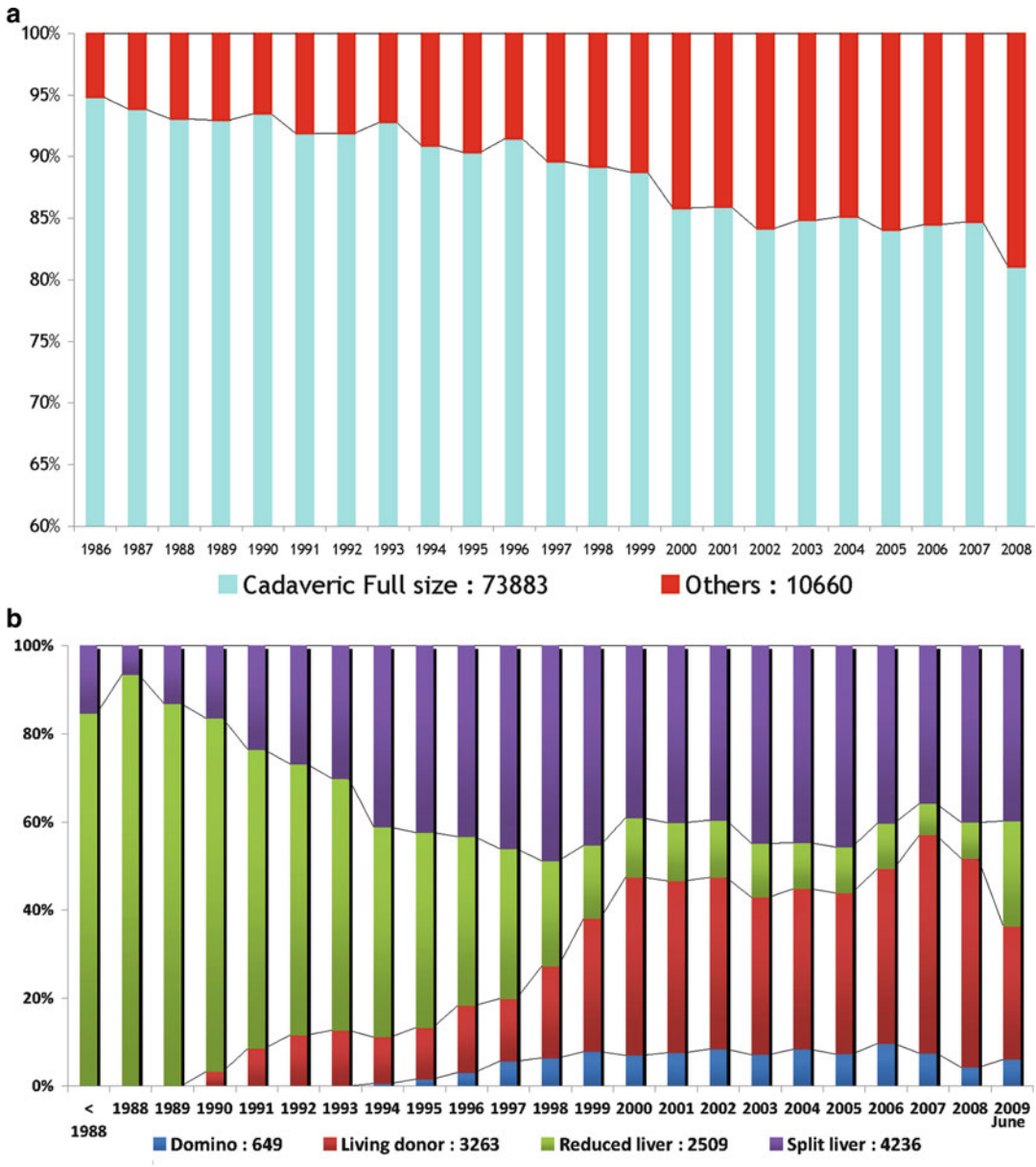

Fig. 6.2 (**a**) Type of liver graft in Europe according to the date of transplantation. (**b**) Alternatives to the use of full-size cadaveric liver grafts in Europe [3]

to grafts from brain death donors (DBD). However DCD donation may not be necessarily a new and additional source of grafts, as data from the Netherlands [20] indicate because the use of DCD organs may have caused a shift from potential heart-beating donors to DCD. Intensive care providers may be encouraging DCD donation rather than awaiting brain death and subsequent heart-beating donation. This development could be reversed during the last years, resulting in an effective increase in organ availability.

In DCD organs, the effects of cold ischemia are superimposed by the injury occurring during warm ischemia. Biliary epithelium is particularly vulnerable to ischemia/reperfusion injury and a high incidence of biliary strictures and/or bile

cast syndrome [21, 22] has become of concern. Ischemic cholangiopathy has been reported in 9–50% of DCD recipients. This complication tends to present within the first few months after OLT and may resolve with biliary drainage, require repeated interventions, or lead to graft loss and retransplantation.

In the future extracorporeal machine perfusion of liver grafts may be a potential feature to overcome ischemic cholangiopathy. Various techniques have been investigated in animal studies including normothermic or subnormothermic perfusion [23, 24]. Extracorporeal perfusion may have the ability to "recondition" the damaged liver graft that has undergone warm ischemic injury during DCD procurement [25, 26].

Patient and graft survival rates similar to those of DBD OLT can be achieved by using controlled DCD grafts and very restrictive criteria, despite a higher risk of biliary stricture [27]. Recommended Practice Guidelines have been published recently by ASTS [28] and are similar to selection criteria recommended by European centers [22, 27, 29]. Considering organ shortage and death on the waiting list DCD grafts remain a small but valuable resource.

Living Donor Liver Transplantation

Unlike kidney transplantation, there has not been clear-cut evidence for a significant advantage in post-transplant survival after living donation yet. The overall results with good patient and graft survival combined with acceptable donor morbidity and mortality has led to the acceptance of LDLT in the transplant community.

Left-lateral LDLT in children has become a standard procedure with excellent results, whereas LDLT in adults has still some conflicting issues. The number of LDLT procedures peaked in 2001 in Europe and the US, thereafter showing a significant decrease of cases in the US and no further increase in Europe. In the assessment of the reason for this development LDLT grafts were most likely to fail because of graft-related issues [10]. Recipients have a higher risk for primary non-function or dysfunction due to small for size and a significantly higher risk for technical failures, especially biliary and vascular complications. Additionally the mortality risk of approximately 0.2% and morbidity risk of 11-28% for donors represent non-negligible limitations for the use of LDLT grafts.

LDLT accounts for less than 5% of all liver transplants in Europe and US, respectively [9, 10]. The number of LDLT in Asia has continued to increase due to the limitations in DBD caused by legal and cultural restrictions on deceased organ donation. Ninety-five percent of all OLTs in Asia excluding mainland China are LDLT [30].

One of the main advantages of LDLT is the precise scheduling of the procedure due to independence of waiting time and available liver grafts. Therefore OLT can take place according to disease severity and recipient conditions. Especially for patients suffering from hepatocellular carcinoma, LDLT represents a useful treatment option to reduce waiting time and consecutive disease progression.

A potential survival benefit due to decreased death on the waiting list and reduced disease progression has to be balanced with higher morbidity and mortality following transplantation. Future application of LDLT will be based on the accurate definition of risks imposed on donors compared with potential benefits realized by recipients.

Conclusion

The progress of transplantation is limited by organ shortage. Several strategies have been developed to overcome this problem during the last few decades. Most important for increasing the pool of deceased donor seems to be education of the public and physicians. It is important to increase the awareness for organ donation and transplantation. ICU staff must be continuously contacted and informed about the benefits of transplantation, and guidelines should be established to support them with donor management. With the current organ shortage a number of patients are rejected as recipients although they may derive a significant benefit from this OLT.

It remains a formidable challenge to balance the demands of individual autonomy of the recipient and the utility of the donor organ on a background of justice and equity.

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