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REVIEW

# Renal transplantation from extended criteria cadaveric donors: problems and perspectives overview

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## Summary

The critical shortage of organs available for renal transplantation has led to the consideration of alternative strategies for increasing the donor pool. Recently, the cadaveric kidney donor pool extended to donors who might have been deemed unsuitable in early times, leading to the concept of marginal donors and more recently to the notion of expanded criteria donors. Such organs are eligible for organ donation but, because of extreme age and other clinical characteristics, are expected to produce allograft at risk for diminished post-transplant function. Thus, the challenge is now to reduce the difference between graft outcome from patients grafted with marginal and 'optimal' donors. This implies appropriate transplantation strategies during pre-, peri- and post-transplantation phases including reduction of cold ischemia time, recipient selection, adaptation of immunosuppressive drug regimens, increase in nephron mass by dual kidney transplantation, and improvement in the graft selection process using histological criteria. This review summarizes current definition of a marginal donor and provides some guidance for clinical management of such transplant.

## Why grafting a marginal kidney?

In spite of considerable progress in improving short- and long-term graft survival after renal transplantation, numerous problems that interfere with successful outcome remain unresolved. One is the growing discrepancy between availability of organ donation and the increasing need for kidney grafts because of the rising incidence of end-stage renal disease [1]. This generates a great disparity between patients waiting for and those receiving renal transplants, and this situation is likely to worsen in the future. Thus, according to United Network for Organ Sharing (UNOS) data registry [2], the annual increase of the number of transplantation procedures is 4% whereas the number of patients on the transplant waiting list increases by about 20% per year. In parallel, the overall annual mortality rate for patients on waiting lists for renal transplantation is estimated to be 6.3% [3]. This critical shortage of organs available for renal transplantation has led to the consideration of alternative strategies to increase the donor pool [4]. One of the strategies is the expansion of the cadaveric kidney donor pool to include those considered as unsuitable in early times, the use of organs from older donors emerging as the most obvious option. Thus, before 2001, approximately 50% of cadaveric donors were over 60 years of age, therefore considered as of advanced age. Most of these kidneys were discarded because of the possible increased risk of primary nonfunctional and suboptimal allograft survival.

In parallel, global donor characteristics were changing with an increasing number of elderly donors with a history of hypertension and diabetes, deceased because of stroke or other cardiovascular causes [5]. In France, during the last decade mean cadaveric donor age has increased from 39 to 48.5 years and in 2005, 26.8% of French donors were over 60 years of age ([6] as per Agence de la Biomédecine reports, 2006). These two parameters (necessity to increase the number of organs

 

available and change in donor characteristics) led in the early 1990s to the concept of marginal donors and more recently to the notion of expanded criteria donors (ECD) defined by the UNOS as the donors who, because of extremes age and other clinical characteristics, are eligible for organ donation but are expected to produce allograft at risk for diminished post-transplant function [4,7]. Today, renal transplantation using marginal kidneys has clearly increased the number of grafted patients and the benefits of such strategy is demonstrated by the better patient survival compared with patients maintained on dialysis, with a gain in life expectancy ranging from 3 to 9 years [3]. The challenge is now to reduce the difference of outcome between patients grafted with marginal donors and those grafted with optimal donors. This implies the recommendation of appropriate transplantation strategies during pre-, peri- and post-operative management.

## Definition of a marginal donor

Before 2002, no universal or unequivocal definition of what constitutes a marginal transplantable kidney was available and, intuitively, most kidneys likely to display poor graft outcome because of the clinical characteristics of the donor – advanced age, impaired donor hemodynamics, prolonged cold ischemia time, and elevated serum creatinine prior transplantation – were discarded [6]. This has stimulated investigations designed to quantify the magnitude of increased graft failure risk relative to kidneys procured from ideal donors.

To expand the existing donor selection criteria, Port *et al.* [7] identified in a retrospective study four donor factors significantly associated with poor graft outcome. Using Cox regression models, expanded-criteria donor kidneys were defined as those with a relative risk of graft failure greater than 1.7, corresponding to a 70% higher risk of graft failure compared with ideal kidneys. All donors aged over 60, and donors aged 50–59 with at least two of three additional risk factors were considered as marginal. The three additional risk factors identified in this study were cerebrovascular accident as a cause of death, history of hypertension, and serum creatinine above 1.5 mg/dl prior to transplantation. This definition of expanded-criteria donor has now been validated by a consensus meeting organized by the American Society of Transplantation in Crystal City and is used to develop guidelines for the management of marginal kidneys [4].

According to this definition and after adjustment between donor and recipient variables, graft survival in recipients of kidneys from expanded-criteria donors was 92.3%, 84.5%, and 68%, respectively, 3 months, 1 year and 3 years after transplantation. In comparison, survival of grafts from nonexpanded-criteria donors was 94.6%, 90.6% and 79.7%, respectively, for the same periods [4]. Nyberg *et al.* [5,8] confirmed the strong correlation between donor age, cerebrovascular accident as cause of death, renal function status before transplantation and history of hypertension with early renal dysfunction at 30 days and 6 months after transplantation. In a French retrospective study by the Etablissement Français des Greffes, Pessione *et al.* showed in a multivariate analysis that only cerebrovascular cause of death, history of hypertension, and serum creatinine above 150 μmol/l were associated directly with decreased graft survival whereas donor age over 60 was considered as a dependent risk factor for cerebrovascular lesions present in the donor [9]. To improve the stratification and the identification of deceased donor kidneys with an increased risk of early graft dysfunction and graft loss, Nyberg *et al.* [5] devised another scoring system, the Deceased Donor Score (DDS). Among the seven donor variables significantly influencing the creatinine clearance of recipients at 6 months (age, creatinine clearance, history of hypertension, Human Leucocyte Antigen (HLA) mismatch, cause of death, ethnicity and cold ischemia time) five have the strongest independent influence on the graft outcome (Table 1). In this score, groups were graded in the order of increasing risk for graft failure (higher the DDS score means higher the risk). When DDS score was greater than 20, the 6-year graft survival was <70% compared with more than 80% when the DDS score was below 20.

## Outcome following marginal kidney transplantation

Kidney transplantation enhances quality of life and improves patient survival in all patient groups [10]. However, the survival benefits seen in recipients of marginal kidney transplants are inferior compared to recipients of standard criteria donor kidneys. Using OPTN/SRTR data, Danovitch *et al.* [11] reported that the annual death rate for recipients of ECD kidneys was 100/1000 patients-years at risk compared to 48/1000 patients-years at risk for recipients of standard criteria kidneys. The adjusted patient survival at 1 and 5 years for ECD kidneys was 90.6% and 69%, compared with 94.5% and 81.2% for non-ECD-kidneys [1]. In 2001, Ojo *et al.* [3] demonstrated that patient survival was significantly better in recipients of a marginal kidney than in those remaining on hemodialysis. In this study, definition of marginal donor kidney was based on the following pretransplant criteria: donor age more than 55 years, cold ischemia time more than 36 h, 10-year history of donor hypertension or diabetes mellitus, and nonheartbeating donor. Five-year patient survival was 74% in the marginal donor

**Table 1.** Deceased Donor Score for scoring adult donors in cadaver transplantation (5).

| Variable | Score |
|---|---|
| Age (years) | |
| <30 | 0 |
| 30–39 | 5 |
| 40–49 | 10 |
| 50–59 | 15 |
| 60–69 | 20 |
| >70 | 25 |
| History of hypertension | |
| None | 0 |
| Yes | |
| Duration unknown | 2 |
| <5 years | 2 |
| 6–10 years | 3 |
| >10 years | 4 |
| Creatinine clearance (ml/mn) | |
| >100 | 0 |
| 75–99 | 2 |
| 50–74 | 3 |
| <50 | 4 |
| HLA mismatch, no of antigens | |
| 0 | 0 |
| 1–2 | 1 |
| 3–4 | 2 |
| 5–6 | 3 |
| Cause of death | |
| Noncerebrovascular accident | 0 |
| Cerebrovascular accident | 3 |
| Total points | 0–39 |

group and 80% in the ideal kidney group ($P < 0.001$). The average increase in life expectancy for recipients of grafts from marginal donors was 5 years compared with the matched-cohort of patients on the waiting list [3].

The indices of renal allograft performance such as delayed graft function (DGF), acute rejection and allograft survival are also often inferior in ECD transplants [3,12,13]. In a study from the UNOS registry, 5-year graft survival was 42.3% in a group of donors older than 60 and 61.4% in a group of donors aged between 19 and 50 [13]. Studies concerning older kidneys procured on autopsy showed a progressive age-related decrease in the number and size of glomeruli [14]. Older grafts had a reduced functional mass of nephrons that is probably inappropriate for the functional requirements of recipients [15,16]. Moreover, grafts using marginal kidneys are more sensitive to insults during the pre-, peri- and post-operative course of renal transplantation resulting in progressive decline in renal function and finally contributing to graft failure (Fig. 1). Experimental renal allograft models have demonstrated a strong correlation between prolonged cold ischemia time, donor age and renal allograft dysfunction [17]. According to the UNOS registry, the percentage of DGF for an equal cold ischemia time is greater for kidneys from older donors (51–65), compared to younger donors [19–30] [4]. One study suggested that kidneys from older donors are associated with an increased risk of early interstitial acute graft rejection which has a significant negative impact on graft survival [18]. Notwithstanding these

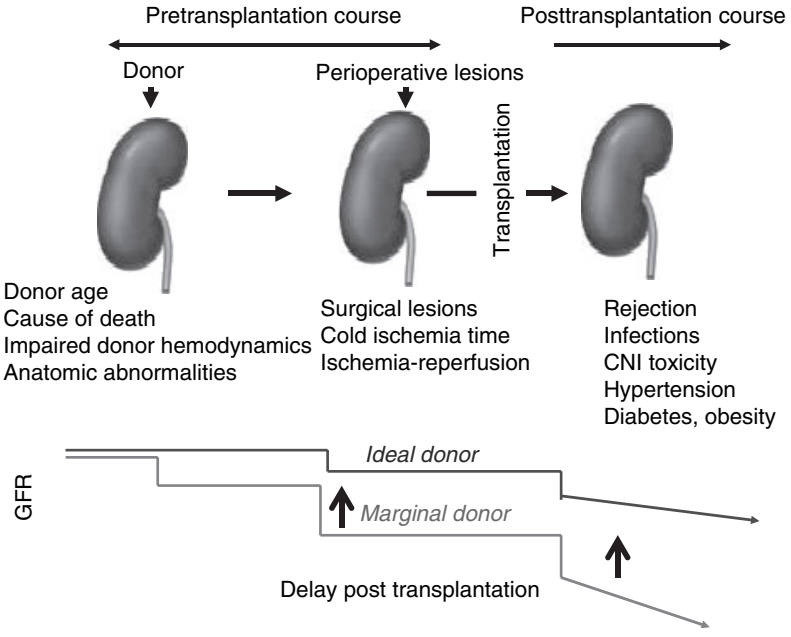


**Figure 1** Influence of pre- and post-transplant associated factors on graft outcome from marginal and optimal donors. (GFR, Glomerular Filtration Rate).

 

reports, large studies and analysis from transplant registries show inferior graft survival for ECD kidneys when compared to standard criteria donor kidneys. On average, the adjusted graft survival in ECD kidney is 8% lower at 1 year and 15–20% lower at 3–5 years after transplantation compared with standard criteria donor kidneys [1,11]. However satisfactory results using marginal donors have also been reported. In 2006, we reported in a retrospective study graft outcome of 170 kidney transplantations performed in eight centers in France between 1992 and 1998 [6]. This case-controlled multicenter study was designed to compare the fate of transplants performed with 'marginal' kidneys defined by their secondary acceptance by centers after primary refusal by two ore more other transplant centers to the outcome of transplantation with 'optimal kidneys' directly accepted by centers. Analysis of the principal causes of kidney refusal revealed classical characteristics of marginal donor kidney including advanced donor age, abnormal preharvesting serum creatinine, impaired donor hemodynamics and anatomic abnormalities. Our study revealed that 5-year graft survival rate, using discarded kidneys, was not statistically different from the results observed in the control group (70.4% vs. 76.7%, respectively). Furthermore, transplantation of kidneys from the study group was not associated with a significantly increased mortality. Although creatinine clearance at 5 years was significantly higher in the control group than in the study group (48.5 ml/min and 33.3 ml/min, respectively), this study demonstrates that such marginal discarded grafts provide acceptable survival rates, suggesting that in numerous situations, the decision to refuse them may be unjustified.

## How to optimize outcome of marginal kidney grafts

Kidney grafts from marginal donors are more sensitive to pre- and post-transplantation insults and have impaired ability to repair tissue and parenchyma [18]. The goal should therefore to optimize renal functional reserve and the number of functioning nephrons which will likely reduce or eliminate differences in outcome between grafts from optimal and marginal donors. Such strategies include reduction of cold ischemia time, recipient selection, adaptation of immunosuppressive drug regimens, increase in nephron mass by dual kidney transplantation, and improvement in the graft selection process using histological criteria.

### Improved kidney preservation strategies

It appears essential to shorten cold ischemia time in marginal donors to reduce the risk of DGF and improve graft outcome. In the Eurotransplant Senior Program, an allocation scheme based on the concept of age-matching between donor and recipient over 65 years of age, and reduction of cold ischemia time from 19:00 h to 12:00 h, improved 1-year graft survival rates from 79% to 86%. Such improved kindly preservation strategy should encourage organ-sharing organizations operating in large geographical areas to consider restricting organ exchange to optimal kidneys. Improved preservation of marginal kidneys may also reduce the risk of DGF. This includes the use of pulsatile perfusion machines [19,20], and protective agents to spare the organ from reperfusion injury, such as superoxide dismutase, a scavenger of oxygen free radicals [21] or platelet-activating factor receptor antagonists [22].

### Recipient selection

Kidneys from elderly donors may display glomerular sclerosis and/or tubulointerstitial lesions, and grafting such kidneys in young recipients may result in suboptimal function and reduced long-term graft survival. Thus age-matching from elderly donors to elderly recipients with lower metabolic demand has been proposed [23,24]. This was also applied in the successful allocation scheme of the Eurotransplant Senior Program. The soundness of such a strategy is also strengthened by the findings in a report by Kasiske [25] clearly demonstrating that while renal transplantation from older donors to older recipients did not improve overall graft survival, worse results were obtained when grafts from older donors were used in young recipients. This may be because older donor grafts elicit a stronger immune response in the early period after transplantation [26] and should therefore be preferred for older recipients with a reduced alloimmune response.

However, it should be noted that the performance of a marginal allograft is related to the recipient's metabolic demands rather than to his or her age. Thus, other criteria such as body surface – matching between donor and recipient – should also be considered to prevent the development of hyperfiltration markers such as hypertension and proteinuria [27].

### Immunosuppressive regimen

Pretransplant histological lesions sensitize renal allografts to nephrotoxic drugs, especially calcineurin inhibitors (CNIs). Three preliminary reports from uncontrolled studies [28,29] have suggested that the use of CNI-free immunosuppression [mycophenolate mofetil (MMF), antithymocyte globulin, and steroids] decreases the incidence of Delayed Graft Function (DGF), with acceptable renal function and acute rejection incidence in recipients of suboptimal kidneys. More recently, CNI-free immunosup-

pression including ATG induction, sirolimus, MMF and steroids have been reported in dual kidneys transplantation with controversial results, showing either a clear benefit [30,31] or no advantage [32] compared with CNI-based therapy. New CNI-free immunosuppressive trials using other therapy such as costimulation blockade are currently specifically designed in renal recipients from ECD donors.

### Donor selection

The usual expanded-criteria donor model incorporates donor clinical criteria (age, history of hypertension, serum creatinine, and cause of death), but does not include a histologic indicator of the structural integrity of the marginal kidney. Several studies have evaluated the reasonable concept that preimplantation biopsy of kidneys from old or expanded-criteria donors can help identify usable kidneys [33]. A preliminary uncontrolled study [34] suggested that kidneys from donors over 60 but under 75 years of age can be considered for transplantation, with satisfactory 1-year graft survival rate if the average level of glomerulosclerosis is <15%. Survival of kidney grafts from donors older than 60 and allocated for single or dual transplantation on the basis of biopsy findings before transplantation was similar to that of single grafts from younger donors, and substantially better than that of single grafts from donors older than 60 when those grafts were selected and allocated on the basis of standard clinical criteria. In this study, donor kidneys were selected for transplantation according to histologic criteria indicative of the mass of functioning nephrons. The criteria provided a thorough assessment of the changes in vessels, glomeruli, tubules, and the interstitium. More recently, Remuzzi *et al.* [35] assessed outcome among histologically evaluated graft recipients older than 60 years of age. Pending histological scoring of vessels, glomeruli, tubules and connective tissue, (0 if no changes were observed to 3 if marked changes were observed), kidneys with a global score up to 6 were considered for use as single or dual transplants, while those with a score of 7 or greater were discarded. Graft survival rate in recipients of histologically evaluated marginal kidneys did not differ from that in recipients of kidneys from donors under 60, and was better than that in recipients of kidneys not evaluated histologically from donors over 60 years of age. Thus, adding histological criteria to evaluation of marginal donors will likely improve graft outcome and might help to expand the donor-organ pool for transplantation.

### Dual kidney transplantation

An alternative approach for reducing the number of discarded kidneys and increasing the nephron mass of marginal kidneys may be the implantation of dual marginal kidneys. Data from the first registry patients show that recipients of dual kidneys from elderly donors have a significantly decreased incidence of DGF and better renal function and graft survival than recipients of a single kidney harvested from donors of similar age [36]. The short-term results reported in this early study were good, with a 100% graft and patient survival 6 months after transplant and with major surgical complications incidence fully comparable to patients that received a single kidney [37]. More recently, acceptable long-term results from several studies corroborated the value of this strategy in increasing the donor pool [38,39] but found a high incidence of primary nonfunction. Finally, results from the UNOS registry database comparing the outcome of 403 dual adult kidney transplantations (DKT, mean donor age of 60.8 years) with 11 033 single kidney transplantations (SKT) showed similar graft outcome when SKT recipients were grafted with donors over 55 years of age [40].

The main question is to define precise criteria to determine whether a recipient of a marginal donor kidney should undergo single or dual transplantation, and thus to compare benefits and drawbacks of each strategy. A recent paper [37] analyzed graft survival of single or dual kidney transplants from expanded-criteria donors allocated on the basis of clinical or preimplantation histologic evaluation. ECD criteria in this study included donor age >60, history of diabetes or hypertension, and urinary protein excretion up to 3 g/24 h. Graft outcome in dual transplant recipients who had their graft evaluated histologically before implantation was similar to that of recipients grafted with a single transplant from younger donors. Finally, dual transplant outcome with the above biopsy-based strategy appear to be better than those of dual transplants based on clinical score (donor age, donor-calculated creatinine clearance). Such results strongly suggest that histological criteria should be included in the choice between single and dual kidney transplantation from a marginal donor.

## Concluding remarks

The use of marginal donors has introduced a new dimension to the process and outcome of kidney transplantations. On the one hand, the utilization of marginal donors has expanded the donor pool, but on the other hand when using current criteria, recipients transplanted with such kidneys are by definition likely to have inferior graft and patient survival. The main question is therefore, how to optimize the outcome of grafting of such kidneys to reduce the wide variation between outcomes for grafts from optimal and marginal donors. Improving the selection process by routine use of histological criteria will

certainly reduce this discrepancy in the future. However, the key to such optimization is probably to be found in specific considerations in the practical management of transplantation. These include improvement in the capacity of the graft to repair parenchyma lesions, such as reduction of cold ischemia times and use of modified immunosuppression regimens to minimize CNI toxicity. Specific allocation policies are also mandatory to define the best donor–recipient pair, taking into account recipient age and immunological risk, and the connection between nephron mass provided and the recipient's metabolic demands. We believe that such precautions will significantly improve in the future the outcome of grafts from marginal donors.

## Authorship

V.A. and P.G. wrote the paper. P.L. and P.G. carried out the senior revision. M.M. and K.D. analysed data.

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