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Extended Criteria Kidney Donors: Benefits, Risks, and Optimal Use

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Introduction

It has been clear for many years that kidney transplantation offers an improved quality of life as compared to dialysis for selected patients with end stage renal disease. However, in 1999, Wolfe and others circumvented this problem by comparing survival in transplanted patients with those on dialysis who were selected for the waiting list (1). They showed that while survival in the immediate post transplant period was worse for transplant recipients, by about 3 months post transplantation, survival was equal, and over the long term, survival was significantly better for those individuals receiving transplants. Subsequently, Fenton et al, using a large Canadian database confirmed these findings and emphasized that they were true for older patients as well as diabetics and also for patients with one or two significant comorbidities, providing they were selected for the transplant list (2). While a potential problem with these analyses was the failure to censor patients if they were placed on hold on the waiting list, and the potential bias, since selection of the recipient was up to the physician or surgeon, Vandewoude and colleagues utilized a European database with computer allocation of organs and censoring of patients when placed on hold and were once again able to demonstrate a very significant survival benefit associated with transplantation (3). As a result of these studies, and continually improving outcomes in transplantation, very appropriately, more patients are being referred for consideration of transplantation, waiting lists are increasing while the number of deceased donor organs is static, and as a result, waiting time for transplantation is increasing significantly. The negative impact of this increase in waiting time is emphasized by the data of Meier-Kriesche et al showing that longer waiting times on dialysis are associated with significant reductions in post transplantation survival (4).

Clearly, based on this information, the optimum form of transplantation would be a living donor transplant prior to the need for dialysis. However, the number of living donors available is limited and many people are not diagnosed with end-stage renal failure until they are close to or already need dialysis. While newer innovations such as paired living donor exchange and list exchange may slightly increase the number of feasible living donors, most patients are left with a dilemma as to whether they should simply accept the longer waiting times for a deceased donor transplant or look at other alternatives. This article will discuss one of those alternatives, for example, the use of extended criteria donor renal transplants to shorten waiting time to transplantation.

Results using extended criteria donor kidneys

Prior to 2001, many single center studies had been published comparing transplant outcome in recipients of older versus younger donor kidneys. While most suggested that results obtained with older donors were not as good as those when younger donors were utilized, the data were not uniform, likely owing to different selection criteria beyond age.

In 2001, Ojo and colleagues were the first to look at the UNOS database utilizing a rigorous definition for extended criteria donor kidneys as those coming from donors with one of the following: more than 55 years of age, from non heart beating donors, with a cold ischemia time greater than 36 hours or with either high blood pressure and/or diabetes for more than

10 years (5). At 5 years, graft survival using so called ideal donor kidneys was 72% versus 59% for extended criteria donor kidneys ($p > 0.001$).

A further analysis of the UNOS data involving 29,068 first deceased donor transplants from 1995 – 2000 was undertaken by Port and colleagues (6). They defined extended criteria donor kidneys as those with the relative risk of graft loss > 1.7 as compared to so called ideal donor kidneys. This was found to include all donors aged 60 years of age or older, and those aged 50 – 59 years with at least two of cerebrovascular accident as a cause of death, renal insufficiency (serum creatinine > 135 μmol) and hypertension. It was also clear that the relative risk of graft loss increased as each factor was added. A deceased donor kidney from a donor 60 years of age or older who died from a cerebrovascular accident with a creatinine > 135 μmol and with a history of hypertension had a relative risk of graft loss of 2.69. This translated into three year graft survival of 49% versus 79% for kidneys from so called ideal donors.

It is also appropriate to look at non-heart beating donors, which have recently received a good deal of attention. A detailed discussion of non-heart beating donors is beyond the scope of this article. However, the Ottawa group showed that the utilization of non-heart beating donors could increase the number of deceased donors by anywhere from 30 – 87% (7). This is for a region that already has among the highest donor rates in Canada. Having said that, it seems clear that non-heart beating donors should be considered as extended criteria donors based on recent results from the Netherlands (8). A study by Kaizer and colleagues compared results in 176 kidney transplants from heart beating donors with those in 100 transplants from non-heart beating donors. One year graft survival was 92% versus 83% ($p < 0.03$). A multivariate analysis showed that the utilization of a non-heart beating donor independently influenced graft survival with an increase in the relative risk of graft loss of 2.38.

Ojo and colleagues took their analysis one stage further in understanding that dialysis itself is associated with incremental mortality compared to transplantation, so that they also assessed and compared mortality effects of transplantation with an ideal donor versus that achieved with an extended criteria donor versus survival associated with remaining on the transplant list (5). As compared to recipients of ideal donors, those receiving an extended criteria donor had a higher relative risk of dying in the peritransplant period, which did not become equivalent to that of remaining on the waiting list until approximately 180 days versus 120 days for ideal donor kidneys. Nevertheless, over the long term, transplantation of an extended criteria donor kidney was associated with a significant reduction in mortality as compared to remaining on the waiting list, albeit the reduction in mortality over the long term was approximately 0.25 versus approximately 0.5 achieved with ideal donor kidneys.

Who should receive an extended criteria donor kidney?

Based on the information available, statistically, kidneys from extended criteria donors are not likely to provide acceptable kidney function for as long as those from ideal donors. It is clear that patients with end stage renal disease, even with transplants, have a shortened survival as compared to age matched healthy controls. However, the survival time is much shorter for older than for younger patients with end stage renal disease. Accordingly, the negative consequences of increased time on the waiting list are greater for older individuals, since this may use up most or all of their remaining survival time and the survival benefit which might accrue from confronting the increased short term mortality associated with transplantation is much smaller. At the present time, many centers, including our own, have separate waiting lists for patients willing to receive extended criteria donor kidneys. Since these waiting lists include a much smaller number of patients than the total waiting list, the waiting time for an extended criteria donor kidney has been significantly shorter than that for an ideal organ. Accordingly, the decision as to who is appropriate to receive an extended criteria donor kidney relates to a consideration of anticipated lifespan versus waiting time. In programs where waiting times are shorter for ideal kidneys, fewer patients, if any, should be advised to accept an extended criteria donor kidney. On the other hand, for programs with longer waiting lists, it may be quite appropriate to advise older patients to go on the waiting list for extended criteria donor organs. Younger patients, with a longer potential lifespan, can afford to wait the extra time for an ideal kidney and should be encouraged to do so.

Several published manuscripts have looked at this question in mathematical terms. Jassal and others, in a decision analysis of transplantation in the elderly, showed that the survival advantage of transplantation decreased considerably with increased waiting time. At 6.7 years of waiting time, the quality adjusted life expectancy of dialysis for a 65-year old equaled that of transplantation. Transplantation remained economically attractive for a non-diabetic 65-year-old patient only if the transplant became available within 22 months of wait listing (9). Schnitzler and his colleagues asked how much longer an individual would have to wait after refusing a kidney from an extended criteria donor before the poorer outcomes and increased costs of waiting on dialysis would outweigh the benefits gained from receiving an ideal donor kidney? Using a Markov model over 20 years, they showed that this varied by recipient age: for someone less than 30 the time was 4 years, but for someone over 60 the time was 11 months (10). This data was considered by Gaston and others, when they suggested in their article on management of the waiting list, that the following candidates should receive an extended criteria donor kidney (11). Depending on the local waiting time it was felt that such kidneys should be directed towards any candidate over 60 years of age, any diabetic over 40 years of age, any candidate with failing vascular access, and any candidate whose expected waiting time exceeds their life expectancy.

More recently, Merion and colleagues compared mortality after extended criteria donor kidney transplantation versus that in a combined standard therapy group of non extended criteria donor recipients and those still receiving dialysis in 109,127 American patients receiving dialysis and added to the kidney waiting list between January 1st, 1995 and December 31st, 2002 with follow-up to July 31st, 2004 (12). Overall, cumulative survival of recipients receiving an extended criteria donor kidney did not equal that of standard therapy patients until 3.5 years post transplantation. However, long term relative mortality risk was

17% lower (95% confidence interval 0.77 – 0.9, $p < 0.001$). Subgroups with a significant survival benefit from receiving an extended criteria donor kidney included patients older than 40 years, non-sensitized patients, and those with diabetes or hypertension. In organ procurement organizations with long waiting median times (> 1350 days) extended criteria donor recipients had a 27% lower risk of death (95% confidence interval 0.64 – 0.83, $p < 0.001$). In areas with shorter waiting times, only recipients with diabetes demonstrated a survival benefit from receiving an extended criteria donor kidney. This study reinforces the comments above. However, these data will likely increase the number of patients who go on extended criteria donor kidney waiting lists. As a consequence, the waiting time for these organs would be expected to grow, which will reduce the benefit and might eventually eliminate it altogether. At our centre we have decided to offer extended criteria donor organs to patients over 55 years who have been put on the list within 3 years as well as diabetics. This is in the context of mean waiting times of 6 – 7 years from starting dialysis.

In addition to the important benefits outlined above of allocating extended criteria donor kidneys to older recipients, since such individuals are likely to have shorter survivals, any limitation on the long term graft survival associated with extended criteria donor kidneys might be minimized. Accordingly, the results of the Eurotransplant Senior Program are of interest (13). In this program, donor kidneys from patients more than 65 years of age were allocated to recipients more than 65 years of age. Only the recipients with peak panel reactive antibody less than 5% receiving their first transplants were included. If donor creatinine clearance is less than 70 ml/min, double kidney transplants were performed. Results from this program were compared to older donor kidneys allocated by HLA matching which is the standard allocation method for Eurotransplant. At 3 years, the results of 876 kidneys allocated according to the seniors program were compared with 345 organs allocated based on HLA. 3 year graft survival was not significantly different at approximately 68% in both groups.

Can we improve outcome with transplantation of extended criteria donor kidneys?

In addition to determining which patients' survival would be optimized by receiving an extended criteria donor kidney, it seems reasonable to consider how results might be improved utilizing such organs. Such benefits might accrue by modifying donor selection, donor management, and recipient management. Recipient management is beyond the scope of this article and hence the focus will be on donor selection and management.

In order to optimize outcome with extended criteria donor kidneys, one would like to understand why the outcome is worse. Unfortunately, that is not entirely clear although it has been suggested that outcome might be worse because of impaired function with reduced nephron mass, longer cold ischemia time, increased delayed graft function, increased immunogenicity, and impaired ability for tissue repair.

Clearly, some patients do well with extended criteria donors. This suggests that it may be possible to improve outcome by being more selective in which donors are utilized. Of

course, the corollary of that statement is that the selection of fewer kidneys means fewer patients benefit with less overall benefit to the system.

Three different ways of selection have been considered in the literature: donor pathology, donor renal function, and scoring systems using a combination of both. Gabor and colleagues were among the first to suggest that donor baseline biopsies could be helpful (14). Their study of 65 baseline donor biopsies compared results in donor kidneys with and without more than 20% glomerulosclerosis. Those kidneys with more scarring had an incidence of delayed graft function of 87% versus 33% ($p < 0.05$), poor function at 6 months of 20% versus 2% ($p < 0.05$) and graft loss of 38% versus 7% ($p < 0.04$). Since then, a number of other studies have reassessed the importance of donor renal pathology. Cockfield and others retrospectively reviewed 291 implant patient biopsies and found that fibrous intimal thickening was the only pathologic feature associated with graft loss (relative risk 3.72, $p = 0.0021$) and that it was the single most important predictor of delayed graft function ($p = 0.005$) being more important than donor age (15). At our Centre, Karpinski retrospectively reviewed 57 transplants from 34 older donors and found that glomerulosclerosis did not predict outcome. Rather severe vascular disease was significantly associated with delayed graft function and worse renal function at 1 year (16). Edwards and colleagues reassessed the utility of glomerulosclerosis in 2004 (17). They looked at 257 donors who had a biopsy of both kidneys. 57% had a concordance of the percentage of glomerulosclerosis. 20% had more than 20% glomerulosclerosis in one kidney and less than 20% in the other. 5% had more than 20% glomerulosclerosis in one kidney with 0 – 5% in the other. However, if the creatinine clearance was more than 80 ml/min there seemed to be no impact of more than 20% glomerulosclerosis on the outcome. In addition to these differences regarding the benefit of pathology, it is clear that waiting for renal biopsy results increases the cold ischemia time which may have a particularly negative effect in extended criteria donors and significantly increases cost.

The utility of donor renal function to select optimal extended criteria donors has also been assessed. Carter and colleagues utilized the UNOS database with 33,595 deceased donor transplants since 1994. There were 4,732 deceased donors aged 55 years or older with 2,570 having a calculated creatinine clearance of $< 80\text{ml}/\text{min}$ and 2,162 donors with a calculated creatinine clearance of $\geq 80\text{ml}/\text{min}$ (18). When the calculated donor creatinine clearance fell below $80\text{ml}/\text{min}$ there was a progressive decline in graft survival at 1 and 2 years. Nyberg developed a scoring system using Mayo Clinic data and tested it against results obtained at the University of Minnesota. The system was further refined using UNOS data (19). The scoring system included five variables: age, cause of death, donor creatinine clearance, history of hypertension, and HLA mismatch. Each of these had points awarded, a grade from A – D was awarded on total points, and six year graft survival was predicted on the grade such that: grade A (0 – 9 points) had a six year graft survival of just over 80% whereas grade D (30 – 39 points) had an approximate six year graft survival of 63%. Singh and colleagues, using single centre data, subsequently compared four scoring systems for prediction of subsequent renal function defining a poor outcome as a creatinine clearance of $< 30\text{ml}/\text{min}$ at one month and one year (20). They found that both the Nyberg system and donor creatinine clearance were predictive but that donor creatinine clearance alone was sufficient.

Double kidney transplantation

If the poor results utilizing extended criteria donor organs are related to reduced functional nephron mass from scarring, then the provision of more nephron mass might improve outcome. This philosophy was responsible for the suggestion that utilizing two kidneys per recipient instead of one from extended criteria donors might improve results. This approach has been undertaken by a number of Centres, including our own, and a dual kidney registry was organized by Dr. Ed Alfrey, with initial publication of results in 2003 (21). In this study, 239 recipients of dual kidney transplants from nine Centres were compared with 4,746 recipients of single kidneys from older donors from the UNOS database. The incidence of delayed graft function was similar at 32% for dual transplants and 35% for single transplants. Serum creatinine at three years was slightly lower in the dual transplants at 185 μmol versus 202 μmol in single transplants. Actuarial graft survival at three years was 73% for dual organs versus 65% for singles, a difference which was not statistically significant. More recently, this group compared single versus dual kidney transplantation in recipients aged 55 years or older (22). 113 patients received transplants from 1995 to 1999. If the donor admission calculated creatinine clearance was $< 90\text{ml}/\text{min}$ (43 – 89) the kidneys were used as doubles, and as a consequence there were 39 dual and 61 single transplants with a median followup of 6 years and 11 months. The waiting time for dual transplants was 440 \pm 38 days versus 664 \pm 51 days ($p = 0.002$). As expected, the donor age for dual transplants was 61 versus 48 for single transplants ($p = 0.001$). Graft survival at 8 years was 70% for dual transplants versus 59% for single transplants.

Our centre took a similar approach to utilizing kidneys from extended criteria donors as single or double kidney transplants. We considered extended criteria donors to be 60 years of age or older, or those with a history of hypertension and/or diabetes, or those with a severe systemic atherosclerosis found at harvesting. Kidneys that were transplanted as single transplants if the donor biopsy score was less than or equal to 3 (0 – 3 points each for vascular disease, glomerulosclerosis, interstitial fibrosis, and tubular atrophy) and/or calculated creatinine clearance of 80ml/min or more, whereas double transplants were done if the donor biopsy score was 4 – 6 and/or calculated creatinine clearance was 60 – 79 ml/min. Graft and patient survival and renal function were compared in 47 single transplants and 50 double transplants, which were compared to low risk deceased donor transplants done over the same time period (23). There was no difference in graft survival at 5 years which was 77 versus 81%, in patient survival at 5 years which was 85 versus 91%. At 5 years calculated creatinine clearance for single low risk kidneys ($n = 173$) was 50 \pm 21 ml/min, for double high risk kidneys was 43 \pm 26 ml/min, and for single high risk kidneys was 38 \pm 15 ml/min. renal function in single high risk kidneys was significantly less than that of single low risk kidneys ($p < 0.05$) but there were no significant differences otherwise.

We have concluded that acceptable results can be obtained with single and double extended criteria donor kidneys with selection based on renal function and pathology. On the one hand, the significantly lower renal function in the single high risk cases could lead to worse long term outcomes in that group. Contrarily, the similar graft and patient survival in the single high risk group might suggest that more kidneys should be used as singles and fewer as doubles in the extended criteria donor group.

Recently, Remuzzi and others compared their experience with 62 double kidney transplants from older donors, using pathologic criteria with 248 kidneys not evaluated pathologically and transplanted as singles (24). One hundred and twenty-four were from younger donors and an equal number from older donors. Graft survival was 94% at 23 months in the double and low risk single group and 77% in the high risk single group ($p < 0.02$). The authors concluded that histologic evaluation is important to optimize results of transplantation with extended criteria donors. While their results with these high risk kidneys are excellent, since they did not compare doubles to singles using pathology, I do not believe they can say pathology was the most important criterion. It may have simply been the decision to do dual transplants. It makes sense that extended criteria doubles might do better than singles, but since only half the patients are transplanted, the practice cannot be recommended without better data regarding selection versus outcome.

Management of cold ischemia

Rosengard and colleagues have shown that regardless of the cold ischemia time, the incidence of delayed graft function was significantly higher for kidneys with donors aged 51 – 65 versus those aged 19 – 30 (25). Accordingly, when transplanting extended criteria donor kidneys, it is critical to minimize cold ischemia time and to manage it optimally. Recently, many US centers have used pulsatile perfusion, at least for extended criteria donor kidneys, based on their belief that the incidence of delayed graft function was lower with using this methodology and that an assessment of the perfusion characteristics of these higher risk kidneys was useful in deciding whether or not to use them. However, no large randomized controlled trials exist comparing pulsatile perfusion to cold storage. Nevertheless, recently, Schold and colleagues analyzed the effect of pulsatile perfusion using the Scientific Registry of Transplant Recipients in the US (26). They found that regardless of cold time, the odds ratio of delayed graft function was significantly less when cold ischemia was managed with pulsatile perfusion as compared to cold storage. Furthermore, multivariate analysis showed a significant reduction in death censored graft loss in kidneys with a cold ischemia time of 24 or more hours as well as in transplants performed from 1998 – 2003 using pulsatile perfusion. There did not appear to be any significant difference in graft survival with ideal donor kidneys whereas there was a borderline improvement in extended criteria donor kidneys.

Conclusions

Extended criteria donor kidneys, as used currently, provide worse graft function and long term survival. However, they provide acceptable function and still offer a significant survival benefit as compared to dialysis. This benefit will be greater for older patients because of their shortened lifespan, which increases the adverse effect of waiting. The benefit of transplantation with extended criteria donor kidneys depends on local waiting time. In general, more patients will benefit the longer the local waiting time for deceased donor kidneys. Therefore, deceased donor kidneys should be offered to those over 55-60 years of age and/or younger diabetics because of the reduced expected long-term survival. However, careful individualized explanation and informed consent is mandatory and, in my view, a

separate list is optimal. Patients who agree to be on the extended donor list should also remain on the ideal donor list and be offered whichever organ they come up for first.

Clinical and pathologic scoring systems are available to determine which extended criteria donor kidneys to use but none have proven to be ideal. Most useful are donor age, renal function, and possibly pathology. Acceptable short term results have been obtained with dual kidney transplantation, but while the data are suggestive, it is not clear that such kidneys provided an advantage over single kidneys or how to determine which kidneys to use as double versus single. It seems clear that the disadvantages of prolonged cold ischemia are of greater consequence when transplanting extended criteria donor kidneys. Accordingly, every attempt to minimize cold ischemia should be made. Pulsatile perfusion may improve results of transplantation with extended criteria donor kidneys but prospective randomized controlled trials are needed.

In summary, it seems that the utilization of extended criteria donor kidneys can significantly improve survival for a subset of transplant recipients. More studies are required to optimize results obtained with extended criteria donor kidneys but clearly this donor source should not be overlooked. It is likely that optimization of the results from the transplantation of extended criteria donor kidneys will only be obtained with a better understanding as to those factors which diminish long term outcomes.

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