TRANSPLANT INTERNATIONAL

Transplant International ISSN 0934-0874

ORIGINAL ARTICLE

Optimizing utilization of kidneys from deceased donors over 60 years: Five-year outcomes after implementation of a combined clinical and histological allocation algorithm

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Keywords
allocation algorithm, DKT, ECD, graft survival, kidney transplantation.

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Conflicts of interest
The authors have declared no conflicts of interest.

Received: 23 August 2012
Revision requested: 2 November 2012
Accepted: 16 May 2013
Published online: 19 June 2013

doi:10.1111/tri.12135

Summary

This 5 year observational multicentre study conducted in the Nord Italian Transplant programme area evaluated outcomes in patients receiving kidneys from donors over 60 years allocated according to a combined clinical and histological algorithm. Low-risk donors 60–69 years without risk factors were allocated to single kidney transplant (LR-SKT) based on clinical criteria. Biopsy was performed in donors over 70 years or 60–69 years with risk factors, allocated to Single (HR-SKT) or Dual kidney transplant (HR-DKT) according to the severity of histological damage. Forty HR-DKTs, 41 HR-SKTs and 234 LR-SKTs were evaluated. Baseline differences generally reflected stratification and allocation criteria. Patient and graft (death censored) survival were 90% and 92% for HR-DKT, 85% and 89% for HR-SKT, 88% and 87% for LR-SKT. The algorithm appeared user-friendly in daily practice and was safe and efficient, as demonstrated by satisfactory outcomes in all groups at 5 years. Clinical criteria performed well in low-risk donors. The excellent outcomes observed in DKTs call for fine-tuning of cut-off scores for allocation to DKT or SKT in high-risk patients.

Introduction

Kidney transplantation is considered the treatment of choice in patients with end-stage renal disease [1]. However, the number of kidney transplant patients has remained fairly stable in Italy with about 1500 transplants performed annually for over 6500 candidates on the active waiting list, with an average waiting time of

2.8 years and a mortality rate in waiting list of 1.9% [2].

Expanded donation criteria are now commonly applied to increase the donor pool. Although expanded criteria donor (ECD) organs are associated with an increased risk of primary nonfunction (PNF), delayed graft function (DGF) and significantly lower graft survival compared to standard organs [3–5], satisfying midterm outcomes have been documented with improved survival rates generally observed after about 1.5 years post-transplant when compared with that of patients in waiting list [6,7]. Nevertheless, long-term data are still needed in this population [6,7] for whom the return to dialysis after transplantation can be particularly deleterious, with higher death rates compared with that of never transplanted patients [8].

Dual kidney transplantation (DKT) has been added as an option allowing the use of kidneys that would otherwise be discarded. In a context of scarce resources and ageing donors, proper selection and allocation criteria are crucial to optimise the utilization of kidneys offered while maintaining the quality of results. Objective predictive tools to assess kidney graft quality are needed. Although many evaluation criteria exist, none of them in itself offers the necessary power to predict graft outcomes [9]. Age alone cannot be retained as the only risk factor affecting long-term graft function, even though advanced donor age strongly influences post-transplant outcomes [10,11]. Donor-estimated glomerular filtration rate has been suggested as a parameter sufficient for allocation of ECD kidneys into single kidney transplant (SKT) or DKT [12]. However, creatinine levels can be significantly altered by the acute changes occurring during donor death or can remain normal despite severe chronic damages with a decreased functional reserve [13]. Preimplantation kidney biopsy has been proposed as an additional assessment tool, however, feasibility is conditioned by round the clock availability of a pathologist [14]. Composite scoring systems have been introduced in an attempt to improve the predictive power, but none of them has been convincing or practical enough to be widely used, accepted and shared by different donor service areas [9].

The objective of this study was to evaluate the efficiency of a combined clinical and histological allocation algorithm for ECD organs introduced in the early 2000s in the Nord Italia Transplant programme (NITp) area.

The NITp is an inter-regional transplant agency founded in Milan in 1976 and currently comprising 6 Italian regions: Lombardia, Liguria, Veneto, Friuli-Venezia Giulia, Marche and the Autonomous Province of Trento. This area counts 129 intensive care and 42 transplant units (15 for kidney transplantation, five for kidney and pancreas, nine for liver, six for heart, two for heart and lung, five for lung, one for the intestine) for a population of 19 million inhabitants.

Based on the satisfactory outcomes observed in renal transplants from organs of donors 60–70 years of age without significant associated risk factors, the NITp introduced a combined clinical and histological algorithm applied to donors over 60 years of age, using clinical criteria only for low-risk donors and combined histological and clinical evaluation in high-risk donors, thus considerably reducing the number of histological procedures performed when compared to policies of preimplantation biopsy in all donors > 60 years.

The objective of this retrospective analysis was to document 5-year outcomes in the recipients of kidney transplant from donors ≥ 60 years of age allocated according to the NITp for DKT or SKT.

Materials and methods

Study design

Thirteen centres belonging to the NITp area, four of which performing DKT, contributed data to this observational, multicentre study. Data from all recipients of a kidney transplant from donors ≥ 60 years allocated according to the algorithm described below and transplanted between January 2003 and December 2004 were collected retrospectively with a follow-up period of 5-year post-transplant.

Data were obtained according to the standard regulations of the NITp network for data registration and use, and for the preservation of patients' anonymity and privacy. Donor and recipients characteristics were documented, as well as graft function, patient and graft survival that were assessed over a 5-year period.

The frequency of visits was left to the clinician's judgment based on the centre's routine practice. The selection of the immunosuppressive regimen was left at the centres discretion, according to standard protocols.

Donors and recipients selection

Overall NITp allocation procedures are described in details on the website of the centralized immunology laboratory in Milan [15]. Kidneys with major macroscopic alterations such as severe atherosclerosis of the renal artery or tissue focal scarring were discarded. Kidneys retained were classified in two groups (low and high risk) on the basis of clinical and histological criteria and allocated for SKT or DKT as shown in Fig. 1.

Kidneys from donors aged between 60 and 69 years without clinical risk factors were allocated to SKT without further histological analysis and classified as low-risk SKT (LR-SKT).

Preimplantation biopsy was performed on high-risk grafts procured from donors ≥ 70 years or 60–69 years with at least one clinical risk factor (creatinine clearance

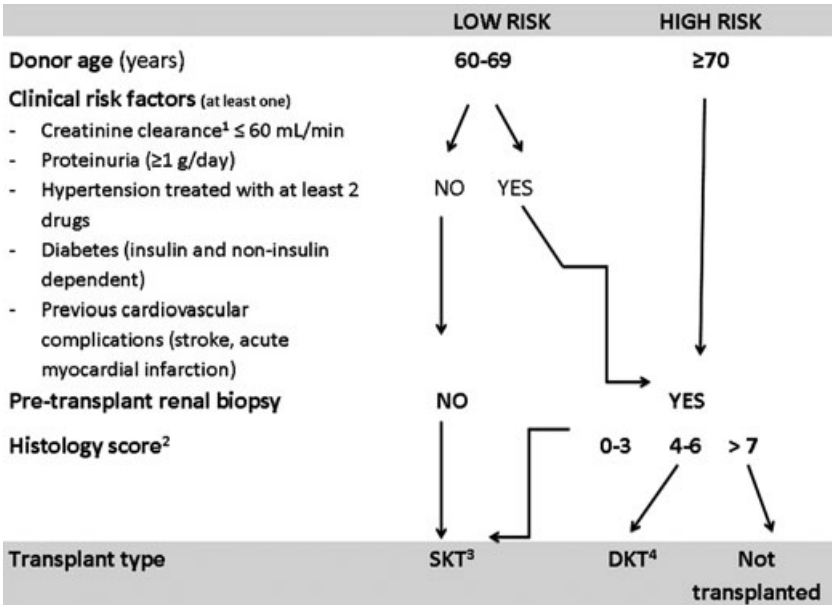


Figure 1 Nord Italian Transplant programme (NITp) allocation algorithm for donors over 60 years of age. [1]Estimated by the Cockcroft–Gault formula. [2]Histology score for severity of chronic renal damage quantified as described by Remuzzi [17]. [3]SKT: single kidney transplant. [4]DKT: double kidney transplant.

≤ 60 ml/min, proteinuria obtained on a single urine sample, hypertension treated with at least two drugs, diabetes mellitus type 1 and 2 according to patient's medical history, previous cardiovascular complications) as defined in Fig. 1. Depending on histology score (see histological assessment below) high-risk grafts were allocated as SKT (high-risk SKT; HR-SKT) or DKT (high-risk DKT; HR-DKT). Grafts allocated as DKT remained at the centre that had performed the histological evaluation whereas for SKT, one kidney remained at the DKT centre and the other was assigned to the procuring transplant centre, regardless of the number of HLA-mismatches.

Donors evaluated or allocated outside of this protocol (grafts not biopsied or different allocation rules) were excluded from the study.

A computer-generated list was used for allocation. For SKT recipients, donor was selected on the basis of ABO blood group matching, HLA-matching, negative lymphocytotoxic cross-matching, waiting time and, if possible, matching according to sex, age (maximum age difference of 15 years) and body weight (recipient weight should not be in excess of 30% of the donor's weight) [16]. A separate list was used for DKT recipients allocated on the basis of age ≥54 years, absence in the recipient's serum of donor-specific antibodies, no surgical contraindication to DKT, BMI ratio between donor and recipient ≥1 whenever possible. There were no restrictions based on immunological risk (any panel reactive antibody – PRA, providing negative Complement dependent cytotoxicity cross-match) and HLA matching was not considered while specific written informed consent was obtained for DKT. Patients undergoing retransplantation were admitted for SKT while all DKTs had to be first transplants.

Histological assessment

Twenty-four hour pathologist was only available at four centres performing DKT, hence histological evaluation was done at one of these latter, based on geographical proximity to the procuring centre.

Two biopsies were obtained from the superior pole of each kidney. The majority of centres used a 16-gauge trucut needle while in some cases wedge biopsies were performed. The specimens were processed as follows: fixation in formalin, microwave paraffin embedding, 5 μ thick sectioning, staining with hematoxylin and eosin, Periodic acid Schiff, Masson's trichrome, elastic Van Gieson (3 h procedure). Tissue samples had to be adequate for quantitative scoring of chronic renal damage (25 glomeruli) as described by Remuzzi *et al.* [17], a 12 point score obtained by the sum of the scores attributed to 4 variables (score of 0–3 each): glomerular sclerosis (GS), tubular atrophy (TA), interstitial fibrosis (IF) arterial and arteriolar narrowing. Grafts with a global score ranging from 0 to 3 were allocated for SKT (HR-SKT), those with a score from 4 to 6 for DKT (HR-DKT) whereas those with a score of seven or greater were not considered suitable for transplantation.

Statistical analysis

Continuous data are expressed as mean values and standard deviation (SD) and compared by means of Student's *t*-test. Group differences were compared using chi-square test. Multivariate analysis was performed by analysis of variance (ANOVA) and ANOVA for repeated measures. Survival curves were estimated using Kaplan–Meier method and compared using log-rank test. A *P*-value lower than 0.05 was considered statistically significant. All variables with *P*-value <0.2 at univariate analysis were also analyzed with Cox proportional hazards model. All statistical analyses were performed using SAS software version 9.1.3 (SAS Institute, Inc., Cary, NC).

Results

Study population

Two-hundred and eighty-nine donors ≥ 60 years were evaluated. Of those, 76 (26%) were discarded: 59% of them because of atherosclerosis, 33% because of histological chronic damage (score ≥7) and 8% for other reasons. Of the remaining 213 donors used (74%), 11 were not evaluated according to the protocol algorithm and 12 were not used for transplant in the NITp area. Hence, a total of 190 donors ≥60 years were enrolled (66%).

Among high risk donors (64), all expected DKTs (40) were performed whereas 7 (14%) of the expected HR-SKTs (48) were discarded. Among low risk donors (126), 18 (7%) of the expected LR-SKTs (252) were discarded. Reasons for exclusion were based on macroscopical findings at the time of transplant. A total of 315 renal transplants were performed: 40 HR-DKTs, 41 HR-SKTs and 234 LR-SKTs.

Donor and recipient demographics are summarized in Table 1. Mean donor age was 66.1 years (SD 4.6) with a range comprised between 60 and 82 years. As expected from the design of the study, high risk donors were significantly older with a mean age of 72.7, 70.2 and 64.3 years in HR-DKT, HR-SKT and LR-SKT groups, respectively ($P < 0.001$). Serum creatinine, although within the normal range in all groups, was higher in the HR-SKT and HR-DKT groups (1.1 mg/dl and 1.0 mg/dl, respectively) compared to 0.9 mg/dl in the LR-SKT group ($P = 0.015$). The mean donor creatinine clearance (estimated by the Cockcroft–Gault formula) was 76.5 ml/min in HR-DKT group, significantly lower than that of HR-SKT and LR-SKT groups, 78.9 and 93.3 ml/min, respectively ($P = 0.002$). The main cause of donor's death was cerebrovascular disease (79%) with no significant differences among groups. All biopsies were adequate for quantitative scoring according to the requirements of at least 25 glomeruli per sample.

Subjects who received the organ from high risk donors were older (mean age 61.6 years) than those receiving the organ from low risk donors (mean age 56.6 years, $P < 0.001$) as an effect of age matching. Consistently with the allocation protocol, the mean HLA-mismatch was lower in LR-SKT (3.2) when compared to HR-DKT patients (4.1) for whom HLA matching was not required ($P < 0.001$). Most patients were receiving their first graft and consequently, PRA was low in all groups although a higher percentage of patients with PRA ≥10% was observed

Table 1. Donors and recipients baseline characteristics.*

	HR-DKT *N* = 40	HR-SKT *N* = 24	LR-SKT *N* = 126	*P*-value
Donors				
Male sex *N* (%)	14 (35.0)	13 (54.2)	74 (58.7)	0.032
Age (years) (mean; SD†)	72.7; 4.4	70.2; 4.7	64.3; 3.0	<0.001
Min–Max	64–82	60–78	60–69	
Serum creatinine (mg/dl) (mean; SD)	1.0; 0.6	1.1; 0.6	0.9; 0.3	0.015
Creatinine clearance‡ (ml/min) (mean; SD)	76.5; 35.4	78.9; 25.0	93.3; 27.3	0.002
Vascular cause of death *N* (%)	35 (87.5)	19 (79.2)	98 (77.8)	0.405
Recipients	*N* = 40	*N* = 41	*N* = 234	
Male sex *N* (%)	31 (77.5)	24 (58.5)	143 (61.1)	0.116
Age (years) (mean; SD)	61.6; 4.5	61.6; 6.0	56.6; 7.5	<0.001
Min–Max	54–74	47–73	28–72	
HLA mis-matches (mean; SD)	4.1; 1.2	3.5; 1.1	3.2; 1.1	<0.001
Panel Reactive Antibody >10% *N* (%)	3 (7.5)	3 (7.3)	44 (18.8)	0.054
Retransplantation *N* (%)	0	2 (4.9)	22 (9.4)	0.091
Cold ischemia time (h) (mean; SD)	16.8; 4.1	18.6; 4.6	15.7; 4.7	0.001

*Continuous data compared by means of Analysis of Variance (ANOVA): group differences compared using chi-square test.
†Standard deviation.
‡Estimated by the Cockcroft–Gault formula.

in LR-SKT ($P = 0.054$). Mean cold ischemia time (CIT) was higher in the HR-SKT group (18.6 h versus 16.8 and 15.7 h in HR-DKT and LR-SKT groups, respectively; $P = 0.001$) as a result of the centralisation of histological evaluation in centres with DKT programme and subsequent reallocation of one kidney in case of suitability for 2 SKTs.

Immunosuppressive treatment most often prescribed was the association of calcineurin inhibitors (CNI), mycophenolate mofetil (MMF) and steroids (252 patients, 80%) followed by mTor inhibitors, MMF and steroids (38 patients, 12%). This latter regimen was prescribed more often in HR-DKT patients (16 of 40 patients, 40%) when compared to HR-SKT (6 of 41 patients, 15%) and LR-SKT (16 of 234 patients, 7%), while respective numbers for the association of CNI, MMF and steroids were 60%, 76% and 84% ($P < 0.001$). Most patients were still receiving steroids after 2 years of follow up (58%).

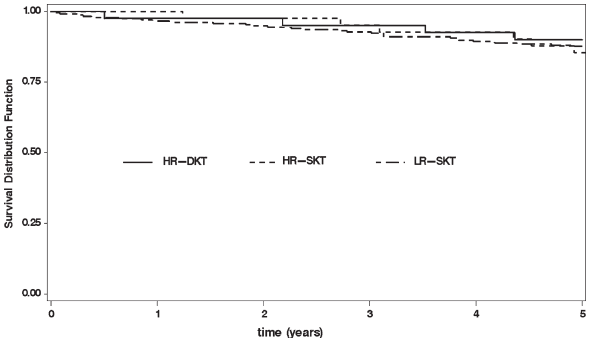
Outcomes

Mean follow-up after transplantation was 63.5 months (SD 24.2) with no significant differences among groups.

Kaplan–Meier estimates of patient and graft survival are shown in Figure 2. Graft survival rates (nondeath censored) at 1, 3 and 5 years were 93%, 88% and 85%, respectively, for HR-DKT; 100%, 93% and 78%, respectively, for HR-SKT; 92%, 84% and 76%, respectively, LR-SKT. Graft survival rates (death censored) at 1, 3 and 5 years were 95%, 92% and 92% respectively for HR-DKT; 100%, 95% and 85%, respectively, for HR-SKT; 97%, 93% and 88%, respectively, for LR-SKT. Patient survival rates at 1, 3 and 5 years were 97%, 95% and 90%, respectively, for HR-DKT; 100%, 95% and 85%, respectively, for HR-SKT; 97%, 93% and 88%, respectively, for LR-SKT. No statistically significant differences among groups were observed in any of the analyses performed.

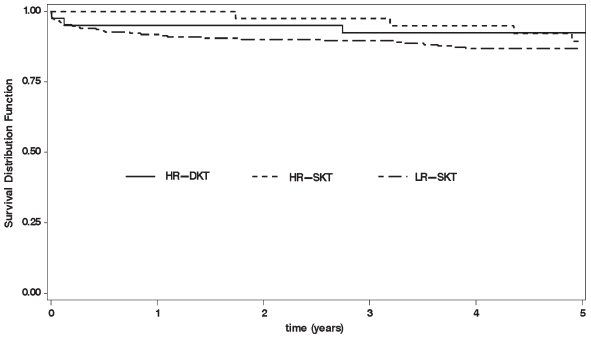
Data on death and graft loss are shown in Table 2. Of the 45 patients who died in the course of the follow up, 39 had a functioning graft, with a balanced distribution among groups. The main cause of death was cardiovascular disease (17 patients), followed by infection (16 patients). Forty-three grafts were lost, with rejection as the main cause (21 patients). Primary nonfunction occurred in 1 HR-DKT and 3 LR-SKT. Of the 21 rejections, 3 were acute rejections, 1 in the HR-SKT group (noncompliance 6 years after transplant) and 2 in the LR-SKT at 3 months (recurrence of acute rejection) and 17 months (associated with BK nephropathy). Five rejections were observed within 1 year of transplant, all in the LR-SKT group.

Delayed graft function occurred more frequently in HR-SKT (18 patients, 44%), compared to LR-SKT (77 patients, 33%) and HR-DKT (7 patients, 18%) ($P = 0.051$).



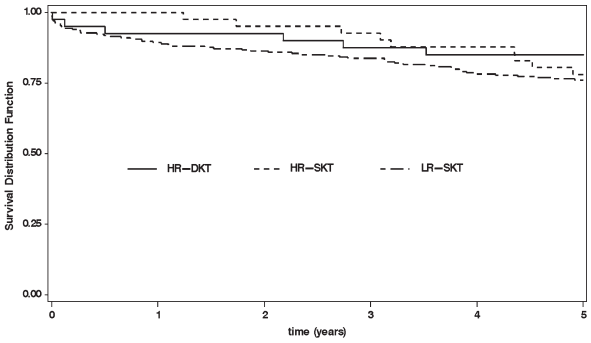
PATIENT SURVIVAL $P = 0.948$

Time (y)[2]	0	1	2	3	4	5
HR-DKT	40	39 (1)	39 (0)	38 (1)	37 (1)	36 (1)
HR-SKT	41	41 (0)	40 (1)	39 (1)	38 (1)	35 (3)
LR-SKT	234	226 (8)	222 (4)	217 (5)	209 (8)	205 (4)



GRAFT SURVIVAL (death censored) $P = 0.496$

Time (y)[1]	0	1	2	3	4	5
HR-DKT	40	37 (2)	37 (0)	35 (1)	34 (0)	34 (0)
HR-SKT	41	41 (0)	39 (1)	38 (0)	36 (1)	32 (2)
LR-SKT	234	209 (19)	202 (4)	196 (1)	183 (6)	178 (0)



GRAFT SURVIVAL $P = 0.459$

Time(y)[2]	0	1	2	3	4	5
HR-DKT	40	37 (3)	37 (0)	35 (2)	34 (1)	34 (0)
HR-SKT	41	41 (0)	39 (2)	38 (1)	36 (2)	32 (4)
LR-SKT	234	209 (25)	202 (7)	196 (6)	183 (13)	178 (5)

Figure 2 Kaplan–Meier curves of patient and graft survival (censored and non for death)1. [1]Comparison among groups by log rank test. [2]Number of patients at risk and (number of events) are reported. Survival distribution function. Time (years).

Table 2. Death and graft loss over the entire follow-up.*

	HR-DKT	HR-SKT	LR-SKT	*P*-value
	N = 40	*N* = 41	*N* = 234	
Mean follow-up (months) (mean; SD†)	65.3; 21.9	67.5; 17.6	62.5; 25.6	0.430
Death *N* (%)	5 (13%)	6 (15%)	34 (15%)	0.942
Graft loss *N* (%)	3 (8%)	6 (15%)	34 (15%)	0.746
Death with functioning graft *N* (%)	4 (10%)	5 (12%)	30 (13%)	
Cause of death	*N* = 5	*N* = 6	*N* = 34	
Cardiovascular *N*	2	3	11	
Infection N	3	2	12	
Neoplasia *N*	0	0	3	
Other *N*	0	1	8	
Cause of graft loss	*N* = 3	*N* = 6	*N* = 34	
Rejection *N*	1	5	15	
Thrombosis *N*	1	0	9	
Primary nonfunction *N*	1	0	3	
Other N	0	1	7	

*Continuous data compared by means of Student's *t*-test: group differences compared using chi-square test.
†Standard deviation.

Table 3. Multivariate analysis.*

	P-value	HR†	C.I.‡
Patient survival			
Recipient age ≥60 vs. <60 years	<0.001	5.139	2.505–10.542
Creatinine clearance <60 vs. ≥60 ml/min	0.073	2.198	0.930–5.192
HR-DKT vs LR-SKT	0.160	0.455	0.152–1.364
HR-SKT vs LR-SKT	0.213	0.544	0.209–1.416
Graft survival			
Recipient age ≥60 vs. <60 years	0.113	1.451	0.916–2.299
Creatinine clearance <60 vs. ≥60 ml/min	0.050	1.960	1.000–3.843
HR-DKT vs LR-SKT	0.049	0.398	0.159–0.997
HR-SKT vs LR-SKT	0.332	0.708	0.353–1.422

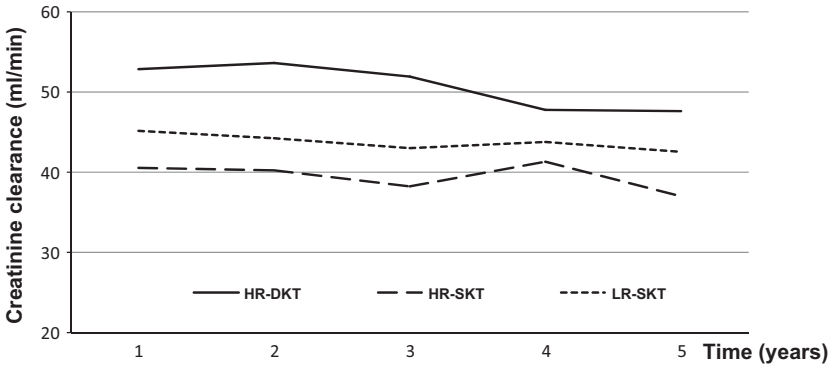
*Performed by Cox Model and adjusted for: high- or low-risk donor, HLA mis-matches, cold ischemia time, donor cause of death, Panel Reactive Antibody.
†Hazard ratio.
‡Confidence interval.

The multivariate analysis (Table 3) showed that donor and recipient characteristics did not significantly affect patient and graft survival, with the exception of recipient age which was the only independent risk factor for patient survival (recipient age cut off at 60 years, $P < 0.001$, Hazard ratio – HR = 5.139) while donor creatinine clearance was the only independent risk factor for graft survival (creatinine clearance cut off at 60 ml/min as threshold between mild and moderate to severe renal insufficiency, $P = 0.050$, HR = 1.960). In addition, better graft survival was observed in HR-DKT compared to LR-SKT ($P = 0.049$, HR = 0.398). We also performed a multivariate analysis by sub-group. The analysis conducted on the larger group (LR-SKT) confirmed the overall analysis while the data obtained for the other 2 groups showed no statistically significant associations between donor/recipient variables and outcomes, probably because of the small sample size (data not shown).

Mean creatinine value at 1 and 5 years was 1.6 mg/dl (SD 0.71) and 1.8 mg/dl (SD 0.84) for HR-DKT, respectively; 1.9 mg/dl (SD 0.76) and 2.1 mg/dl (SD 1.35) for HR-SKT, respectively; 1.8 mg/dl (SD 0.61) and 1.8 mg/dl (SD 0.77) for LR-SKT, respectively. There were no statistically significant differences among groups at either timepoints. Highest and lowest mean creatinine clearance at 1 year was observed in the HR-DKT (52.8 ml/min) and HR-SKT (40.6 ml/min) while LR-SKT had intermediate values (45.2 ml/min), $P = 0.003$. Trends remained in this direction over time although differences were not statistically significant at 5 years (Figure 3).

Discussion

The effectiveness of allocation routines for renal transplant is challenged by the chronic lack of organs and the continuing ageing of donors and recipients. Safe predictive algorithms are needed to warrant the success of transplantation in the majority of patients while making the best of a restricted donor pool. For ECD organs, the sole clinical evaluation does not appear sufficient and the combination with histological evaluation has been proposed. Indeed, a recent retrospective review of biopsied kidneys from donors aged 50 years or older, confirmed that combined criteria had better predictive value of graft function and survival



HR-DKT (N^2)	37	37	35	34	33
HR-SKT (N^2)	37	37	34	30	22
LR-SKT (N^2)	189	179	163	152	138

Figure 3 Creatinine clearance over time in the three study groups. [1]Estimated by the Cockcroft–Gault formula. [2]Patients with measurements are reported; comparison among groups performed by analysis of variance (ANOVA) at 1, 3 and 5 years with $P = 0.003$, 0.001 and 0,070, respectively. Creatinine clearance (ml/min). Time (years).

versus single criteria [18]. Appropriate profiling and post-transplant management [19] and pretransplant biopsy of kidneys from donor over 60 years for allocation to SKT or DKT [14] warrant similar short term graft and patient survival in ECD versus standard criteria donors (SCD) transplants.

Preimplantation histological assessment is a valuable tool for kidneys allocation when GS, TA, IF and vascular damage are scored in the same biopsy [20] with high interobserver agreement if IF and TA are evaluated as one entity [21]. It has been established that vasculopathy in donor biopsies is the most relevant single parameter and the major determinant of short-term and long-term outcome of the kidney graft whereas global GS is frequently overestimated [20,22,23]. Of note, acceptable 3-year graft survival rates are generally observed despite findings of GS involving over 25% of the donor biopsy sample [24,25].

Based on these favourable results, the NITp developed a composite donor selection algorithm with preimplantation biopsy performed only in donors at higher risk (according to age, history of hypertension, diabetes, creatinine clearance <60 ml/min or other risk factors that could affect renal function). This evaluation and allocation algorithm appeared easy to use in common daily practice across 13 centres with different standards despite their belonging to the same organization. Moreover, the data obtained at 5 year follow up showed that this approach was safe and efficient and did not prolong CIT which was within standard range of 15.7–18.6 h, as already demonstrated by other authors using donor biopsy in their allocation routine [14].

Patient and death censored graft survival rates at 5 years were above 85% in all groups and graft function remained fairly stable, within stage 3 of chronic kidney disease, throughout the follow up. Acceptable DGF rates were observed in all groups considering respective donor clinical risk and histological score, while PNF was seen in only 4 cases. There were no statistically significant differences among groups for any of the variable analyzed over time, although the HR-DKT group tended to perform somewhat better at 5 years while somewhat worse renal function was seen in the HR-SKT group. Possibly, DKT provided better nephron mass than any SKT while their being only first transplant might have slightly skewed results towards better outcomes. Nevertheless, graft function parameters reported in our study, including those of the least performing group, were similar or better than that reported in the literature [19,26].

Clearly, the need to thoroughly assess ECD kidneys differs among donor service areas, depending on the age distribution of the donor pool. In the last 10 years in the NITp area the percentage of donors ≥60 years has increased threefold from 12% in the decade 1990–1999 to 34% in the years 2000–2010 and representing now more than half of the donor pool [15]. Similar ageing trends stimulated other groups in identifying optimized allocation rules, like the Eurotransplant Senior Programme that also proved effective in increasing the number of kidneys from elderly donors actually used, shortening the waiting time for elderly recipients without negatively affecting graft and patient survival [27,28]. In our series, donors up to 82 years of age were used and overall, the optimisation of the use of ECD organs compensated the relative loss of SCD over time. Furthermore by restricting allocation of ECD kidneys to older recipients, we were also able to decrease waiting time (11 months for ECD vs. 28 months for SCD) in this population of patients [25,15] thus

avoiding the deleterious effect of longer dialysis time on graft and patient survival after transplantation [29].

The observational nature of the study should be discussed as a potential limitation in the interpretation of data. Indeed, while the allocation algorithm was standardized across all participating centres, other procedures did not follow a common scheme. While follow up routine, such as for instance, the frequency of visits, should not have a particular impact, the imbalance observed in treatment protocols might have biased the outcomes. In fact, the association of mTor inhibitors and steroids was more frequently used in HR-DKT patients. However, differential treatment protocols according to the patient profile are common in transplant practice and a perfectly randomized approach might not be ethical. Importantly, in contrast with most of the literature on this topic, the study was conducted in multiple centres across a large geographic area, demonstrating the usefulness and efficiency of a shared allocation algorithm in real life, with satisfying outcomes observed in all groups.

Another point of discussion should regard the allocation routine. Firstly, separate lists were used for SKT and DKT, however no ethical solution can be proposed as specific rules and informed consent were applied in each case. Secondly, the algorithm was defined empirically rather than based on a stratified analysis of outcomes. It is comforting thought to find similar schemes in the literature, in particular for histology scores [30,31], showing a certain degree of common intuition that will need to be confirmed by more extended prospective experience. Because cut off values represent the critical point of any algorithm, we acknowledge the uncertainty of performing one DKT where two SKTs could have been performed safely or *vice versa*. Nevertheless considering renal function values in our elderly population of donors, we feel that only few singles kidneys with sufficient function might have been missed for SKTs. Because DKTs performed extremely well in our series, we need to discuss the possibility of increasing the histological threshold. Overall, the composite clinical and histological algorithm evaluated in this study proved to be efficient and easy to apply in routine practice in an area where ECD organs offered are on the increase.

Well selected subsets of ECD donors offer excellent 5 year outcomes when properly allocated. The use of simple clinical criteria to allocate kidneys from low risk donors is a significant finding in terms of workload and costs, considering that this latter group was the most numerous. Further prospective experience is needed and like another group that used a similar routine including the same histological score for allocation to DKT or SKT [30], we acknowledge the need to revisit histological cut off scores in high risk patients in order to maximise the use of ECD organs.

Authorship

PES: collecting data and writing of manuscript. SS: designing the protocol, enrolling patients and writing of manuscript. DFN: collecting data, analyzing data. RG: designing the protocol, collecting data. FI, BL, GM, GE, DD, ME, GMT, BA, LC, SA and CS: enrolling patients. RP: designing the protocol, enrolling patients and writing of manuscript.

Funding

The authors have declared no funding.

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