Nephrol Dial Transplant (2007) 22: 2693–2700
doi:10.1093/ndt/gfm226
Advance Access publication 23 April 2007

Original Article

NDT
Nephrology Dialysis Transplantation

Long-term outcome of third kidney transplants

Alexandre Loupy[1], Dany Anglicheau[1], Caroline Suberbielle[2], Arnaud Méjean[3], Frank Martinez[1], Julien Zuber[1], Marie-France Mamzer-Bruneel[1], Henri Kreis[1], Eric Thervet[1], Nicolas Thiounn[3] and Christophe Legendre[1]

[1]Service de Transplantation Rénale et de Soins Intensifs, Hôpital Necker, APHP, F-75015 and Université René Descartes, F-75006, [2]Laboratoire d'Histocompatibilité, Hôpital Saint-Louis, APHP, and [3]Service d'Urologie, Hôpital Necker, APHP, F-75015 and Université René Descartes, F-75006, Paris, France

Abstract

Third renal transplants are historically associated with a poor prognosis. An analysis was undertaken to assess long-term outcomes of third grafts and identify variables associated with long-term graft survival. Fifty-six third grafts performed between 1974 and 2005 were compared to control groups of 1965 primary and 301 second grafts performed during the same period. Kaplan–Meier analysis showed a graft survival rate of 91%, 72% and 58% at 1, 5 and 10 years, respectively, for third transplants. Graft and patient survival of third grafts were similar to those of first and second transplants. Univariate analysis showed that HLA-A mismatch ($P < 0.01$), absence of calcineurin inhibitor as part of the initial immuno-suppressive regimen ($P = 0.03$), acute rejection ($P = 0.04$) and transplantation prior to 1990 ($P = 0.04$) were associated with a poor third graft survival. Multivariate analysis indicated that 1 year serum creatinine (HR = 1.02, $P = 0.001$), 1 year proteinuria (HR = 1.84, $P = 0.01$), absence of calcineurin inhibitor (HR = 10.6, $P = 0.01$) and complete HLA-A match (HR = 0.13, $P = 0.03$) were independently associated with graft loss.

Although third graft recipients have a range of risk factors previously associated with poor patient and graft outcome, that remain difficult to delineate in a retrospective analysis due to the possible selection of the third transplant candidates, these results suggest that third graft and patient survival rates could be similar to those of first and second transplants.

Keywords: outcome; prognosis; retransplantation; third kidney transplantation

Introduction

Repeated renal transplants are historically associated with a poor prognosis. The United Nations Organ Sharing (UNOS) registry reports 1- and 5-year survival rates of 91% and 70%, respectively, for first renal transplants compared with 88% and 65% for repeated renal transplants, primarily second grafts [1]. Retransplanted patients were once considered to be at higher risk of graft failure than first graft recipients. However, graft survival rates following retransplantation have improved substantially in recent years [2,3]. Indeed, it has recently been demonstrated that the long-term survival of second transplants may be similar to that of primary transplants [4]. It has also been proven that the cost effectiveness of transplantation for end-stage renal disease patients shows benefits over dialysis even for retransplanted patients [5,6].

Large series have paid considerable attention to second transplants, but the literature documenting outcomes following third transplants is comparatively poor. One of the only studies of third kidney transplants has reported 1- and 5-year graft survival rates of 90% and 62%, respectively, among a cohort of 38 patients [7]. This generated controversy about whether patients should be offered a third graft given the growing discrepancy between the number of available donor organs and the number of patients awaiting transplantation.

Recipients of a third graft constitute a unique population for several reasons, including a long medical background and a history of immuno-suppressive therapy that often entails comorbidity, numerous surgical interventions leading to surgical problems for retransplantation and a high level of panel reactive antibody (PRA). Consequently, these patients accumulate a number of risk factors that have previously been associated with poor patient and graft outcome [2,7–9].

Correspondence and offprint requests to: D. Anglicheau, Service de Transplantation Rénale et de Soins Intensifs, Hôpital Necker, 149 rue de Sèvres, 75743 Cedex 15 Paris, France.
Email: dany.anglicheau@nck.aphp.fr

Among the 2127 grafts performed in France in 2003, 1828 were first (86%) and 299 (14%) were retransplants [10].

Given the shortage of deceased-donor kidneys, the increasing numbers of patients awaiting a retransplantation and the debate about appropriate allocation, it is of utmost importance to assess the long-term outcome of third grafts and to identify variables associated with long-term graft survival. In this study, we report our experience with 56 consecutive third transplants performed at two French centres from March 1975 to January 2005 compared with a control group of 1965 first and 301 second renal transplantations performed at the same centres over the same period. The aim of the study was to determine the long-term outcome of third grafts and to identify the factors associated with third graft long-term survival.

Patients and methods

Patients receiving a first, second or third renal transplant between 1974 and 2005 at two centres (Necker Hospital and Saint-Louis Hospital, Paris, France) were eligible for inclusion in the analysis. Simultaneous kidney-pancreas and kidney-liver transplantations were excluded. Pre-transplant monitoring was standardized and included systematic anti-HLA antibody research every 3 months and after immunogenic events (blood transfusion, first or second transplant nephrectomy). All immunological analysis was undertaken in the same laboratory (Saint Louis Hospital, France). Patients eligible for transplantation had to satisfy the following immunologic criteria: ABO compatibility, historical and current negative complement-dependent cytotoxicity IgG T- or B-cell cross-match and the absence of class I or II against actuarial donor-specific antibodies. A positive lymphocytoxic IgM B-cell cross-match was not a contraindication for transplantation.

Among patients receiving a calcineurin inhibitor, blood concentration was monitored by whole blood radioimmunoassay which targeted a cyclosporine trough level of 150–250 ng/ml initially and 100–200 ng/ml 1 month after transplantation and a tacrolimus trough level 10–15 ng/ml initially and 7–10 ng/ml thereafter. Biopsy-confirmed acute rejection episodes were treated by steroid bolus of 500 mg for 3 days followed by progressive decreases according to centre protocol.

Data collection

Data were extracted from two computerized databases, DIVAT network (Données Informatisées et VAlidées en Transplantation) and CRISTAL (French National Transplant Database). The DIVAT database consisted of all pre- and post-transplant clinical and biological data of all patients transplanted at our institution, collected by an independent research assistant. Data evaluations are undertaken annually by an independent auditor, confirming the database validity with <1% error.

The following criteria were extracted from the database: number of previous transplants, donor and recipient age and gender, donor type (deceased or living), cold ischaemia time, causal nephropathy, class I peak PRA level, HLA-A, HLA-B, HLA-DR mismatch, transplantation date, date of graft loss and death, cause of graft loss and death, delayed graft function and acute rejection episodes. Additional biological and clinical data concerning the third graft group were extracted from patient medical reports: previous graft survival time, cause of previous graft loss, acute rejection episodes. In addition, operative procedures and surgical complications were recorded, as well as serum creatinine and proteinuria at 3, 6, 12 and 24 months. Graft loss was defined as a return to chronic dialysis or death with a functioning graft. Delayed graft function was defined as the need for $\geq$1 dialysis session during the first week post-transplant. From 1993, acute rejection episodes were all biopsy-proven and graded according to Banff criteria.

Statistical analysis

Results are expressed as numerical values and percentages for categorical variables and as means (±SD) for continuous variables. Comparisons of baseline characteristics between the first, second and third graft groups were based on the χ^2 test for categorical data and *t* test for continuous data. Graft and patient survival curves from date of third transplantation to last data collection (5 December 2005) were estimated using the Kaplan–Meier method. Data analysis concerning date of transplantation was stratified by pre-cyclosporine versus cyclosporine periods. The effect of clinical and biological variables (PRA value, HLA matching, previous graft survival duration, patient and donor age, cold ischaemia time, date of transplantation, calcineurin inhibitor use, delayed graft function, acute rejection occurrence, serum creatinine, proteinuria) on graft survival was assessed using the log-rank test. Cox proportional hazard modelling was used to determine risk factors for graft failure, using the following variables: HLA-A mismatch, acute rejection episodes, serum creatinine at 1 year, daily proteinuria at 1 year, calcineurin inhibitor use as part of the initial immunosuppressive regimen, graft survival of less than six months and date of transplantation. All tests were two-sided. Statistical analyses were performed using Statview 5.0.1® software (Abacus Concepts, Inc. Berkeley CA, USA). Probability values <0.05 were regarded as statistically significant.

Results

Study population

In total, 2322 renal transplants were undertaken between 1974 and 2005, of which 1965 were first transplants (84.6%), 301 (13%) were second transplants and 56 (2.4%) were third transplants. Four patients received a fourth transplant and one a fifth transplant and were excluded from the analysis. The majority of patients received a graft from a deceased donor (94%). Mean follow up of third grafts was 6.6 years (5–249 months).

Demographic and baseline characteristics are shown in (Table 1). Malformative uropathy (kidney dysplasia, hypoplasia or agenesia) as causal nephropathy was

Table 1. Demographic and baseline characteristics

	Third grafts ($n=56$)	Second grafts ($n=301$)	First grafts ($n=1,965$)
Recipient age (years)			
Mean ± SD	42 ± 11	39 ± 11	41 ± 13
Range	19–64	14–68	5–75
Age at first transplant (years)	27 ± 12	–	–
Age at second transplant (years)	32 ± 12	–	–
Age at third transplant (years)	42 ± 11	–	–
Donor age			
Mean ± SD	37 ± 12*	41 ± 13	43 ± 14
Range	10–62	10–76	10–83
Male recipient (%)	38 (68%)	193 (64%)	1238 (63%)
Cold ischemia time (hours)			
Mean ± SD	24 ± 10	24 ± 9	23 ± 9
Range	3–57	2–48	1.8–59
Deceased donor (%)	54 (96%)	292 (97%)	1827 (93%)
Acute rejection rate (%)	47%	–	–
Mean% peak class I PRA ± SD	53 ± 36*	28 ± 30	7 ± 18
Mean% peak class II PRA ± SD	45 ± 36	–	–
PRA number (%)			
Class I and class II <25%	18%	–	–
Class I or class II ≥25% and <80%	30%	–	–
Class I or class II ≥80%	51%	–	–
HLA mismatch (mean ± SD)			
HLA A	0.8 ± 0.7	0.8 ± 0.7	0.9 ± 0.7
HLA B	0.9 ± 0.7	1.0 ± 0.7	1.0 ± 0.7
HLA DR	0.7 ± 0.6	0.7 ± 0.7	0.6 ± 0.7
No. of total HLA mismatches (%)			
>2	36%	–	–
≤2	64%	–	–
No. of HLA-A mismatches (%)			
0	38%	–	–
1	44%	–	–
2	17%	–	–
No. of HLA-B mismatches (%)			
0	28%	–	–
1	53%	–	–
2	17%	–	–
No. of HLA-DR mismatches (%)			
0	38%	–	–
1	54%	–	–
2	8%	–	–
Delayed graft function (%)	51%	51%	45%
Survival time of second transplant (years)	4.9 ± 5.6	–	–
Survival time of first transplant (years)	2.5 ± 3.9	–	–
Estimated GFR at 1 year (ml/min)	51 ± 18	–	–

PRA, panel reactive antibody; HLA, human leukocyte antigen; GFR, glomerular filtration rate estimated by the Cockcroft formula [11].
*$P < 0.05$ compared to second and primary grafts.

more frequent among the recipients of a third graft (11%) than recipients of a second (2.3%) or first (1%) graft ($P < 0.05$). Recipients of a third graft had a mean previous graft survival time of (2.5 ± 3.9) years for their first transplant and (4.9 ± 5.6) years for their second transplant. Their first and second grafts survived less than one year in 58% and 27% patients, respectively. Recipients of a third graft were highly sensitized, with significantly higher class I PRA than second transplant recipients (Table 1). Acute rejection rate was high in third graft recipients (47%). Sixty-four percent of third graft recipients had ≤2 total HLA mismatches (A + B + DR) confirming the close HLA matching policy in retransplanted recipients.

Recipients of a third graft had their first and second transplantation performed before 1990 in 96% and 68% of cases, respectively. In these patients, first grafts were performed between 1968 and 1995 and second grafts between 1968 and 2002. Forty-five third grafts (80.4%) were carried out after 1990, the date from which cyclosporine was used as first-line therapy, whereas 11 grafts (19.6%) were performed from 1975 to 1990.

Among third transplant recipients, all patients received induction therapy, consisting of OKT3 monoclonal antibodies from 1981 to 1990 ($n=14$), horse or rabbit antithymocyte globulin (ATG) polyclonal antibodies since 1978 ($n=28$), or basiliximab since 1996 ($n=14$). All patients received steroids and a purine inhibitor [azathioprine ($n=20$) since 1997, mycophenolate mofetil ($n=36$)]. Ciclosporin was added to the previous dual therapy in 1990 and tacrolimus in 1995.

Overall, 44 patients (79%) received a triple-drug regimen consisting of a calcineurin inhibitor, a purine inhibitor and steroids.

Patient and graft survival

Patient survival rates were 98%, 96%, 89% at 1, 5 and 10 years, respectively (Figure 1A). Third graft recipient survival was not statistically different from that of first or second graft recipients. Among the 56 recipients of third grafts, seven patients died. Four died from severe bacterial infections involving lung, heart and wound, one patient died from coronary disease and the cause of the other two deaths was unknown. Graft survival following a third transplant was 91%, 72% and 58% at 1, 5 and 10 years, respectively (Figure 1B), similar to survival rates for first and second transplants. Of the 22 grafts lost, the cause was chronic rejection in nine cases (41%), hyperacute rejection in three cases (14%), death with a functioning third graft in four patients (18%), vascular thrombosis in two cases (9%), causal nephropathy recurrence in one patient (4%) and surgical complications in three patients (14%). A high rate of surgical (especially urological) complications was observed (12%), as the result of leakage and strictures, but had no impact on graft survival. Among recipients of a third graft, mean serum creatinine at 1, 5 and 10 years were 114 ± 86 μmol/l, 149 ± 71 μmol/l and 155 ± 85 μmol/l, respectively. Mean estimated glomerular filtration rate (Cockcroft–Gault [11]) and proteinuria at 1 year were 51 ± 18 ml/min/1.73 m^2 and 0.56 ± 1.2 g/day, respectively.

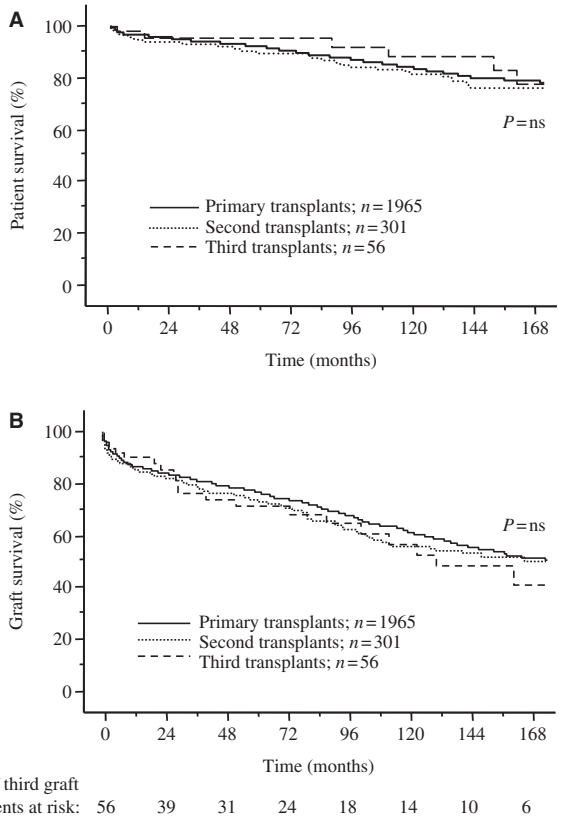

Fig. 1. (**A**) Patient survival and (**B**) graft survival for third, second, and first renal transplants performed between 1974 and 2005 (Kaplan–Meier estimates).

Risk factors for loss of third graft

Five-year and 10-year graft survival were significantly lower in patients who experienced one or more acute rejection episodes (84% *vs* 58%, $P = 0.035$ and 72% *vs* 44%, $P = 0.048$, respectively) (Figure 2). Early rejection (during the first month post-transplant) was significantly related to graft loss ($P = 0.038$), while late rejection (>1 month) showed only a trend ($P = 0.08$).

Patients grafted before 1990 experienced worse third graft survival than patients transplanted after 1990 (46% *vs* 78%, $P = 0.044$ at 5 years and 37% *vs* 64%, $P = 0.04$ at 10 years). This may be due to the reduction in acute rejection rate which was observed over the study period [81% of patients transplanted before 1990, 50% transplanted during 1990–2000 and 25% after 2000 ($P = 0.009$)], possibly related to the introduction of calcineurin inhibitors (77% of patients experienced acute rejection before calcineurin inhibitors *vs* 37% afterwards, $P < 0.05$). Correspondingly, 5- and 10-year third graft survival was significantly higher in patients receiving a calcineurin inhibitor as part of the initial immuno-suppressive regimen (91% *vs* 41%, $P = 0.023$ and 59% *vs* 41%, $P = 0.052$, respectively) (Figure 3).

Univariate analysis also showed that HLA-A mismatch was negatively associated with long-term third graft survival: graft survival rate at five and 10 years was 100% and 90% in the absence of HLA-A mismatch, *vs* 46% and 38% for at least one HLA-A mismatch, respectively ($P < 0.01$). HLA-DR and HLA-B mismatches had no significant effect on graft outcome. Interestingly, there was a trend to association of first graft duration of less than 6 months and long-term third graft loss ($P = 0.059$). Recipient and donor gender, age, cold ischaemia time, delayed graft

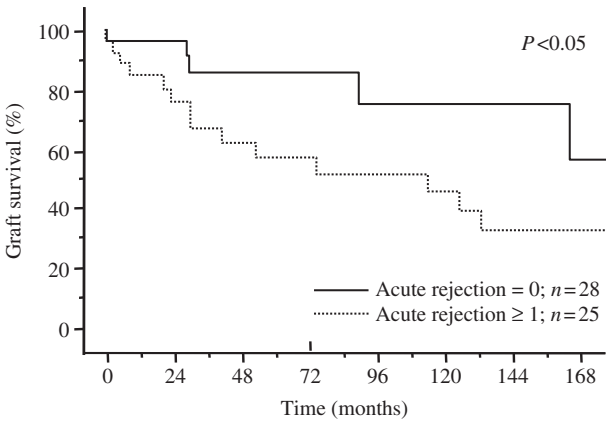

Fig. 2. Effect on acute rejection occurrence on third graft survival (Kaplan–Meier estimates).

function and anti-class I or II sensitization had no significant impact on third graft outcome.

Risk factors for loss of third graft

Multivariate analysis showed that serum creatinine and proteinuria at one year, full HLA-A match and calcineurin inhibitor use were independently associated with the risk of graft failure (Table 2). Mean serum creatinine at one year was 195 ± 13 µmol/l in patients who lost their graft compared to 123 ± 3 µmol/l for surviving transplants ($P < 0.01$); mean daily proteinuria at one year was 1.2 ± 2 g/day *vs* 0.14 ± 0.2 g/day, respectively ($P < 0.01$). Absence of a calcineurin inhibitor was the major predictor of third graft loss (relative risk 10.6). Date of transplantation and acute rejection occurrence were not independently associated with graft survival.

Immunological findings

When available, sera were evaluated for class I and II PRA levels prior to each transplantation and after graft nephrectomy. In total, 89% of patients experienced at least one graft removal. Thirty-six patients underwent the removal of the first graft while 28 underwent removal of the second graft. Mean class I PRA level increased from (8 ± 12%) before the first graft to (32 ± 8%) before the second graft and 36 ± 12% before the third graft ($P < 0.001$) (Figure 4). Recipients undergoing graft removal between the second and third transplantation had a higher PRA (49 ± 16%) compared to recipients without first or second graft removal (20 ± 12%, $P < 0.01$).

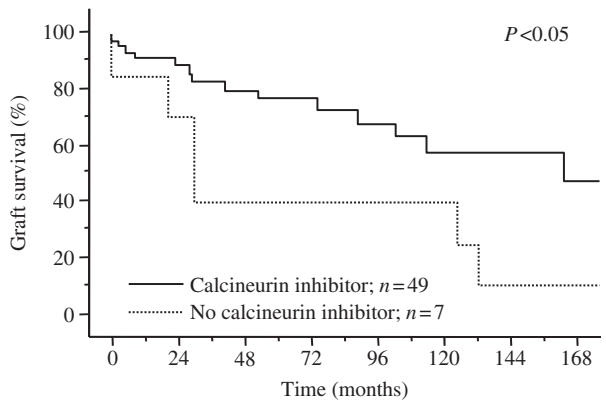

Fig. 3. Effect of inclusion of a calcineurin inhibitor as part of the initial immunosuppressive regimen on third graft outcome (Kaplan–Meier estimates).

Table 2. Multivariate analysis of risk factors of long-term third graft lost

Variable	Relative risk	*P* value
Serum creatinine at 1 year	1.02	0.0015
Proteinuria at 1 year	1.84	0.01
Absence of calcineurin inhibitor	10.6	0.01
HLA-A 0 mismatch	0.13	0.03

Discussion

Given the shortage of cadaver kidneys donations, it is important to assess long-term outcome of third grafts and to identify risk factors associated with long-term graft survival in order to determine whether patients who already lost two previous grafts should be offered a third graft. In this article, we described the long-term outcome of 56 third renal transplants performed between 1974 and 2005 compared with renal outcome of a control group of first and second renal transplantations performed in the same centres over the same period of time and identified factors associated with graft survival. Our results indicate that third graft prognosis dramatically increased over time and can raise adequate 5 and 10 year graft survival of 72% and 58% respectively, similar to those of first and second transplants.

Kidney re-transplantation has been historically associated with a poor prognosis. Fasola *et al.* [12] reported in a retrospective monocentric review of 64 third grafts performed between 1968 and 1983 a 1-year graft survival of 74% and Imagawa *et al.* [13] reported in 1988 in a large number of re-grafts a 1-year survival rate of 56.9%. Noteworthy, these two studies stressed the re-transplant outcome prior to cyclosporine introduction in immuno-suppressive protocols. In the cyclosporine era, re-transplant outcome may have improved. Hagan *et al.* [7] retrospectively reviewed the outcome of 38 third grafts performed in Ireland between 1974 and 2001 and reported a 1- and 5-year graft survival rate of 90% and 62%, respectively but did not study the impact of immuno-suppression and/or date of transplantation on graft outcome. Moreover, recent studies stressed the improvement of second kidney transplant outcome even for short and long-term [4,14,15]. Coupel *et al.* [4] reported in a monocentric retrospective study of 233 second and 1174 first transplantations similar short- and long-term survival rates. In this study, HLA-DR mismatch, acute rejection and 1-year serum creatinin had a significant impact on graft survival and the year of transplantation played a significant role in acute rejection occurrence.

Third graft recipients of transplants performed before 1990 had lower graft survival than third grafts performed after 1990, when cyclosporine was introduced as routine first-line immunosuppressant. Reports in the literature also suggest that graft survival rates after re-transplantation have improved since the introduction of cyclosporine [4,14,15] compared to the pre-cyclosporine era [12,13], although data relate primarily to second transplants. A number of factors may have contributed to this improvement, including improved pre-transplant screening, more sensitive cross-matching, better HLA matching, improved infectious disease prophylaxis and more potent

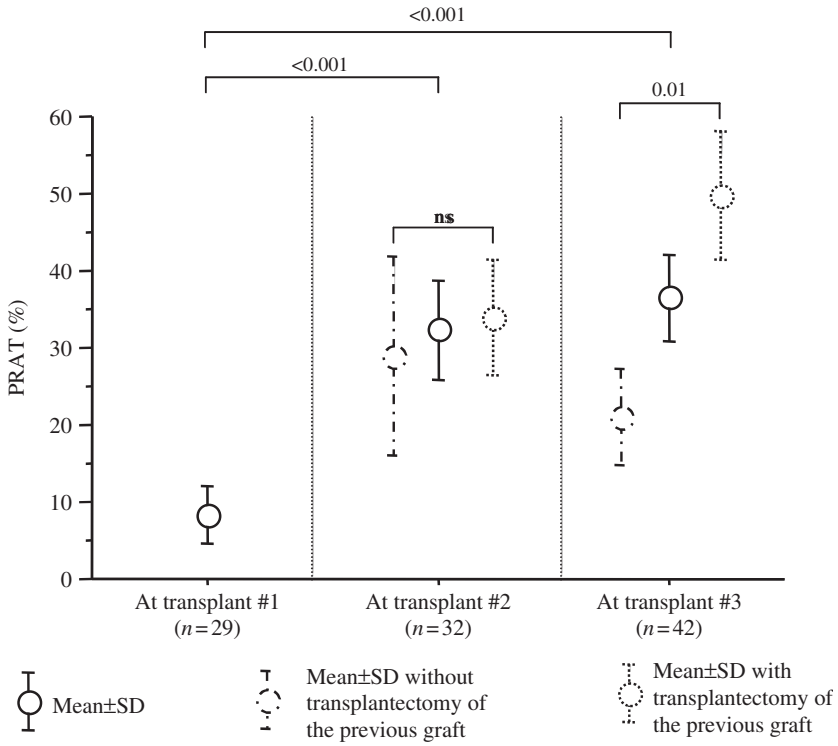

Fig. 4. Anti-T PRA levels prior to transplantation and impact of previous graft nephrectomy.

immunosuppressive regimens, most of which would tend to decrease acute rejection. Acute rejection appears to exert a particularly marked effect on graft survival in re-transplanted patients [4]. These advances may have been especially beneficial for third graft recipients, who are at high immunological risk, raising third graft long-term survival rates to those seen following first or second transplants.

We also showed similar patient survival rates whatever the rank of transplantation. Despite a long history of immunosuppressant, third graft recipient survival was as good for third as for second or first transplant. Malformative uropathy was a more frequent cause of end-stage renal failure among recipients of a third graft in our population, whereas diabetes and vascular nephropathies, leading to cardiovascular complications and death with a functioning graft, were more frequent among recipients of a first or second graft. Early-onset nephropathies leading to end-stage renal disease in pediatrics are of course more likely to necessitate kidney transplantation at an early age and subsequent re-transplantation. It is conceivable that third graft recipients have less vascular damage than recipients for whom cardiovascular disease is the cause of end-stage renal disease, and that this may favour graft and patient survival following re-transplantation. In addition, the lower donor age for third graft patients (probably due to avoidance of marginal donor for third transplant) could positively affect third graft outcome.

Third graft recipients were characterized by a high degree of sensitization, which may explain the high acute rejection rate in this group. Rejection rate fell during the study period, with introduction of calcineurin inhibitors a likely contributing factor. Accordingly, univariate analysis showed that acute rejection and absence of calcineurin inhibitors were associated with a poor third graft survival, whereas multivariate analysis revealed that only calcineurin inhibitor use was independently associated with graft survival.

Univariate analysis also suggested the HLA-A matching could affect long-term third graft outcome while HLA-B and HLA-DR did not. The impact of HLA matching on regraft survival remains controversial. Coupel *et al*. [4] reported that HLA-DR mismatch was independently associated with second graft survival, whilst Farney *et al*. demonstrated in a large series of 420 renal regrafts that HLA matching confers no benefit to graft survival [16]. The literature concerning HLA matching impact on graft survival usually reports benefits of fewer HLA-DR mismatches [4], but a class I HLA matching benefit was also reported, particularly within the first 36 months post-transplant [12].

Multivariate analysis showed that 1-year serum creatinine had an independent impact on long-term graft outcome, confirming previously published data [17,18]. One year proteinuria also exerted an independent effect on third graft outcome. This frequently neglected parameter in transplant patients, which is an indicator of renal lesions and a risk factor for subsequent renal function decline in most nephropathies [19], has also been proved to be associated with poor renal outcome in renal transplantation [20].

Our study shows a high level of sensitization in recipients of a third renal transplant but also a significant rise in PRA value following the removal of the previous graft. Previous studies have shown that the presence of a first transplant is associated with a lower incidence of PRA [21,22]. In contrast, the graft removal is often followed by a rise in anti-HLA antibodies, suggesting that the presence of a non-functioning graft may either regulate the capacity of the recipient to mount an immune response to the donor's major complex antigens or absorb a low level of antibodies [23], as it has been suggested by the study of rejected graft eluates [24]. Although evidence exists on the PRA increase after a previous graft removal, the clinical relevance of a primary allograft nephrectomy on subsequent renal transplantation outcome remains controversial. In a retrospective study of 127 second kidney graft recipients, Douzidjan *et al*. [22] reported a significant impact on pre-sensitization and risk of acute rejection, but no impact on early graft outcome. Other authors have reported similar findings [15,16] while experimental and clinical evidence from Lair *et al*. [23] indicated no beneficial effect of a first rejected graft remaining *in situ* at the time of a second transplant. In this study, it's noteworthy that for the six third graft patients (11%) without graft removal before the third graft, all the third grafts are still functioning. All their grafts were performed in the cyclosporine era from 1991 to 2004, consistent with the fact that allograft nephrectomy was more frequently required in the pre-cyclosporine era [21]. Unfortunately, due to the small sample size in each group, the impact of previous graft removal on third graft survival could not be assessed in this study.

The main limitation of this study is the small sample size that may account for confounding factors particularly over a long period of time. The other limitations include the retrospective and single centre nature. While single-centre studies usually include small numbers, with a low statistical power for some parameters, they also offer homogeneity with respect to medical management, especially for the comparison of long-term outcome of first, second and third grafts. These results may not, however, be applicable to other populations of renal transplant recipients with different clinical characteristics or different immunosuppressant regimens. The analysis of this study included the use of multivariate analysis, but an effect of residual confounding factors that were not evaluated cannot be excluded.

Lastly, the third transplants spanned a period of 32 years, but 80% of grafts have been performed after 1990 where cyclosporine was routinely used. Although the management of kidney transplantations has changed in such a long period of time, interestingly, we did not find any significant improvement of long-term survival of the first grafts during the study period contrary to the third grafts of which the prognosis was spectacularly improved with time. These results are in accordance with those of Meier-Kriesche *et al*. [3] who recently showed that first renal transplant long-term results remain largely unchanged over the time while a dramatic improvement of the re-transplants graft survival is observed.

Lastly, despite a manifest similar graft survival in the three groups confirmed by the Kaplan–Meier analysis, the negative impact of the graft ranking in the entire cohort when corrected for all other variables can not be formally ruled out. This would have been performed by a multivariate analysis including the whole cohort of patients with the classical risk factors including the categorization of the number of transplant. However, we were not able to perform this analysis due to missing data regarding some classical risk factors associated with graft survival in patients transplanted before 1985.

Conclusion

In conclusion, third grafts had more benefits of improved pre-transplant screening and post-transplant management. Although third graft recipients have a range of risk factors previously associated with poor patient and graft outcome, that remain difficult to delineate in a retrospective analysis due to the possible selection of a third transplant candidate, these results suggest that third graft and patient survival rates could be satisfactory and similar to those of first and second grafts.

Acknowledgments. The authors wish to thank Sophie Lechaton, and Pascal Dabi and Emilie Savoye from Agence de la Biomédecine for their help in patient data retrieval.

Conflict of interest statement. None declared.

References

1. United Nations Organ Sharing Registry. Available at: www.unos.org. Accessed 5 June 2006
2. Cho YW, Cecka JM. Cadaver-donor renal retransplants. *Clin Transpl* 1993; 469–484
3. Meier-Kriesche HU, Schold JD, Kaplan B. Long-term renal allograft survival: have we made significant progress or is it time to rethink our analytic and therapeutic strategies? *Am J Transplant* 2004; 4: 1289–1295
4. Coupel S, Giral-Classe M, Karam G *et al*. Ten-year survival of second kidney transplants: impact of immunologic factors and renal function at 12 months. *Kidney Int* 2003; 64: 674–680
5. Hornberger JC, Best JH, Garrison LP, Jr. Cost-effectiveness of repeat medical procedures: kidney transplantation as an example. *Med Decis Making* 1997; 17: 363–372
6. Matas AJ, Gillingham KJ, Payne WD, Dunn DL, Gruessner RW, Sutherland DE *et al*. A third kidney transplant: cost-effective treatment for end-stage renal disease? *Clin Transplant* 1996; 10: 516–520
7. Hagan C, Hickey DP, Little DM. A single-center study of the technical aspects and outcome of third and subsequent renal transplants. *Transplantation* 2003; 75: 1687–1691
8. Cabacungan C. Regrafts. *Clin Transpl* 1992; 00: 347–356
9. Hirata M, Terasaki PI. Renal retransplantation. *Clin Transpl* 1994; 419–433

10. National Report from the Etablissement Français des Greffes [EFG], 2003.
11. Cockcroft DW, Gault MH. Prediction of creatinine clearance from serum creatinine. *Nephron* 1976; 16: 31–41
12. Fasola CG, Kim YS, Morel P *et al*. Kidney retransplantation: patients with a failed second kidney transplant should be considered for a third transplant. *Transplant Proc* 1991; 23: 1336
13. Imagawa DK, Cecka JM. Renal regrafts. *Clin Transpl* 1988; 387–398
14. Mitsuishi Y, Cecka JM. Recent improvements in cadaver-donor kidney retransplantation. *Clin Transpl* 1991; 281–291
15. Bryan CF, Baier KA, Nelson PW *et al*. Long-term graft survival is improved in cadaveric renal retransplantation by flow cytometric crossmatching. *Transplantation* 1998; 66: 1827–1832
16. Farney AC, Matas AJ, Noreen HJ *et al*. Does re-exposure to mismatched HLA antigens decrease renal re-transplant allograft survival? *Clin Transplant* 1996; 10: 147–156
17. Salvadori M, Rosati A, Bock A *et al*. One-year post transplant renal function is a strong predictor of long-term kidney function: results from the Neoral-MOST Observational Study. *Transplant Proc* 2003; 35: 2863–2867
18. First MR. Renal function as a predictor of long-term graft survival in renal transplant patients. *Nephrol Dial Transplant* 2003; 18 [Suppl 1]: i3–i6
19. Jafar TH, Stark PC, Schmid CH *et al*. Proteinuria as a modifiable risk factor for the progression of non-diabetic renal disease. *Kidney Int* 2001; 60: 1131–1140
20. Fernandez-Fresnedo G, Plaza JJ, Sanchez-Plumed J *et al*. Proteinuria: a new marker of long-term graft and patient survival in kidney transplantation. *Nephrol Dial Transplant* 2004; 9 [Suppl 3]: iii47–iii51
21. Roberts CS, LaFond J, Fitts CT *et al*. New patterns of transplant nephrectomy in the cyclosporine era. *J Am Coll Surg* 1994; 178: 59–64
22. Douzdjian V, Rice JC, Carson RW *et al*. Renal retransplants: effect of primary allograft nephrectomy on early function, acute rejection and outcome. *Clin Transplant* 1996; 10: 203–208
23. Lair D, Coupel S, Giral M *et al*. The effect of a first kidney transplant on a subsequent transplant outcome: an experimental and clinical study. *Kidney Int* 2005; 67: 2368–2375
24. Martin L, Guignier F, Mousson C *et al*. Detection of donor-specific anti-HLA antibodies with flow cytometry in eluates and sera from renal transplant recipients with chronic allograft nephropathy. *Transplantation* 2003; 76: 395–400

Received for publication: 12.12.06
Accepted in revised form: 22.3.07