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Retraction

Retracted: The Impact of Graft Nephrectomy on Subsequent Transplants: Multivariate Analysis of Risk Factors for Second Graft Loss and for Multiple Transplantations–A Single-Center Retrospective Study

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At the request of the authors and the hospital, the article titled "The Impact of Graft Nephrectomy on Subsequent Transplants: Multivariate Analysis of Risk Factors for Second Graft Loss and for Multiple Transplantations–A Single-Center Retrospective Study" [1] has been retracted. The data reported in the article were not reviewed by the Renal Transplant Unit of the Royal London Hospital before submission. The data is not a complete capture and as a result is not an accurate reflection of the effect of the intervention.

References

[1] E. Giorgakis, A. Syed, and H. Gonzalez, "The impact of graft nephrectomy on subsequent transplants: multivariate analysis of risk factors for second graft loss and for multiple transplantations–A Single-Center Retrospective Study," *ISRN Transplantation*, vol. 2013, Article ID 362571, 9 pages, 2013.

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Research Article

The Impact of Graft Nephrectomy on Subsequent Transplants: Multivariate Analysis of Risk Factors for Second Graft Loss and for Multiple Transplantations–A Single-Center Retrospective Study

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Introduction. The management of a failed primary allograft remains unclear and the evidence of the effect of transplantectomy to future transplants conflicting. Aim of this study is to review the impact of failed primary graft nephrectomy on future transplants. *Materials/Methods*. Retrospective study of 101 patients retransplanted in a single institution. Median follow-up was 68 months. Patients were divided into two groups; G1 ($n = 49$) was the nephrectomy group; G2 ($n = 52$) was the graft *in situ* group. The patients' and second graft survival were analysed with the Kaplan-Meier method. The patients' and transplant characteristics were analyzed with student's t-test. The retransplant risk factors and the risk factors for multiple transplants were obtained via a logistic regression model. *Results*. The odds of second graft loss post-transplantectomy were high (OR = 5.24). Demographics, HLA mismatch and first graft rejection rates were similar among the two groups and did not affect the outcome. Transplantectomy accelerated the loss of a future failing graft. Multivariate analysis showed transplantectomy as independent risk factor for second allograft loss. Transplantectomy and younger age are significant independent risk factors for future multiple transplants. *Conclusion*. Transplantectomy of the failed primary graft is an independent risk factor for retransplant loss and for multiple renal transplants.

1. Introduction

The high success rates of primary kidney transplants and longer graft life due to better immunosuppression have led to a larger number of transplant patients living longer and inevitably a larger patient population with failed primary kidney transplants [1, 2]. The same level of successful outcomes has not been achieved for patients who are retransplanted in terms of lifespan of the second allograft [2, 3]. There has been little research looking at retransplantation in patients with a failed primary kidney transplant and how to achieve the best outcome. It is still very controversial when the primary kidney transplant fails how best to manage these patients.

Failed allografts *in situ* still stimulate immunoreactivity and are known to cause a chronic inflammatory response as measured by an increase in CRP, ESR, EPO resistance, hypoalbuminaemia, and malnutrition [4, 5]. Ayus et al. looked at 10,000 patients with a failed primary allograft in the United States and found that there was an improvement of morbidity and mortality in the patient group where the allograft was removed [6]. These benefits of graft nephrectomy notwithstanding, leaving the primary graft *in situ* allows avoiding the high surgical risk of such a procedure in an immunosuppressed patient with multiple commorbidities. John and Kevin observed raised panel reactive antibody (PRA) levels after graft nephrectomy [7]. A recent study by Schleicher et al. demonstrated that graft nephrectomy is associated with increased PRAs, worse graft survival after retransplantation and increase rates of primary nonfunction (PNF) and acute rejection; they also concluded that

transplantectomy of the first graft and high PRA levels are independent and significant risk factors associated with retransplant loss [5].

Primary end-point of this study was the effect of a failed primary allograft removal on the graft and patient survival after renal retransplantation. By means of multivariate analysis, it was further attempted to identify renal retransplantation and multiple retransplantations' risk factors.

2. Patients and Methods

This is a retrospective study of the patients who underwent renal allograft retransplantation in a single institution in the period between June 1, 1984, and August 8, 2012. There were a total of 101 patients retransplanted; since a subgroup of these patients were retransplanted two or three times, the total number of retransplantations performed was 122.

Patients were split into two groups. Those included in group 1 (G1, $n = 49$) underwent transplantectomy prior to retransplantation, while for patients of group 2 (G2, $n = 52$) no transplantectomy was performed. Patients in both arms were further subdivided into those who received single ($n = 81$) versus multiple (two or more) retransplantations ($n = 20$). This latter group included 19 patients who underwent 3 transplantations ($n = 15$, G1 and $n = 4$, G2) and a single patient who had 4 transplantations ($n = 1$, G2).

Primary endpoints were patient survival, second graft survival, and rate of acute rejections. The effects of patient demographic characteristics, HLA matching and cold ischemia time on the transplant outcome, the second transplant rejection rates and the risk factors for second graft loss and for multiple retransplantations were further reviewed.

Data were collected retrospectively. Data were obtained from the validated database employed in our unit, namely, the FileMaker Pro 5.5v1 (FileMaker, Inc.). Mismatch and cold ischaemia times (CITs) were retrieved from the unit's transplant audit registry which is incorporated on the Filemaker database. The immunological data obtained from the Filemaker and transplant audit registry were cross-referenced with the database of the clinical transplantation laboratory of our hospital institution. The flow cytometric and complement dependent cytotoxicity (CDC) crossmatching was obtained from the clinical transplantation laboratory archives. CDC crossmatching was performed in all retransplant recipients. Retransplantation was held in the presence of positive crossmatch.

Graft function in the early posttransplant period was being monitored by means of serum creatinine levels and diuresis. Suspected perfusion defect was being investigated via means of graft Doppler ultrasound. Renal allograft rejection in this study was a biopsy-proven pathological diagnosis. Graft failure was heralded by the return to hemo- or peritoneal dialysis or by graft nephrectomy. The follow-up period since the first retransplantation ended on February 2, 2012 (range: 6–342 months).

Null hypothesis of this study was that the graft survival after retransplantation is not affected by prior nephrectomy of the failed allograft. Patient survival and graft survival were analysed by the Kaplan-Meier method. G1 group was further compared to G2 group using Student's t-test. Variables were presented as mean ± standard deviation or the median. A value of $P < 0.05$ was considered statistically significant. A backward logistic regression model was employed for multivariate analysis of the factors associated with multiple retransplantations and multiple graft nephrectomies. Statistical analysis was performed using Statistical Product and Service Solutions (SPSS) 14.0 for Windows computer software, T-Test Statistics Calculator [6], Logistic Regression version 05.07.20 [7], and calculator for Survival Probability (Kaplan Meier method) [8].

3. Results

Of 101 patients undergoing second renal transplantation, 49 (48.5%) had the failed allograft removed (group 1, G1), while 52 (51.5%) had their nonfunctioning graft left *in situ* (Group 2, G2). Among the patients of G1, 15 (30.6%) received a second retransplantation ($n = 15$), whereas in G2, 5 patients underwent multiple retransplantations (second retransplantation $n = 4$, third retransplantation $n = 1$).

A total of 20 patients required multiple retransplantations. They were further subdivided into 19 patients having required three renal transplants (15 patients in G1 and 4 in G2) and a single patient who required 4 transplants (in G2); 12 patients in G1 and 12 patients in G2 received living donor allografts (24.4% and 23.1% resp.).

Transplantectomy indications were perioperative graft vascular compromise due to renal arterial or venous thrombosis, control of hemorrhage, sepsis, or refractory BK infection with ongoing rejection. Further indications were graft intolerance syndrome, recurrent urinary tract infections, or graft nephrectomy for recurrent primary disease or refractory active rejection in view of a future retransplantation.

The majority of the first grafts in G1 were lost because of rejection (46.9%). 14 patients (28.6%) lost their graft in the immediate posttransplant period for mechanical reasons; namely, 9 grafts (18.4%) were lost in the perioperative period due to thrombosis in the graft vascular stem; 3 grafts had to be explanted for control of bleed; a single kidney was infarcted due to renal artery dissection; 2 more allografts failed due to hypoperfusion or technical reasons with no further information available (Table 1).

Since this study includes a significant number of patients that had their first transplant managed in varying hospitals through extended chronic periods prior to their referral to our center, there was no consistent universally accepted protocol in terms of transplantectomy criteria nor a reliable universal database; thus, apart from these 28.6% of cases where nephrectomy was mandated because of perioperative graft vascular incidents, the decision for removal of the failed graft was taken on a patient-by-patient basis and on the discretion of the local joined attending transplant team.

The two groups were similar in terms of age, ethnic origin, or gender among the two groups or across the subgroups that received multiple transplantations (Table 2). This notwithstanding, multiple-transplant patients in the graft *in situ* group tended to be younger (mean age 15.6 versus 26.45 years

Table 1: Causes of the first renal allograft loss in the nephrectomy group (G1).

First graft loss aetiology	Number of patients (G1, $n = 49$)	%
Rejection	23	46.9
Renal vein thrombosis*	6	12.2
Renal artery thrombosis*	3	6.1
Haemorrhage*	2	4.1
Arterial dissection*	1	2
Infarction due to hypoperfusion*	1	2
Other technical*	1	2
Sepsis/BK	1	2
MGGN/HUS	2	4.1
Chronic allograft nephropathy	4	8.2
Other/not recorded	5	10.2

*Perioperative sequelae.

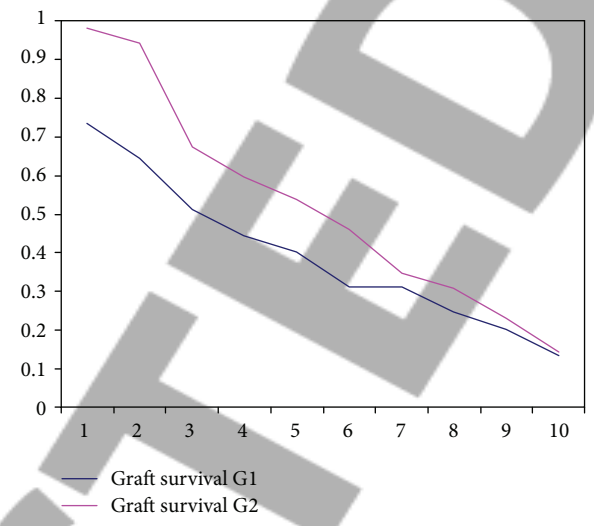

Figure 1: Graft survival (years).

in the respective subgroup among the nephrectomy patients, $P = 0.06$), and vertical analysis of the age distribution showed that G2 patients who received multiple transplants were younger than the overall population ($P = 0.003$); similar tendency was noted in the nephrectomy population, even though it did not reach statistical significance ($P = 0.06$). Male patients were more likely to undergo retransplantation (2 : 1 in the nephrectomy group and 3.33 : 1 in the controls), even though both genders were equally likely to receive multiple transplantations.

76% of the patients received organs from deceased donors. This was consistent among the two groups (75.5% versus 76.3% and 23% versus 24.4%, $P > 0.05$). There was no difference in terms of HLA mismatch or the in comparison of the patients who underwent a single retransplantation versus those who received multiple transplants (>2) (Table 2).

44.6% of the patients had at least one biopsy-proven rejection of their first graft prior to their retransplantation. Even though the percentage of the graft *in situ* patients having had a rejection tended to be higher (50% versus 38.77%), the findings did not reach statistical significance ($P = 0.26$). In reverse proportion, the percentage of nephrectomy multitransplant patients who had a first allograft rejection tended to be higher (33% versus 20%), without achieving level of significance ($P = 0.6$). It was thus concluded that there was no statistical difference in the rejection rates during the first renal transplantation among the two groups (Table 2). This comes into contrast with the rejection rates after the second transplantation among the two groups, which were higher among G1 patients (24.49 versus 21.12%), even though it failed to prove statistically significant with a narrow margin ($P = 0.053$). There was no evidence of increased rates of second graft rejection among the two multitransplantation (>2 transplants) groups. Remarkably, the second transplant rejection rates were significantly higher in the patients who eventually had more than two transplants, as opposed to the patients who received a single retransplantation (65% versus 30%, $P = 0.0027$).

After a median follow-up period of 68 months, 28.7% of patients lost their graft. In G1, through a 51-month median follow-up period, 22 patients (45%) lost their second transplant. In G2, second allograft loss was observed in 7 patients (13.5%) in a median follow-up period of 80.5 months (Table 3). G1 patients had significantly higher odds for losing the second graft (odds ratio 5.24, $P < 0.05$, Table 4). The median second graft survivals were comparable among the two groups (49 months in G1 versus 56.5 in G2), yet the median survival of the failing second transplants was significantly shorter in G1 (29.5 versus 82 months; see Table 5).

There were 4 fatalities in the graft nephrectomy cohort (8.2%) as opposed to no fatalities in the controls; this resulted in a statistically significant difference in the 10 year survival probability among the two groups (G1 survival probability 0.92 CI (0.83–0.998), $P < 0.05$ as opposed to G2 survival probability of 1 CI (1-1), $P < 0.05$). These results were not adjusted to nongraft related-morbidities.

Patient survival notwithstanding, the 1st year graft survival was lower in G1 (0.73 versus 0.98, $P < 0.05$). The same applies for the 2nd- and 5th-year survivals (0.64 versus 0.94 and 0.4 versus 05.42, resp., $P < 0.05$). Despite the increased rates of graft loss in G1 during the first years of retransplantation, the 10-year survival was similar among the two groups (0.13 versus 0.14, $P < 0.05$) (Table 8, Figure 1).

The odds ratio for multiple retransplantations was further assessed. 33.3% of patients of G2 were re-retransplanted, as opposed to 9.6% of the controls (Table 9). G1 patients had significantly higher odds of requiring multiple transplantations in their lifetime, with an odds ratio 4.7 (CI (1.58–14.28), $P < 0.05$). Should the patients awaiting for multiple (≥2) retransplantations be considered, significantly higher proportion of patients (42.2%) in G1 would need multiple retransplantations after the first graft failure as opposed to 7 out of 52 (13.46%) in G2. Odds ratio was 6.87 (CI (2.30–20.54); $P < 0.05$). It was thus strongly suggested that having the first failed allograft explanted was a significant

Table 2: Group characteristics, Student's t-test.

	G1 (transplantectomy group) $n = 49$		G2 (graft *in situ* group) $n = 52$		(P)	
Recipient age (years)						
Overall	29.59 ± 13 (16.59–40.89)		27.23 ± 12.32 (14.97–39.55)		NS (0.32)	
MTx	26.45 ± 11 (15.45–37.45)		15.6 ± 13.87 (1.81–32.68)		NS (0.06)	
(2Tx) versus MTx	30.59 ± 10.43 (20.16–41.02)	26.45 ± 11 (15.45–37.45)	28.36 ± 11.8 (16.56–40.4)	15.6 ± 13.87 (1.73–29.47)	(G1) (.06)	(G2) (.03)
Sex (M/F)						
Overall	33/16 (2 : 1)		40/12 (3.33 : 1)		NS (0.29)	
MTx	7/8		2/2		NS (0.48)	
Ethnic distribution (%)						
Afro-British	3 (6.12)		5 (9.62)			
Asian	3 (6.12)		7 (13.46)			
Bangladeshi	1 (2.04)		0			
Caucasian	36 (73.47)		30 (57.69)		NS (0.23)	
Indian	3 (6.12)		5 (9.62)			
Pakistani	0		1 (1.92)			
West Indian Black	1 (2.04)		1 (1.92)			
Unknown	2 (4.08)		3 (5.77)			
Donor						
Living (%)	12 (24.49%)		12 (23.08%)		NS (0.87)	
Deceased (%)	37 (75.5%)		40 (76.32%)			
HLA mismatch						
Overall	3 ± 1.32 (1.68–4.32)		2.52 ± 1.39 (1.12–3.91)		NS (0.76)	
MTx	3 ± 1.25 (1.75–4.25)		2.2 ± 1.3 (0.9–3.5)		NS (0.24)	
≥1 rejections (first graft)						
Overall (%)	19 (38.77)		26 (50)		NS (0.26)	
MTx (%)	5 (33.33)		1 (20)		NS (0.6)	
≥1 rejections (second graft)						
Overall (%)	19 (24.49)		11 (21.12)		NS (0.05)	
MTx (%)	10 (50)		3 (60)		NS (0.79)	

MTx: multiple renal transplants (>2); HLA: human leukocyte antigen; NS: nonsignificant ($P \geq 0.05$).

Table 3: Retransplantation outcome.

Outcome	G1	G2
Second allograft loss	22 (45%)*	7 (13.5%)
Multiple-transplant (≥3) candidates**	19 (34.69%)***	7 (13.46%)
Multiple transplants (≥3) performed	15 (33.3%)***	5 (9.6%)
Failed second allograft and active on the waiting list	4	2
Failed second allograft and not active on the waiting list	4	0

*The *n* in that calculation was 49 since there was no evidence that the nephrectomy cohort patients who expired during the observation period had a failed graft prior to their death. There was no fatality in the control group.
**Those are patients in need of re-retransplantation, who have either undergone multiple (>2) transplantations or are active for third or fourth time on the transplant list/being worked up for a living donor transplantation. Failed second transplant patients rendered unfit for multiple transplantations or not yet active on the list were not included.
***The *n* in that calculation was 45 instead of 49, since there were 4 fatalities in the nephrectomy cohort with functioning grafts at the time of their death.

Table 4: Odds ratio of second graft loss.

Study group/outcome	2nd graft loss	2nd graft survival
G1	22	27
G2	7	45

Odds ratio, OR = 5.24.
95% confidence interval = (1.98–13.89).

Table 5: Median graft survival (months).

Outcome	G1	G2
Second allograft median survival	49 (6–222)	56.5 (0–276)
Second failed allograft median survival	29.5 (0–276)	82 (24–112)
Median follow-up period	51 (6–222)	80.5 (9–347)

Table 6: Average graft survival 10 years of follow-up, G1 versus G2 (months).

	G1	G2	(*P*)
Second allograft mean survival			
Overall	41.89 ± 38	55.79 ± 31.2	NS (0.066)
MTx	38.29 ± 37.34	77 ± 41.83	NS (0.066)

MTx: multitransplant (>2) patients; NS: nonsignificant.

Table 7: Average graft survival 10 years of follow-up, overall versus MTx (months).

	Overall	MTx	(*P*)
Second allograft mean survival	51.02 ± 35.64	43.13 ± 39.4	NS (0.299)

MTx: multitransplant (>2) patients; NS: nonsignificant.

prognostic factor for future requirements of multiple renal transplantations. Confounders were yet to be considered.

Followingly, multivariate analysis was performed in order to exclude confounders affecting the above observations. (Table 9). Three factors were examined, namely, the age of the recipient, the occurrence of at least a single acute rejection episode on the first transplantation, and nephrectomy of the first failed allograft. The analysis showed that allograft nephrectomy of the first transplant is an independent risk factor for failure of future retransplantations ($P = 0.0001$). The same three factors, that is, age, rejection, and pretransplant nephrectomy were further analysed in order to identify risk factors for multiple (>2) renal transplantations (Table 10). Despite the fact that patients who eventually had multiple transplants had significantly more second graft rejections ($P = 0.003$), this variable was omitted in the regression because the scope of the multivariate analysis was to uncover factors predicting multiple transplantations during or even before the first renal transplant. Two independent risk factors immerged: recipient's age (coef. −0.06, $P = 0.028$) and graft nephrectomy (coef. 1.68, $P = 0.006$). Interestingly enough, in this cohort ($n = 101$), rejection of the first transplant tended to be negatively correlated with multiple future transplantations (coef. −0.88), even though the evidence did not reach statistical significance ($P = 0.13$).

4. Discussion

Since the turn of the century, there have only been a few studies looking at the management of the primary allograft in the light of retransplantation. All of these studies looked at small numbers of recipients from a single center (Table 11). To date, there has been no Cochrane review of the effect of transplantectomy on future transplantations. Published studies may be split into two groups, those which found that graft nephrectomy after graft loss was associated with a negative impact on the life of the second transplanted allograft and those suggesting that there was no significant difference in the life of the second allograft among the two groups. In most studies there was an increase in PRA after allograft nephrectomy and high PRA levels were an important risk factor for Delayed Graft Function (DGF), PNF, and overall graft survival in the second kidney transplants.

In all studies, patients were split into two groups, those who had a transplantectomy prior to their second kidney transplant and those that did not. The rate of graft nephrectomy varied from 31% [11] to 80% [14]. In all cases, it was removed for indications such as perioperative complications, vascular sequelae, haematuria, graft intolerance syndrome, sepsis, graft tenderness, anaemia, adverse effects of immunosuppression, and making space for the new allograft [5, 8, 13, 15]. The indications tended to be different and classifiable into

Table 8: Kaplan-Meier analysis* of 2nd renal graft survivals in 1, 2, 5, and 10 years.

Survival probability	G1 (graft nephrectomy)	G2 (graft *in situ*)
1-year graft survival	0.73 95% CI (0.58–0.88), $P < 0.05$	0.98 95% CI (0.94–1), $P < 0.05$
2-year graft survival	0.64 95% CI (0.47–0.82), $P < 0.05$	0.94 95% CI (0.88–0.99), $P < 0.05$
5-year graft survival	0.4 95% CI (0.2–0.64), $P < 0.05$	0.54 95% CI (0.35–0.72), $P < 0.05$
10-year graft survival	0.13 95% CI (0–0.42), $P < 0.05$	0.14 95% CI (0–0.45), $P < 0.05$

*Log-rank test was not employed.

Table 9: Binary logistic regression analysis of 2nd graft loss risk factors.

Variable	Coefficient	Standard error (SE)	Odds ratio	95% Confidence interval	P
Age	0.05	0.02	1.05	0.99–1.1	0.07
Rejection	0.75	0.57	2.12	0.69–6.5	0.1884
Graft nephrectomy	−2.77	0.71	0.06	0.016–0.25	0.0001

those secondary to graft loss a year after transplant or beyond. Graft loss within the first year resulted in nephrectomy in most cases and is currently the standard of practice in various programs [15].

Lair et al. looked at the largest group to date ($n = 240$), retransplanted in Nantes, France (83 patients in G1 and 157 in G2) [12]. They found no graft survival difference in 1, 5, and 10 years. However, they did note a significant increase in PRA levels in group 2, which did not lead to any significant differences in the outcome.

Ahmad et al. looked at all the patients retransplanted between 1993 and 2005 at Guys Hospital, London [13]. There were 89 patients in total (68 in G1 and 21 in G2). They found no significant difference in graft survival at 1, 3, and 5 years. There was no significant difference between the PRA levels prior to the second transplantation. However, PRA levels did have a statistically significant influence on the outcome for all the recipients.

Hutchon looked at 166 patients retransplanted between 2000 and 2008 at University of Muenster, Germany (121 patients in G1 and 45 in G2) [8] (see Table 6). They found that G1 patients had a shorter graft life. Also PRA levels were statistically higher in G1, and PRA levels of greater than 70% were significantly associated with shorter graft life and increased incidences of DGF, PNF, and acute rejection in all recipients.

Our study included 101 subjects who were divided into two groups of evenly distributed characteristics, covering a minimum postretransplant period of 6 months and a median of 68 months. During this period, 28.7% of retransplanted patients lost their graft. The graft losses were 45% in the nephrectomy group as opposed to 13% in the controls. Kaplan-Meier analysis showed that the graft survival was significantly inferior in the nephrectomy group in the 1st, 2nd, and 5th years. Perhaps nonsurprisingly, the odds of losing the second graft were significantly higher in the nephrectomy group (5.4, $P < 0.05$). The patient's survival marginally varied among the two groups (Kaplan-Meier survival probability 0.92 versus 1 in G1 and G2, resp., $P < 0.05$); the median survival of the second transplant was also comparable. Notably, the median survival of the failing retransplants was significantly shorter in the nephrectomy group. These findings suggested that *even if prior graft nephrectomy does not affect the length of the second graft survival, it does significantly accelerate the pace of the second graft loss should the second graft's function decline.*

The recipients' age, sex, and ethnic origin as well as the HLA mismatch or the donor status (living versus deceased) did not affect the outcome among the two groups. Perhaps predictably the patients who received multiple transplants were younger than the overall population ($P = 0.028$) (see Table 7).

Contrary to Schleicher et al., our cohort failed to prove significant difference in the rates of rejection of the first grafts, even though the percentage of G1 patients who had at least one rejection episode seemed to be higher as opposed to the controls (33% versus 20%, $P = 0.26$). This finding notwithstanding, the second graft rejection rates were remarkably higher among those patients that ended up having multiple transplantations (30% versus 65%, $P = 0.0027$). The second allograft rejection rates also tended to be higher in the nephrectomy group overall.

Interestingly, the latest single-center retrospective study published by Lucarelli et al. [14] proved no significant difference in the graft survival or PRA in their cohort, even though the graft function of the second graft was inferior in the transplantectomy group in 2-year follow-up.

Our finding that the prognosis of the second graft significantly drops after graft nephrectomy comes in agreement with multiple other authors [8–10] and challenges others [14]. Patients who had their failed graft explanted tended to have more rejections on their second transplant, suggesting higher immunoreactivity among this patient population. In our cohort, 28.6% of patients lost their first graft in the immediate

Table 10: Binary logistic regression analysis of multiple (>2) renal transplantation risk factors.

Variable	Coefficient	Standard error (SE)	Odds ratio	95% confidence interval	P
Age	−0.06	0.03	0.95	0.9–0.99	0.0281
Rejection	−0.88	0.59	0.41	0.13–1.31	0.1341
Graft nephrectomy	1.68	0.61	5.35	1.6–17.78	0.0062

Table 11: Summary of previous studies.

Author	Journal	Year	Total (n)	Transplantectomy (G1)	Failed graft *in situ* (G2)	Outcome
Sumrani et al. [9]	Transplantation	1992	95	43	52	Negative impact nephrectomy
Abouljoud et al. [10]	Transplantation	1995	192			Negative impact nephrectomy
Douzdjian et al. [11]	Clinical transplantation	1996	127	40	40	No significant difference graft survival
Yagmurdur et al. [2]	Transplantation proceedings	2005	53	21	32	No significant difference graft survival
Lair et al. [12]	Kidney international	2005	240	83	157	No significant difference graft survival, ↑PRA after graft nephrectomy
Ahmad et al. [13]	NDT	2009	89	68	21	No significant difference graft survival, patient survival, acute rejection, donor type, HLA mismatch, number of transplants, hemodialysis, or nonpretransplant
Schleicher et al. [5]	Transplant international	2011	166	121	45	G1↓ graft survival, ↑PRA, ↑PNF, ↑DGF, ↑acute rejection
Lucarelli et al. [14]	World J Urol	2013	140	112	28	No significant difference in graft survival, PRA, or acute rejection. Better renal function in G2 two years after retransplantation

peritransplant period due to perfusion compromise. Apart from the cases that transplantectomy was a necessity secondary to technical failure or poor organ collection resulting in irreversible graft damage, the patients requiring early nephrectomy might be prone to thrombosis in the allograft for various reasons or be severe vasculopathies; irrespective of the cause, early graft nephrectomy is frequently mandated in early graft loss [14] and should initiate investigations of the recipient in order to exclude causes of further graft failures other than immunological ones. Given the significant percentage of patients requiring transplantectomy for non-immunological reasons, the authors suggest that it is not only the fear of immune sensitization that should be addressed in such cases but also other potential causes of future grafts' loss.

A significant limitation of this study was the fact that in many patients the PRA levels prior to retransplantation could not be retrieved at the time of this analysis nor validated; the authors thus decided that any conclusions drawn on PRA levels might be subject to significant selection bias; this parameter was thus excluded. Further limitation was, of course, its retrospective nature, spanning through various centres and transplant surgeons and long periods of time, resulting in remarkable difficulties in data accessing and validation and variable immunosuppressive maintenance and induction regimes. Followingly, the "era effect" has to be taken into account; this retrospective cohort spans through a period during which remarkable changes have taken place in the field of transplantation, leaving their imprinting in all of its aspects: recipients' characteristics, organ and donor selection criteria, introduction of the CNIs, and beyond. Another shortcoming was the lack of formalised consensus in terms of the indications for transplantectomy, for which reason further analysis of the nephrectomised patients depending on the actual indication for nephrectomy could not be performed. Finally, the incidence of graft intolerance as opposed to septic causes of severe systemic inflammatory response necessitating transplantectomy was not feasible to be assessed.

Multivariate analysis indicated that graft nephrectomy is a significant prognostic factor for the survival of people who have been retransplanted, adjusted for the patient's age and rejections of the first graft. Further multivariate analysis showed that recipient's age at the time of the first transplant as well as transplantectomy of the first graft was independent risk factor, predicting early the risk for multiple future renal transplantations (age coef. −0.06, $P = 0.028$, nephrectomy coef. 1.68, $P = 0.006$); these factors were adjusted to primary graft rejections.

This study focused on the effect of nephrectomy of a failed graft on future transplants, which is only one out of an array of possibilities after graft nephrectomy. Furthermore, the group of nephrectomised patients included those that

had their graft removed perioperatively due to vascular or other technical catastrophes. This subgroup perhaps requires further analysis, since the graft loss aetiology as well as the impact of an emergency transplantectomy in the first posttransplantation year might be different if compared to the indication and impact of a transplantectomy performed as an elective procedure or on the second year after transplantation and beyond.

This retrospective study should probably be followed by well-designed prospective studies with standardized indications for transplantectomy recording the cause of renal failure, the indication for graft nephrectomy, and analysis of the multiple potential outcomes, ranging from no transplantation to multiple transplants. As stated above, the prospective cohorts should be further divided into those transplantectomized immediately versus those transplant in later time, since the aetiology for nephrectomy seems to alter in relation to time since the first transplant. It would also be interesting to compare the graft failure causes and patients' destiny among the two groups and relate the findings to the outcomes.

A failed graft due to a perioperative catastrophe or a graft triggering life threatening sepsis or intolerance syndrome poses no question to the transplant surgeon as to the available options; it has to be removed as a life-saving procedure and the defacto impact on future transplants will have to be dealt with in later time. Furthermore, as it has already been described elsewhere [15], graft loss during the first year constitutes an established indication for transplantectomy, whether due to the risk of graft rupture due to vascular thrombosis or rejection or due to technical complications. After the first year, transplantectomy is considered if loss of graft function is accompanied by immunological intolerance syndrome, cancer, recurrent pyelonephritis, or extreme proteinuria after return to dialysis [15]. Our evidence suggests that these patients are doomed to have worse second graft survival and multiple transplantations.

These notwithstanding, another question remains: what is the appropriate management of the failed graft on an otherwise asymptomatic patient awaiting a new transplant. Guidelines might have been formulated elsewhere but are mostly based on retrospective cohorts and experts' opinion, with the evidence supporting their respective recommendations thus being weak; they should therefore be systemically reviewed and meta-analysed in order to formulate guidelines helping the transplant surgeon tackle this increasingly frequent dilemma not only when dealing with the failed graft on a sick patient, but also when faced with otherwise asymptomatic graft loss: *take out or leave in peace?*

5. Conclusion

This was a retrospective analysis of renal retransplantation after transplantectomy of a primary failed graft versus retransplantation with the failed graft *in situ*. The analysis failed to show graft survival benefit in the transplantectomy group. Early graft survival was worse in the graft nephrectomy group. Nephrectomy of a failed primary graft is an independent significant risk factor for renal retransplantations. Recipient's young age and graft nephrectomy are significant risk factors for multiple renal transplants. Rejection of the primary graft has not been shown to be a significant risk factor to future transplantations.

Systematic reviews are necessary for standardization of the management of a failed graft and for better understanding of the factors implicated in the pathophysiology of multiple renal transplants.

Conflict of Interests

The authors declared that there is no conflict of interest.

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