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ORIGINAL ARTICLE

Single graft loss in dual renal transplant recipients: impact of graft placement on recipient outcomes

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Summary

We aimed to assess the impact of graft placement in dual renal transplantation on the risk for single graft loss and to report recipient outcomes. Between 2004 and 2007, 55 dual renal transplants were performed at our institution. Allografts were placed bilaterally (one in each iliac fossa) in 42 patients and unilaterally (both in the same iliac fossa) in 14 patients. Nine recipients (16.4%) underwent explantation of a single graft as a consequence of vascular thrombosis designated as the SINGLE group, whereas 46 had two functional allografts (DUAL group). There was a higher rate of graft loss in case of unilateral placement ($n = 5/14$) compared with bilateral placement ($n = 4/41$) (35.7% vs. 9.8%, $P = 0.035$). One-year glomerular filtration rate was significantly lower in the SINGLE group (29.4 ml/min/1.73 m^2 vs. 49.4 ml/min/1.73 m^2 in the DUAL group, $P < 0.05$). Significantly, none of the nine recipients of the SINGLE group returned to dialysis with a mean follow-up of 34.1 months. Graft survival at 1 year was 100% and 97.9% in SINGLE and DUAL groups, respectively. Unilateral placement of both allografts is associated with an increased risk of single graft loss and therefore lower renal function at 1 year. However, this strategy is safe in selected indications.

Introduction

Kidney transplantation has become the standard of care in end-stage renal disease as it offers improved survival and quality of life. The disparity between organ supply and demand has led to an increase in the utilization of expanded criteria donors (ECD) to enlarge the pool of kidneys offered for transplantation [1]. However, survival of these marginal kidneys is clearly shorter than ideal allografts [2], mainly because of low nephron mass provided by such suboptimal organs. This obstacle has been overcome by performing dual renal transplantation [3,4], providing recipients with an increased number of functional nephrons.

Dual renal transplantation remains a challenging procedure because of longer length of surgery, recipient age, and associated comorbidities [5,6], and because older recipients often present with significant vascular disease, Thus, unilateral placement of both allografts may be a time-saving option, which is decided by the transplant' surgeon when technically feasible.

Our objective was to assess if unilateral graft placement was associated with an increased risk of losing one allograft. In these cases, recipients are ultimately transplanted with a single marginal kidney from ECD. Their outcome is reported.

Patients and methods

Patient enrollment took place at the Hospital Necker (Paris, France) from November 2004 to September 2007. All patients aged 65 years or more receiving a first kidney transplantation with a low Panel Reactive Antibodies (PRA) <25% were eligible to take part in the observational

study (BIGRE) coordinated by the 'Agence de la Biomédecine'. [7] This study considers a simple clinical criterion, the estimated glomerular filtration rate (GFR) calculated with the Cockcroft and Gault formula, for allocation of marginal kidneys into dual (DKT) or single (SKT) kidney transplantation. Donors aged 65 years or more were required to have at least one of the following risk factors: a history of hypertension, diabetes mellitus, atherosclerotic disease or cardiovascular disease as a cause of death. Kidneys were allocated to DKT or SKT based on maximal donor GFR calculated by the Cockcroft and Gault formula. Grafts from donors with GFR of 30–60 ml/min were allocated into DKT. Those below 30 ml/min were discarded, and those above 60 ml/min were allocated into SKT. Therefore, allocation criteria did not include histologic evaluation of allografts.

The operative technique consisted of classic iliac implantation. Allografts were placed either unilaterally or bilaterally as shown in Fig. 1; reasons for this choice were extensive calcifications on the contralateral iliac artery, or when voluminous native polycystic kidney was an obstacle for kidney implantation. However, in some cases, to avoid a contralateral incision, the transplant surgeon electively decided a unilateral implantation, when allografts size and recipients' vessels rendered this procedure technically feasible. When grafts were inserted bilaterally, urinary reconstruction consisted in pyeloureterostomy, which is the standard technique used at our institution in adult kidney transplantation. In the case of unilateral implantation, ureteroneocystostomy was performed with the ureter of the lower graft, according to Campos Freire technique (modified Lich Gregoir).

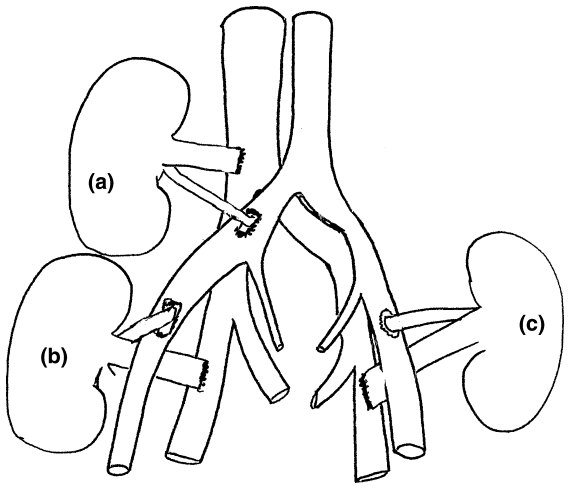

Figure 1 Schematic illustration of graft placement. Dual kidney transplantation may be performed with unilateral (a and b) or bilateral (b and c or a and c) placement of allografts.

In the postoperative period, patients who underwent single graft removal were studied as the SINGLE group, whereas recipients with two functional grafts were placed in the DUAL group.

Graft failure was defined as return to dialysis. GFR was measured at 3 months, 1 year and then yearly with iohexol clearance [8].

Systematic preimplantation biopsies were retrospectively analyzed and the Remuzzi histologic score [9] was calculated. This score (see Appendix) is based on Banff chronic histologic scores including: tubular atrophy/interstitial fibrosis (AT/FI), arteriolar hyalinosis (ah), vascular fibrous intimal thickening (cv), and glomerulosclerosis. Changes in each evaluated component of the kidney tissue (vessels, glomeruli, tubules, and connective tissue) received a score ranging from 0 (if no changes were observed) to 3 (if marked changes were present).

Categorical variables were reported as absolute numbers or percentages and were compared using 2×2 contingency tables and chi-squared tests. Student's *t*-test was used to compare continuous variables (SAS® statistics software; SAS Institute Inc., Cary, NC, USA). *P* values of 0.05 or less were considered to indicate statistical significance.

Results

Fifty-five patients received a DKT during the study, with grafts placed either unilaterally ($n = 14$) or bilaterally ($n = 41$). The mean follow-up time was 34.1 months. None of the 55 recipients was lost to follow-up. Mean age was 69.4 years in recipients and 76.5 in donors. Characteristics of donor and recipients at the time of transplantation and immunosuppressive induction regimen are reported in Table 1. Mean cold ischemia duration was 21.8 ± 5.9 h and mean operative time was 320 ± 83.3 min.

Twenty-five (45.4%) recipients required blood transfusion. Two patients underwent surgical revision for retroperitoneal hematoma and two others required endourologic procedure for ureteral stent placement because of urine leak at the site of the pyeloureterostomy.

Reasons for unilateral implantation of allografts ($n = 14$) were as follows: extensive calcifications in contralateral iliac artery ($n = 7$), voluminous native polycystic kidneys ($n = 2$), and elective choice made by surgeons ($n = 5$).

Nine recipients (16,4%) underwent single graft removal (SINGLE group) after venous thrombosis ($n = 6$), arterial thrombosis ($n = 2$), and uncontrolled bleeding in the hilum ($n = 1$). The 46 other recipients had two functional allografts (DUAL group). Single graft loss occurred within the first 20 days with a mean time of 6 ± 8 days. Five of the 14 patients with both kidneys placed in the same side experienced a single graft loss versus only four of the

41 patients grafted bilaterally (35.7% vs. 9.8%, respectively; chi square: $P = 0.035$). In three of the five cases from the SINGLE group with unilateral placement, the thrombosed kidney was implanted inferiorly (Table 2). In three patients, the reason for unilateral implantation was imposed by vascular condition or previous surgery compromising an easy surgical approach of contralateral iliac fossa (Table 2).

None of the nine recipients of the SINGLE group returned to dialysis. Both the graft and patient survival at 1 year were 100% in the SINGLE group and 97.9% in the DUAL group. One patient from the DUAL group died from pneumocystosis, with a functioning allograft. The 3-month and 1-year mean glomerular filtration rates were significantly lower in the SINGLE group compared with those in the DUAL group (49.4 ml/min vs. 29.4 ml/min at 3 months and 48.2 ml/min vs. 26.7 ml/min, at 1 year, $P < 0.005$) (Table 3) corresponding to an approximate 40% decrease in renal function.

Table 4 shows the range of GFR at 3 and 12 months and the Remuzzi score for all but two patients in the SINGLE group, retrospectively calculated from preimplantation biopsies. The disparity in GFR may be explained by the disparity of histologic lesions in the donor's preimplantation biopsies. Indeed, according to the Remuzzi score, the two kidneys with the lowest GFR at 1 year had the more severe histologic lesions (one would even have been discarded). However, there are too few patients in the single group to draw statistical conclusions about this association.

Table 1. Characteristics of donors, recipients and immunosuppressive induction protocols.

Characteristics	Dual renal transplantation procedures ($n = 55$)
Recipients	
Age (mean ± SD, years)	69.4 ± 5
Sex ratio	1.7
Time on dialysis (mean ± SD, months)	30.4 ± 29.8
Diabetes mellitus (%)	19.2
Coronary disease (%)	13.3
Donors	
Age (mean ± SD, years)	76.5 ± 5.8
Sex ratio	0.6
Hypertension (%)	53
Diabetes mellitus (%)	19.2
Cardiopulmonary arrest (%)	13.6
Collapse (%)	18.4
Number of HLA mismatches (mean ± SD)	4.1 ± 1.1
Estimated GFR* (mean ± SD)	51.1 ± 14.9
Remuzzi score (mean ± SD)	3.4 ± 1.93
Immunosuppressive regimen (%)	
Basiliximab/CsA	62
Basiliximab/FK	15.2
ATG/CsA	12.7
ATG/FK	10.1

SD, standard deviation; sex ratio, male/female; CsA, cyclosporin A; FK, tacrolimus; ATG, anti-thymocyte globulin.
*Glomerular filtration rate was estimated in donors using the Cockcroft and Gault formula.

Table 3. Measured GFR at 3 months and 1 year in DUAL and SINGLE groups.

	DUAL ($n = 46$)	SINGLE ($n = 9$)	P value
Mean GFR at 3 months (ml/min/1.73m^2 ± SD)	49.4 ± 13.7	29.4 ± 9.1	<0.005
Mean GFR at 1 year (ml/min/1.73m^2 ± SD)	48.2 ± 11.2	26.7 ± 8.9	<0.005

GFR, glomerular filtration rate; SD, standard deviation.

Table 2. Detailed information about transplant implantation and allograft loss in the SINGLE group.

No. recipient from SINGLE group	Allograft placement	Reason for unilateral placement*	Location of lost allograft†	Time of allograft loss (postoperative day)
1	UNI	Elective	INF	0
2	UNI	Elective	INF	1
3	UNI	Calcifications	INF	3
4	UNI	Calcifications	SUP	10
5	UNI	Previous surgeries	SUP	0
6	BILAT		L	20
7	BILAT		L	18
8	BILAT		L	2
9	BILAT		L	0

UNI, unilateral placement of both allografts; BILAT, bilateral placement of both allografts.
*The reason for unilateral placement was elective (surgeon's choice), or related to extended calcifications or previous surgeries in iliac fossa.
†In recipients with unilateral placement, allograft may be located superiorly (SUP) or inferiorly (INF). In recipients with bilateral placement, one allograft is located in each iliac fossa (L for left and R for right).

Discussion

Dual renal transplantation and placement of grafts

Dual renal transplantation is a challenging procedure, with both surgical and medical difficulties relating to recipients' comorbidity and suboptimal grafts from ECD [4]. Recipients of dual kidney transplants are often in poor cardio-vascular condition, because of their age as well as their causal pathology and complications resulting from hemodialysis. Thus, calcifications of iliac artery may render graft implantation difficult. To avoid thrombosis of graft artery as well as recipients' femoral artery when extensive arterial calcifications are present, unilateral implantation of both allografts, using common, external and/or internal iliac artery of the same side may be a useful option.

Other situations where this approach may be beneficial is the presence of voluminous native polycystic kidneys; indeed, our strategy in end-stage renal disease patients is not to remove these kidneys as long as they don't require dialysis, leading to the possibility of transplanting polycystic patients with both native kidneys in place [10]. In these cases, our attitude was to perform unilateral and preferably right nephrectomy, at the time of dual transplantation with allografts implanted on the same side. Performing bilateral nephrectomy and bilateral dual renal transplantation at the same time was not considered a reasonable option.

However, in a minority of cases ($n = 5/14$), the decision of unilateral implantation was electively taken by the surgeon where the contralateral iliac vessels were usable. Indeed, when allografts are of small size, and recipients iliac arteries are long enough to provide two different sites of anastomosis that may be clamped electively, unilateral implantation seems to be a good option. The possibility of avoiding another iliac incision and closure leads to a shorter procedure and decreased cold ischemia time.

However, our study clearly highlights the significant risk of graft thrombosis when unilateral implantation is performed ($P = 0.035$). The increased rate of venous thrombosis may be explained by the compression induced by the two allografts 'jammed' in the iliac fossa, creating a compartment syndrome. Moreover, to place both grafts in a limited space, one may logically speculate that anatomic conditions lead to a kind of compromise in allograft implantation and probably suboptimal positioning of both vein and artery, which is a known risk factor for early thrombosis [11]. The limited sample size of the SINGLE group does not allow us to make a statistically significant observation regarding the association with graft loss and superior versus inferior placement or the reason for unilateral implantation (Table 2).

To our knowledge, only two studies have previously reported unilateral placement of allografts in DKT [12,13]; interestingly, the authors report excellent graft survival and advocate this technique as it allows significant reduction in cold ischemia time for the second graft. One should temper these results; Veroux *et al.* [12] do not report a comparison between unilateral and bilateral placements, and therefore cannot conclude about the advantages of this technique. Moreover, patients with severe atherosclerotic aorto-iliac disease were excluded. Ekser *et al.* [13] compared bilateral and unilateral techniques, but their results are biased by the period effect as unilateral placement was performed only after 2003 (vs. 1999 for the bilateral technique). On the contrary, our study is biased by the fact that half of the unilateral procedures were performed because of poor vascular condition with extensive calcifications on the contralateral iliac artery, logically leading to an increased rate of vascular complications and graft loss.

To combine the advantages of performing one incision and still use both iliac arteries, Haider *et al.* [14] report a technique using a midline extraperitoneal approach in 11 patients; according to the authors, this procedure allows

Table 4. Remuzzi score, and GFR at 3 months and 12 months in the SINGLE group.

Dual kidney recipients from the SINGLE group (no)	Remuzzi score	Graft attribution according to Remuzzi's score	Measured GFR at 3 months (ml/min/1.73m^2)	Measured GFR at 12 months (ml/min/1.73m^2)
1	NA	NA	54	53
2	1	Single	44	45
3	3	Single	42	NA
4	NA	NA	35	26
5	3	Single	29	36
6	3	Single	28.9	31.7
7	1	Single	28	42
8	5	Dual	22	19
9	8	No	14	16

For each dual kidney recipient from the SINGLE group, allocation based on histologic parameters would have concluded to single-, dual- or no transplantation (discarded transplants).
GFR, glomerular filtration rate; NA, data not available.

creation of enough space to place both transplants, but surgical outcomes are not precisely reported.

In our opinion, dealing with surgical complications appears to be easier when allografts are located in the two iliac fossa rather than in one. Complications such as a retroperitoneal hematoma or urinary fistula involve only one of the two grafts, and may be managed without jeopardizing both organs. This advantage stays clearly empirical as the small number of adverse events renders statistical analysis invalid.

In our opinion, elective unilateral implantation provides excellent result only when allografts are small in size and recipients present with limited atherosclerotic iliac disease that allows placement of all four vascular anastomosis without kinking or creating a compartment syndrome.

Outcome of patients from the SINGLE group

The outcome of SINGLE group patients shows that renal function is significantly inferior compared with the DUAL group; GFR value is approximately 40% decreased, which fits with the loss of 50% of the nephrons from the same donor. As these patients ultimately receive a single kidney from ECD, shorter graft survival is expected [2,15], although the length of our follow-up does not allow us to reach a conclusion in this regard. However, the impaired long-term graft survival has to be balanced with shorter life expectancy in dialysis for these older recipients. Indeed, some authors demonstrated that receiving a transplant from ECD lowers the mortality in organ procurement organization with long median waiting times [16] and provides patients with a 3- to 10-year increase in life expectancy compared with patients wait-listed on dialysis [5]; to date, (with a mean follow-up of 34.1 months) no patient from the SINGLE group requires hemodialysis, although all of them display chronic renal failure despite kidney transplantation (mean GFR of 29.5 ml/min/1.73 m^2).

The clinical criterion used in this study and based on estimated donor eGFR for allocation of ECD kidneys may be criticized as none of the nine patients from the SINGLE group who lost one kidney returned to hemodialysis during the follow-up suggesting that donor's kidneys may have been transplanted into two recipients, which would have enlarged the recipient pool.

However, creatinine clearance at 1 year was significantly lower in this group than in the DUAL group patients (26.7 ± 8.9 vs. 48.2 ± 11.2, $P < 0.005$). Hariharan *et al.* [17] showed in 2002 that creatinine at 1 year is a prognosis factor for allograft survival and that poor creatinine level (>1.5 mg/l) at 1 year is associated with a markedly reduced graft half-life.

Strikingly, patients from the SINGLE group had GFR at 1 year ranging from 16 ml/min/1.73 m^2 to 53 ml/min/1.73 m^2. This wide interval might be explained by the disparity of histologic lesion in these marginal donors as shown in Table 4 with the Remuzzi score.

Remuzzi proposed a histologic score to allocate marginal kidneys and showed in a prospective cohort study that preimplantation histologic evaluation of kidneys from ECD donors resulted in a similar survival compared with recipients of nonevaluated kidneys from standard criteria donors and in a better survival compared with recipients of nonevaluated kidneys from ECD donors [4].

According to the Remuzzi score, most of the kidneys from the SINGLE group would have been attributed into SKT (score ≤3). However, eGFR of these patients is lower than that of the patients from the DUAL group. This contradiction may be explained by the fact that kidneys from more marginal donors have probably a limited capability of increasing filtration power than standard kidneys in case of loss of one kidney.

Moreover, in the study by Remuzzi *et al.*, primary endpoint was graft survival and almost all histologically evaluated kidneys were assigned to DKT. Therefore, there was no direct comparison of renal function of DKT and SKT allocated with this criteria.

Thus, histologic criterion alone may not be sufficient for the allocation of marginal kidneys. Anglicheau *et al.* [18] showed that among 313 donors, aged above 50 years, the most predictable score for creatinine clearance at 1 year was a composite score including clinical and histologic parameters: donor serum creatinine, donor hypertension and percentage of glomerulosclerosis.

Furthermore, from a practical point of view, histologic evaluation prior to transplantation may not be possible in every center. In our center, renal pathologists are not available during night time and weekends. Waiting for the histologic result would increase the cold ischemia time, which has been associated with poorer graft survival especially in marginal kidneys. As our findings highlight the beneficial input of histologic evaluation, continuous effort should be made to achieve the availability of pathology services at all times. For instance, assigning a reference pathologist on duty for each geographic area would allow every center to ship graft biopsies at the time of organ procurements without detrimental delay.

Conclusion

In our study, unilateral placement of both allografts is associated with an increased risk of single graft loss. However, unilateral placement was mainly performed for imperative indications such as extensive calcifications of contralateral iliac artery. In the absence of optimal conditions to use this strategy (small allografts, limited atherosclerotic disease in the recipient), surgeons should

exercise caution when preferring this approach because of the associated higher risk of graft loss. After single graft loss, renal function at 3 months and 1 year was significantly inferior compared with the DUAL group, but none of the nine recipients returned to dialysis with a mean follow-up of 34.1 months.

Authorship

M-OT: designed study, performed study, and wrote the paper. MR: performed study, collected data, and analyzed data. RS: designed study, collected data, and analyzed data. DC: collected data and analyzed data. AS: collected data. SM: analyzed data and revised manuscript. YR: collected data and analyzed data. HK: collected data. CL: collected data and performed study. AM: designed study, performed study, and analyzed data.

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Appendix: Remuzzi score

This score is based on Banff chronic histological scores including: tubular atrophy /interstitial fibrosis (AT/FI), arteriolar hyalinosis (ah), vascular fibrous intimal thickening (cv) and glomerulosclerosis. Changes in each evaluated component of the kidney tissue (vessels, glomeruli, tubules, and connective tissue) receive a score ranging from 0 (if no changes were observed) to 3 (if marked changes were present).

The vascular score was 3 when the vessel-wall thickness exceeded the luminal diameter or the lumen was occluded; the glomerular score was 3 when more than 50% of the glomeruli were globally sclerotic. The tubular score was 3 when more than 50% of tubules were atrophic, and the connective-tissue score was 3 when more than 50% of the renal parenchyma was replaced by connective tissue.

The sum of these scores was defined as the global kidney score, which could range from 0 to 12. Kidneys with a global score ranging from 0 to 3 were considered for use as single transplants and those with a score from 4 to 6 for use as dual transplants; those with a score of 7 or greater were discarded, since it was assumed that they would deliver an insufficient dose of nephrons, even in a dual transplantation.

Glomerulosclerosis (GS) 0–3	
0: no GS 2: 20–50%	
1: <20% 3: >50%	
Tubular atrophy (TA) 0–3	
0: no TA 2: 20–50%	
1: <20% 3: >50%	0–3: Single kidney transplantation
Interstitial fibrosis (IF) 0–3	
0: no IF 2: 20–50%	4–6: Dual kidney transplantation
1: <20% 3: >50%	
Vascular score 0–3	
0: no lesion	7–12: Discarded
1: vessel-wall thickness < 50% of luminal diameter	
2: vessel-wall thickness = 50%	
3: vessel-wall thickness > 50%	