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(1) title of the article:

Pediatric live kidney transplantation is safe and available for the patients with urological anomalies compared with as well as those with primary renal diseases

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(4) running head

Transplantation for urological anomaly

Abstract

The aim of the current study was to evaluate long-term outcomes of pediatric live kidney transplantation in patients with genitourinary anomalies relative to those with primary kidney diseases. The study included thirty-five pediatric patients who received a live kidney transplantation during the last 25 years (male: 28, female: 6). Median age at the time of transplantation was nine years (1-15 year range), and the median follow-up period was 151 months (6-239 month range). The patients were divided into two groups. The urological group (n=14) included patients with primary obstructive/reflux nephropathy. The renal group (n=20) included patients with primary renal disorders. Differences between groups in graft survival, clinical course and final graft function were evaluated. Original diseases represented in the urological group included seven cases with primary vesicoureteral reflux (VUR) and eight cases with secondary VUR. Diseases in the renal group included eight cases with bilateral hypo-dysplastic kidney, three cases with focal/segmental glomerular sclerosis, two cases with membraneous proliferative glomerulonephritis, two cases with congenital nephrotic syndrome and five cases with other forms of chronic nephritis. Ten of 14 cases in the urological group, relative to six of 20 in the renal group, were pre-emptive. Median age at transplantation was 7.5 or 10 years old, respectively, in the urological or renal group. Twelve kidney recipients in the urological group had also undergone other urinary surgeries, including upper urinary tract drainage, ureteroneocystostomy, augmentation cystoplasty, endoscopic incision of posterior-urethral valve, urethroplasty et al. Cumulative postoperative complications occurred in nine or sixteen, respectively, in the urological or renal group. The acute rejection free and overall graft survival were similar in both groups. One patient in the urological group lost his graft while six patients in the renal group lost their grafts. Thus, the post-transplant clinical outcome of pediatric transplantation in patients with urological anomalies is comparable to that of recipients with

primary renal disease. Appropriate urinary tract reconstruction and management is essential to reduce the risk of graft dysfunction due to urinary problems.

Key words

graft survival, kidney transplantation, pediatric, urological anomaly, outcome

Introduction

Congenital urological anomalies often involve primary vesico-ureteral reflux (VUR), secondary VUR due to lower urinary tract obstruction or neurogenic voiding dysfunction (NVD), ureteral obstructive disease, or cloacal anomalies. Pre-existing voiding dysfunctions in pediatric patients with congenital urological anomalies should be identified and resolved to avoid postoperative obstructive renal allograft dysfunction following kidney transplantation. The aim of pre-transplant urinary tract management is to achieve low-pressure urine storage with adequate bladder emptying involving clean intermittent catheterization. If proper control of the lower urinary tract is achieved, renal allograft and patient survival are equally expected (1, 2). In this study, we compared long-term graft and patient survival rates between patients with genitourinary anomalies and those with primary kidney diseases.

Patients and Methods

Between January, 1980 and December, 2006, thirty-four patients (28 male and six female) under or equal the age of 15 years underwent kidney transplantation at our institute. These pediatric recipients, who accounted for 20% of the 173 kidney recipients during this period, had a median age of nine (1-15) years old. The median follow-up period for these cases was 151 (6-239) months.

Based on the origin of their original renal disease, patients in this study were classified into the urological group (n=14) or the renal group (n=20). Details of the original diseases of these groups are described in Table 1. Except for gender and pretransplant dialysis, there were no significant differences in age, protocol of immunosuppression, or postoperative period between the groups (Table 2). Whereas four patients in the urological group (28.6%) had undergone dialysis preoperatively, 14 patients in the renal group (70.0%) had a history of dialysis. Pre-transplant

surgery for the urinary tract, native nephrectomy and graft outcomes (acute rejection episodes, allograft survival, postoperative complications) were evaluated retrospectively.

Contingency table analyses (chi-square test, Fisher's exact probability) and the Mann-Whitney U-test were used to statistically compare group backgrounds. A Kaplan-Meier (Log-rank) test was used to compare allograft survival rates. This clinical study is in accordance with the Helsinki Declaration in 1975.

Results

PREOPERATIVE SURGERIES (Urological group, Table 3)

There were three patients with high grade primary VUR and pyelonephritis who underwent anti-reflux surgery before the transplantation. One of the three patients, a 14-yr old boy, also underwent a transit nephrostomy for treatment of persistent hydronephrosis after anti-reflux surgery. Another two cases (ages 9 mo, 11 mo) first presented at our clinic with asymptomatic massive VUR and small kidney. All had been maintained by peritoneal dialysis prior to kidney transplantation, and showed no history of febrile urinary tract infections. Because their renal function was so poor, there was not enough time for renal replacement therapy; however since there was no possibility of secondary VUR due to lower urinary tract disorders, they underwent kidney transplantation without any anti-reflux treatment.

Four patients with a history of lower urinary tract obstructions (three with posterior-urethral valve, one with anterior urethral diverticulum) underwent preoperative transurethral incision. Another two patients with posterior urethral valves required upper urinary tract drainage (ureterocutaneostomy and nephrostomy) before kidney transplantation. Augmentation cystoplasty was necessary in one patient with severe non-compliant bladder due to an untreated posterior urethral valve.

Two patients with secondary VURs due to NVDs underwent multiple urinary tract

surgeries: A nine-year-old boy with atresia ani treated by pull-through anoplasty had undergone cystostomy and urethroplasty. A 15-year-old boy with meningomyelocele received augmentation cystoplasty and a urethral sling for non-compliant bladder and urethral sphinctor discoordination, respectively.

A four-year-old boy with dysplastic hydronephrosis had undergone pyeloplasty on his left kidney. Another four-year-old boy with Prune-belly syndrome had undergone periniostomy and ureterocutaneostomy for preoperative dilation of the upper urinary tract and megalourethra. Finally, another ten-year-old boy with VATER (Vertebral defects, Anal atresia, TracheoEsophageal fistula with esophageal atresia and Radial dysplasia) association underwent urethroplasty before the transplantation. There was no history of urinary tract surgeries for patients in the renal group.

NATIVE NEPHRECTOMIES (Table 4)

Native nephrectomy before or at the time of transplantation was performed in both groups. Within the urological group, two native nephrectomies for left-side hydronephrosis had been performed before transplantation to prevent post-transplant infection. A two-year-old boy with congenital nephrotic syndrome (CNS) underwent left native nephrectomy before the transplantation to control severe urinary protein leakage.

In order to secure allograft space, right native nephrectomies (ten cases in the urological group, five in the renal group) were performed simultaneously with the transplantation. This procedure also protected two FSGS patients and two CNS patients against significant urinary protein leakage. In one case, a right multicystic dysplastic kidney (MCDK) was removed because of the pathological diagnosis. A patient with Prune-belly syndrome underwent simultaneous right native nephrectomy because of residual urethral utilization for Mitrofanoff procedure. One CNS patient underwent only the right native nephrectomy at transplantation because the left native kidney had been contracted due to arterial thrombosis.

OUTCOMES OF TRANSPLANTATION

Thirteen of fourteen (92.9%) allografts in urological group patients, and 14 of 20 (70.0%) allografts in renal group patients, have survived (median follow-up period 151 months, range 6-239 months). Three urological group cases and six renal group cases were treated for post-transplant viral infection.

Acute cellular rejection, which occurred in two cases from each group, responded well to treatment (steroid pulse therapy and/or deoxyspergualin). Allograft losses in renal group cases were due to recurrent FSGS, acute anti-ABO blood-type antibody-mediated rejection, post-transplant lymphoproliferative disorder, thrombotic microangiopathy (TMA) or chronic rejections. The only case of allograft loss in the urological group was due to chronic rejection at 12 years and 8 months after the transplantation (Table 5).

Other severe post-transplant complications, including one case of new onset diabetes after the transplantation (NODAT) and one case of drug non-compliance, occurred in the renal group. Graft ureter stenosis, cataracta and TMA occurred in three post-transplant patients in the urological group (Table 6). In addition, three cases in the urological group and seven cases in the renal group showed significant growth retardation (under 2 standard deviations of mean height of healthy Japanese children control).

There was no significant difference between the two groups in frequency of acute rejection-free survival (Figure 1) or in overall allograft survival (Figure 2). In addition, overall allograft survival of pre-emptive cases (n=15) was superior to the survival of dialysis cases before transplantation (n=20) using a Log-rank test (p=0.03) (Figure 3).

Discussion

The two major problems evaluated from pre-transplant cases in the renal group were the

recurrence of original disease and the risk of urinary protein leakage due to CNS. In one case with recurrent FSGS, the patient lost renal graft function 10.7 years after transplantation and required pre-emptive retransplantation. Although there were five cases in which the original disease had a high-risk of recurrence (FSGS and membraneous progressive glomerulonephritis), no prophylactic pre-transplant strategies to combat recurrence were evident. Although native nephrectomy may prevent the recurrence of these original diseases, we generally refrain from the procedure except in cases with severe protein loss. Other cases in the renal group without FSGS demonstrated good allograft function.

Pre-transplant surgery and treatment were essential for patients in the urinary group. Multiple surgeries were necessary to maintain kidney function and to prevent urinary tract infection, which can lead to secondary allograft dysfunction due to deterioration of the drainage system or collection of urine. In the urinary group, three cases with primary VUR underwent anti-reflux surgery to prevent urinary tract infection of the native kidneys. On the other hand, the two cases (ages 9 months, 11 months old) with primary VUR that were referred to our clinic without history of pyelonephritis had undergone no anti-reflux surgery and did not develop urinary tract infection.

While all patients in the urological group achieved long-term stable allograft function successfully, the six secondary VUR patients had needed lower urinary tract management before transplantation. Two patients with NVD required augmentation cystoplasty six months before transplantation. Urinary tract obstructions in two patients with obstructive nephropathy (Prune-belly syndrome and pyeloureteral junction stenosis) had been resolved before transplantation: In one of these cases, lower urinary tract drainage was secured by conducting clean intermittent catheterization through Mitrofanoff tract before transplantation. In order to maintain urinary continence for a long enough period to allow stable renal allograft function, the patient is scheduled for reconstruction of the lower urinary tract in the near future. One case with VATER association had been treated for atresia ani and hypospadias before transplantation.

While the etiology of renal failure for this disease has been reported as renal hypoplasia, the cause of renal dysfunction is actually related to atresia ani-related NVD and congenital urinary tract obstruction. Thus, we classified this patient into the urological group (3,4).

In previous reports, long-term renal allograft function in patients with urological anomalies was shown to be poor (5, 6). More recently however, kidney transplantation in patients with abnormal urinary tracts has been reported to be safe and effective (even in a case with spina bifida) if proper pre- and post-operative management of bladder emptying, including urodynamic assessment, is performed (7,8). We also have performed kidney transplantation in a patient with meningomyelocele. Long-term results of kidney transplantations in patients with urinary tract abnormalities who were treated with incontinent urinary diversion have been reported to be poor (9,10). Overall, we suggest that patients with urological anomalies are viable candidates for kidney transplantation and should not be deprived of its benefits.

There was statistically significant difference between the frequencies of preemptive transplantation in the urological and renal groups (71.4% and 30.0%, respectively, $p=0.02$). Since most cases in the urological group had been followed up for long term period pretransplantly in our urology clinic, it is likely that they were well informed and prepared preemptively for kidney transplantation. In contrast, a large number of renal group patients had sought renal replacement therapy with renal care units outside of our department. Because of these differences in clinical background, preemptive transplantation cases may have been more likely to originate from the urological group rather than the renal group. Since preemptive kidney transplantation can avoid unexpected complications due to dialysis (11), such differences in background may account for differences in graft survival between the members of the two groups, with or without dialysis, before transplantation.

Summary

Among the twelve cases (85.7%) in the urological group who underwent kidney or urinary tract surgery before transplantation, no one experienced severe urological complications after transplantation. Surviving allografts counted 13 grafts in 14 urological group patients (92.9%) and 14 grafts in 20 renal group patients (70.0%). There were no differences in overall or acute rejection-free survival between the two groups. Overall survival of recipients without past dialysis (n=15) was superior to the survival of recipients who underwent transplantation after dialysis (n=19).

Conclusion

The post-transplant clinical outcome of pediatric transplantation in patients with urological anomalies is comparative to patients with primary renal disease. Appropriate and consistent urological strategies are indispensable for reducing the risk of graft dysfunction due to urological problems during follow-up. A preemptive setting may also be preferable in pediatric cases of kidney transplantation.

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Figure legends page

Figure 1.

There was no significant difference in the rate of acute rejection-free survival between the two groups. Sixty to seventy percent of patients were free from acute rejection up to four years after transplantation.

Figure 2.

There was no significant difference in overall allograft survival between the two groups. Ten-year allograft survival rates were 78% and 100% (Kaplan-Meier method) in the renal and urological groups, respectively.

Figure 3.

Overall allograft survival in pre-emptive cases (n=15) is superior to the survival rate of patients receiving dialysis before transplantation (n=19) (p=0.03 by Log-rank test).

Table 1. Original Diseases

Urological Group (n=14)	Primary vesico-ureteral reflux	5
	Lower urinary tract obstruction	4
	Neurogenic vesical dysfunction	2
	Dysplastic hydronephrosis	1
	Prune-belly syndrome	1
	VATER association	1
Renal Group (n=20)	Hypoplastic kidney	8
	Nephritis	5
	Focal segmental glomeruloscrelosis	3
	Congenital nephrotic syndrome	2
	Branchio-oto-renal syndrome	1
	Idiopathic captotarsal osteolysis	1

VATER: Vertebral defects, Anal atresia, TracheoEsophageal fistula with esophageal atresia and Radial dysplasia

Table 2. Patient Backgrounds

	Urological Group (*n*=14)	Renal Group (*n*=20)	
Male / Female	14 / 0	14 / 6	*
Average age at transplantation (yr.)	7 (2-15)	9 (1-15)	
Dialysis before Transplantation	4 (28.6%)	14 (70.0%)	**
Average length of dialysis (mos.)	20 (8-58)	20 (2-82)	
Tacrolimus	10	13	
Cyclosporine	4	6	
Mycophenolate mofetil	9 (64.3%)	7 (35.0%)	
Basiliximab	8 (57.1%)	4 (20.0%)	
Steroid withdrawal	5	3	
Postoperative period (mos.)	38 (18-239)	96 (6-308)	

** p = 0.02
* p = 0.03

Table 3. Preoperative Surgeries in Urological Cases (n=14)

		UNC	PNS	UC	ACP	CS	TUI	Sling	UP
Primary VUR (5)		○	○						
		○							
		○							
Lower urinary tract obstruction (4)									
Posterior urethral valve				○	○		○		
							○		
			○	○			○		
Anterior urethral diverticulum							○		
Neurogenic vesical dysfunction (2)									
Atresia ani						○			○
Meningomyelocele					○			○	
Dysplastic hydronephrosis	Pyeloplasty								
Prune-belly syndrome	Perineal urethrotomy			○					
VATER association	Perineal urethrotomy								○

UNC: ureteroneocystostomy, PNS: nephrostomy, UC: ureterocutaneostomy, ACP: augmentation cystoplasty, CS: cystostomy, TUI: transurethral incision, Sling: urethral sling, UP: urethroplasty

VATER: Vertebral defects, Anal atresia, TracheoEsophageal fistula with esophageal atresia and Radial dysplasia

Table 4. Resection of Native Kidneys before/at Transplantation

	Urological Group (*n*=14)	Renal group (*n*=20)
Before transplantation	Left (2) hydronephrosis	Left (1) CNS
At transplantation		
for graft space	Right (10)	Right (5)
for protection from protein leakage		Bilateral (2) FSGS Right (2) CNS
for other reasons	Right (2) MCDK, ureteral utilization	

CNS: congenital nephrotic syndrome
FSGS: focal segmental glomerulosclerosis
MCDK: multicystic dysplastic kidney

Table 5. Cause of Graft Loss

	Urological group (*n*=14)	Renal group (*n*=20)
Chronic rejection	1	2
AMR	0	1
Recurrent FSGS	0	1
TMA	0	1
PTLD	0	1
Total	1	6

AMR: antigen-mediated rejection
FSGS: focal/segmental glomerulo-nephritis
TMA: thrombotic microangiopathy
PTLD: post-transplant lymphoproliferative disorder

Table 6. Postoperative Complications

	Urological group (n=14)	Renal group (n=20)
Surgery related	3	1
Nephritis	0	3
Bacterial infection	2	1
CMV infection	3	4
VZV infection	0	2
TMA	1	1
NODAT	0	2
PTLD	0	1
Non-compliance	0	1
Total	9	16

TMA: thrombotic microangiopathy
NODAT: new onset diabetes after transplantation
PTLD: post-transplant lymphoproliferative disease

Figure 1. Acute Rejection-free Survival

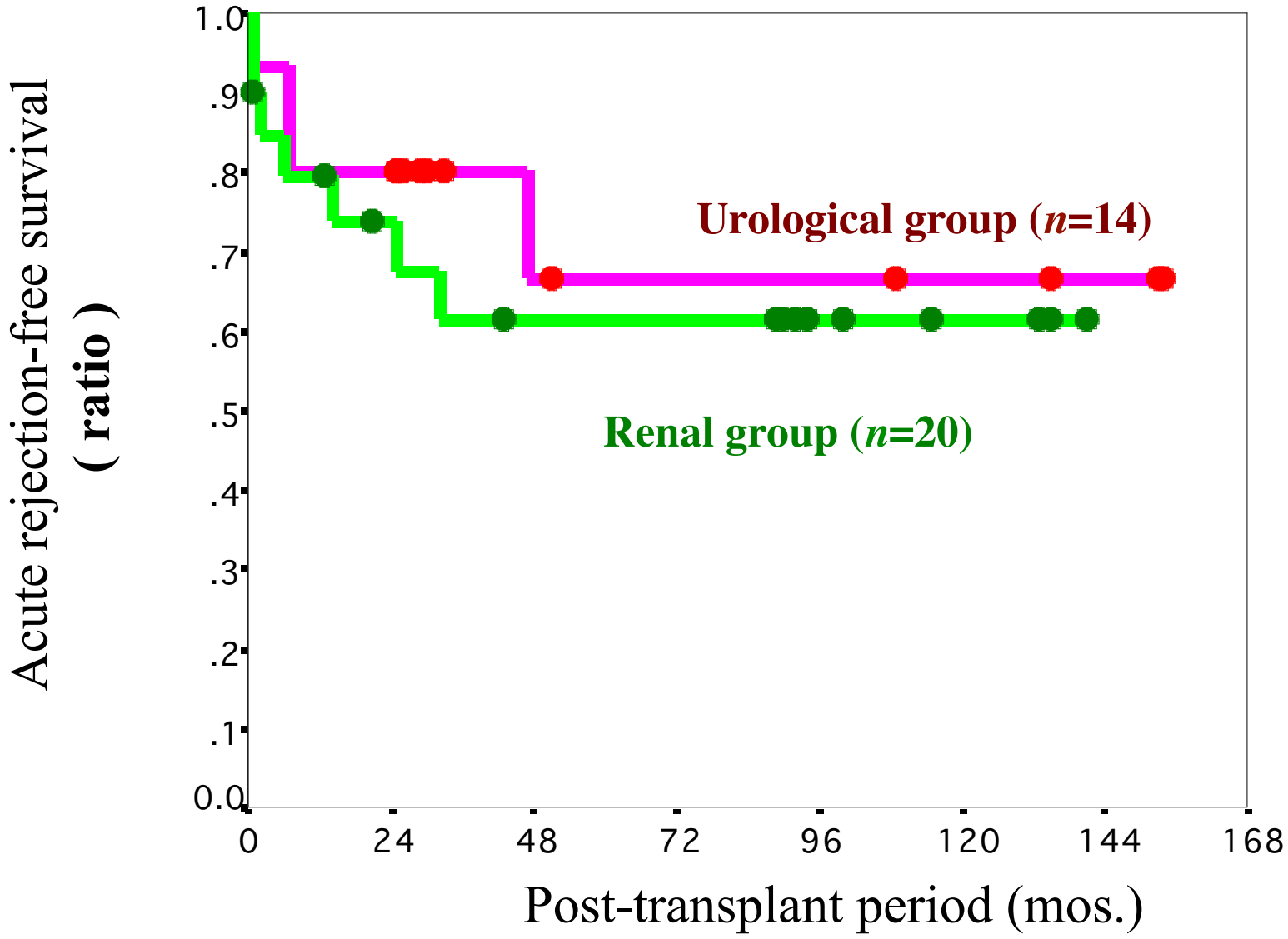


Figure 2. Overall Allograft Survival (Kaplan-Meier method)

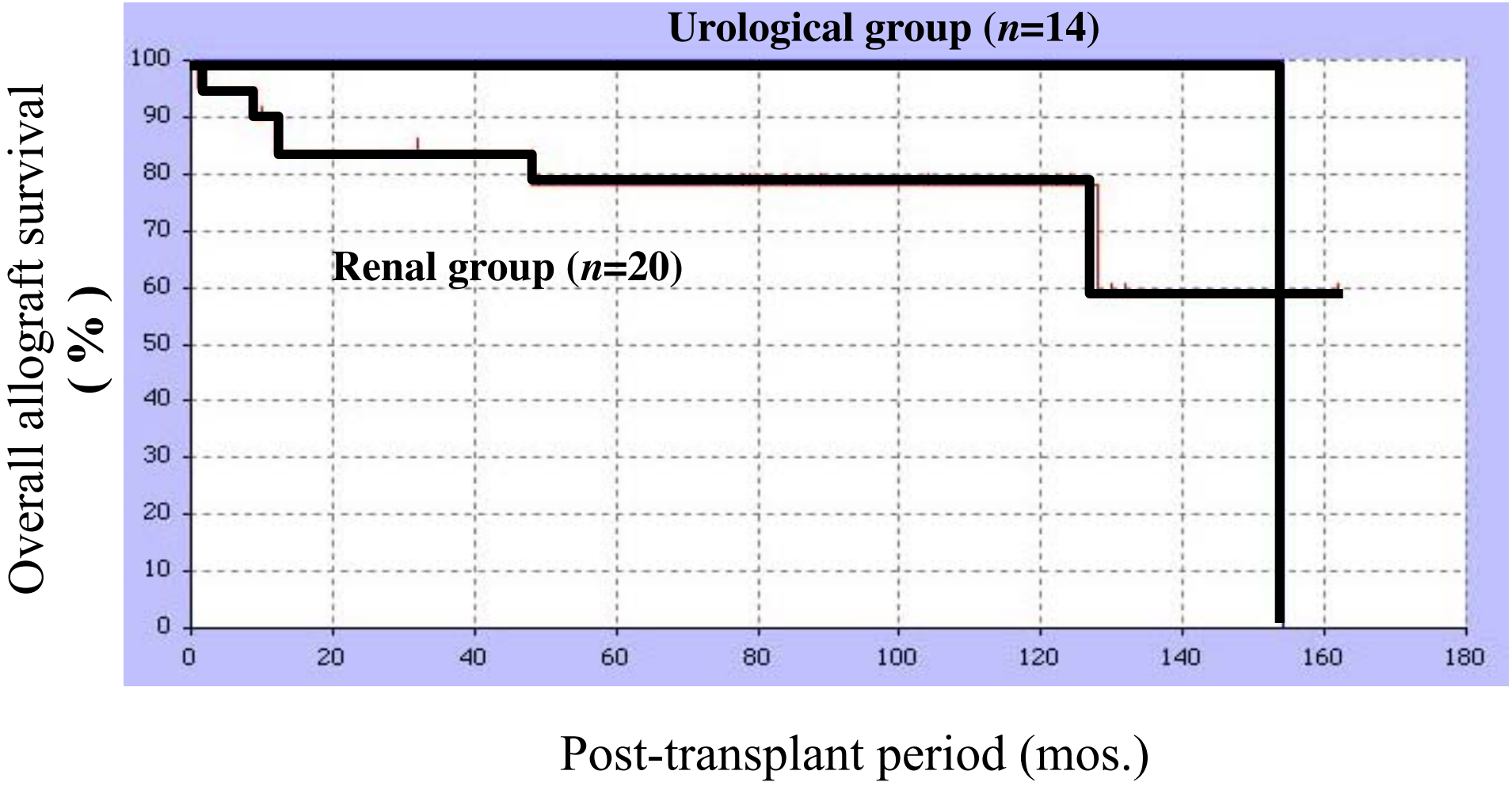


Figure 3. Allograft Survival (Kaplan-Meier method)

