Transplant International

Transplant International ISSN 0934-0874

ORIGINAL ARTICLE

Single-center experience with third and fourth kidney transplants

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Keywords
fourth transplant, kidney retransplantation, kidney transplantation, third transplant.

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Conflicts of Interest
Declares no conflict of interest.

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Received: 9 February 2011
Revision requested: 9 March 2011
Accepted: 16 April 2011
Published online: 16 May 2011

doi:10.1111/j.1432-2277.2011.01269.x

Summary

Kidney retransplantation is often associated with a higher immunological risk than is primary renal transplantation. Faced with increasing organ shortage and growing waiting lists, results of kidney retransplantation are of particular interest. Fifty-six third and fourth kidney transplants were analyzed retrospectively. Parameters included patient and donor demographics, operative details, incidence of surgical, immunological and infectious complications and patient and graft survival. Patients receiving third kidney grafts had 1- and 5-year patient/graft survival rates of 97.4%/72.9% and 88.9%/53.6%, respectively. Episodes of acute rejection and delayed graft function were observed in 44% and 49% of these patients. Fourth kidney transplantation was associated with 1- and 2-year patient/graft survival rates of 84.8%/68.5% and 63.6%/47%, respectively. Acute rejection and delayed graft function occurred in 33% and in 60% of cases. Acceptable patient and graft survival may be achieved after third and fourth kidney transplantation. Graft losses in this sensitized population are mainly because of rejection. Profound immunosuppression may lead to major infectious problems.

Introduction

Kidney transplantation is the treatment of choice for end-stage renal disease. Although impressive improvements in renal graft survival have been achieved over the past decades, graft loss because of chronic rejection still constitutes a major problem. Real half-life of primary deceased donor kidney grafts has been estimated at 8 years [1].

A significant survival benefit of kidney transplant recipients over patients on long-term dialysis or compared with those who are awaiting transplantation has been well documented [2]. Even retransplantation of the kidney may decrease long-term mortality of patients with end-stage renal disease [3–5]. Analogously, subsequent retransplantation, i.e. third or fourth transplantation, is thought to exert a survival benefit that is similar to – albeit lower than – that of dialysis. Thus, increasing numbers of patients are considered for a third or fourth kidney transplant. Nevertheless, the expected survival benefit has to be balanced against an increased risk for infectious complications and malignancies because of long-term immunosuppression that is necessarily more powerful in multiple transplant recipients because of the sensitization acquired through previous transplants. However, data on patient and graft survival after third and fourth kidney transplantation are scarce [6–17].

As of December 2010, 360 patients were listed for kidney transplantation at our center with 95/360 (26.4%) awaiting retransplantation. While the majority (71/360, 19.7%) need a second allograft, 16 (4.4%) are listed for a third kidney transplant, six patients for a fourth transplant, and two for their fifth transplantation. The growing

number of kidney retransplants in often presensitized patients significantly contributes to the lengthening of waiting lists. In this context, a profound knowledge of prognosis as well as various risks may help in carefully utilizing deceased donor kidneys.

Here, we report on the outcome of 56 third and fourth kidney transplants performed at our center since 1997. Analysis particularly focused on patient and graft survival as well as on immunological, surgical and infectious complications.

Patients and methods

Patient cohort

All renal third and fourth transplantations performed at our center between January 1997 and July 2008 were retrospectively analyzed and grouped according to third or fourth transplant.

The study population consisted of 41 third and 15 fourth kidney transplantations. Four patients received both a third and consecutively a fourth renal allograft. These four patients were included in survival statistics for patient and graft survival in both groups. Three patients received a combined liver–kidney transplant (one third-kidney and liver, one third-kidney and liver-retransplant, one fourth-kidney and liver).

Data on transplantation and hospital stay as well as follow-up data were collected from hospital records. The parameters analyzed included patient and donor demographics, cause of end-stage renal disease, cardiovascular risk profile, type of donor [deceased or living, expanded criteria donors (ECD)], HLA mismatches, CMV mismatch, degree of sensitization [level of panel-reactive antibodies (PRA) – peak PRA and preoperative PRA], cold ischemia time, anastomosis time and immunosuppressive therapy. Graft and patient survival were calculated at 1, 2, 3 and 5 years, and the frequency and type of acute allograft rejection, rate of delayed graft function, as well as incidence of severe surgical and infectious complications and severe drug-related toxicity were analyzed. Delayed graft function was defined as the need for postoperative dialysis. PRA-level was measured by complement-dependent cytotoxicity (CDC). Our local institutional review board issued a waiver under a minimal risk protocol.

Immunosuppression

Immunosuppressive therapy was to a large extent patient-tailored and therefore heterogeneous (Table 1). Before 2001, immunosuppression was mainly based on a triple-drug regimen (calcineurin inhibitor, MMF/Aza, steroids) ± induction with IL2-R-antagonists or antithymocyte globulin (ATG). Since then, prophylactic immunosuppression has consisted of alemtuzumab induction (±additional rituximab), tacrolimus and steroids ± MMF. Induction protocol comprised plasmapheresis in five cases: Three patients had peak PRA-levels of 100%, 82%, and 68%. One patient had a repeated HLA mismatch and one patient underwent plasmapheresis because of positive pretransplant cross-match (peak PRA 26%) testing positive for donor-specific antibody (HLA A24). Because of repeated positive cross-matches and peak PRA of 100% one patient was preconditioned by immunoadsorption while being on the waiting list. Antibody levels could be reduced effectively resulting in negative pretransplant cross-match with a deceased donor. Acute graft rejection was treated with 3×500 mg methylprednisone and in case of antibody-mediated rejection with plasmapheresis ± additional ATG or rituximab.

Table 1. Immunosuppressive protocols.

Third transplant	*n*
CNI + MMF/Aza + steroid	12
ATG + CNI + MMF + steroid	6
IL2-RA + CNI + MMF + steroid	7
+ plasmapheresis	2
Alemtuzumab + FK506 + steroid	7
+ rituximab	2
+ rituximab + plasmapheresis	1
+ plasmapheresis	1
Alemtuzumab + FK506 + MMF + steroid	2
+ immunoadsorption	1
Fourth transplant	
ATG + CNI + MMF + steroid	5
IL2-RA + CNI + MMF + steroid	2
Alemtuzumab + FK506 + steroid	1
+ rituximab	1
+ rapamycin	1
Alemtuzumab + FK506 + MMF + steroid	1
+ rituximab	2
+ rituximab + plasmapheresis	1
FK506 + rapamycin + steroid	1

Statistical analysis

For descriptive statistical analysis, mean values, standard deviations, absolute and relative frequencies were calculated. Patient and graft survival was evaluated according to Kaplan–Meier survival statistics. Statistical analysis was performed with the SPSS statistical package (SPSS 11.0 for windows, Chicago, IL, USA).

Results

Cohort

The collective included 41 third and 15 fourth kidney transplants. Baseline characteristics of donors and

Table 2. Demographic data and baseline characteristics of renal third and fourth graft recipients.

Characteristic	Third transplant (n = 41) n (%)	Fourth transplant (n = 15) n (%)
Recipient age (year)	43.9 ± 10.9	42.9 ± 7.7
Recipient gender		
Male	22 (53.7)	4 (26.7)
Female	19 (46.3)	11 (73.3)
Cause of endstage renal disease		
Glomerulonephritis	17	4
Pyelonephritis or reflux nephropathy	8	5
Diabetes mellitus	2	1
Hypertension or renovascular disease	2	1
Congenital/hereditary*	7	2
Autoimmune†	4	1
Unknown	1	1
Type of donor		
Deceased	39 (95.1)	12 (80)
Expanded criteria donor	12 (30.7)	1 (7.7)
Donation after cardiac death	0 (0)	0 (0)
Living	2 (4.9)	3 (20)
Donor age (year)	45.9 ± 14.3	44.5 ± 12.1
Antigen mismatches HLA-A, B, DR (no.)	2.3 ± 1.5	2.9 ± 2.0
PRA-level		
Peak PRA-level (%)	51 ± 32	69 ± 29
Preoperative PRA-level (%)	20 ± 23	27 ± 31
CMV mismatch D+/R–	7/40 (17.5)	0/15 (0)
Cold ischemia time (hour)‡	17.1 ± 5.9	15.8 ± 6.9
Warm ischemia time (min)	29 ± 8	37 ± 14

Values are expressed as mean ± standard deviation or absolute numbers and percentages.
*Included polycystic kidney disease, nephronophthisis, Alport's disease, Morbus Bourneville-Pringle, congenital renal abnormalities, deficiency of adenosine-phosphoribosyl-transferase.
†Included Goodpasture syndrome, Wegener's granulomatosis, IgA nephropathy, systemic lupus erythematodes.
‡Cold ischemia time from living donor transplants included.

recipients are shown in Table 2. Mean recipient age was similar in both groups. The predominant causes of end-stage renal disease in both groups were glomerulonephritis, pyelonephritis and autoimmune renal disease (Wegener's granulomatosis, Goodpasture syndrome, Alport syndrome, and systemic lupus erythematodes). The majority of patients received kidneys from cadaveric donors (95.1% in third and 80% in fourth transplants), with 30.7% and 7.7% of donors having expanded criteria in third and fourth transplants, respectively. Mean donor age was 45.9 ± 14.3 and 44.5 ± 12.1 years. Mean peak PRA-level in third graft recipients was 51 ± 31%, with 31/41 patients displaying a PRA-level >20%; mean PRA-level at the time of transplantation was 20 ± 23% in this cohort. In fourth renal allograft recipients mean peak PRA-level was 69 ± 29%, with 14/15 patients showing >20% PRA; mean PRA-level at transplantation was 27 ± 31%. The incidence of coronary risk factors as well as the presence or absence of a history of myocardial infarction pretransplant is depicted in Table 3.

Table 3. Cardiovascular risk profile of third and fourth graft recipients.*

Risk factor	Third transplant (n = 41)	Fourth transplant (n = 15)
Hypertension (%)	35 (85)	12 (80)
Smoking (%)	5 (12)	0
IDDM (%)	2 (5)	2 (13)
Age > 50 years (%)	12 (29)	5 (33)
BMI > 30 kg/m^2 (%)	2 (5)	0
History of myocardial infarction (%)	1 (2)	0
Angina pectoris (%)	2 (5)	1 (7)

*Hyperlipidemia was not documented in all cases and therefore was not included in the analysis.

Transplant outcome was evaluated on the basis of patient and graft survival as well as the frequency of delayed graft function and acute rejection (Fig. 1, Table 4).

Third renal transplantation

Patient survival after 1 and 5 years was 97.4% and 88.9%, respectively. One-year and 5-year graft survival was 72.9% and 53.6%, respectively. Delayed graft function was noted in 20/41 patients. A total of 22 rejection episodes were observed in 44% of patients; 64% of rejection episodes were antibody-mediated, while 36% were classified as T-cell-mediated rejection (Banff grade I–II). Ultimately, six patients lost their kidney graft because of rejection within 6 months post-transplantation. Six patients died during the entire observation period: Two patients died from cardiovascular events (myocardial ischemia 6 years following transplantation with previous graft loss, n = 1; aortic dissection 4 years post-transplant, n = 1). Two patients died of multiorgan failure, one after a very complicated postoperative course on day 102 (n = 1) and one 7 years following transplantation after earlier graft loss (n = 1). One patient died of a hepatic tumor 8 years post-transplant after previous graft loss, and one patient died for unknown reason with a functioning graft 4.9 years following transplantation. The two patients in this group receiving a combined liver–kidney transplant are both alive with two functioning grafts without any rejection of their renal allograft in the post-transplant course.

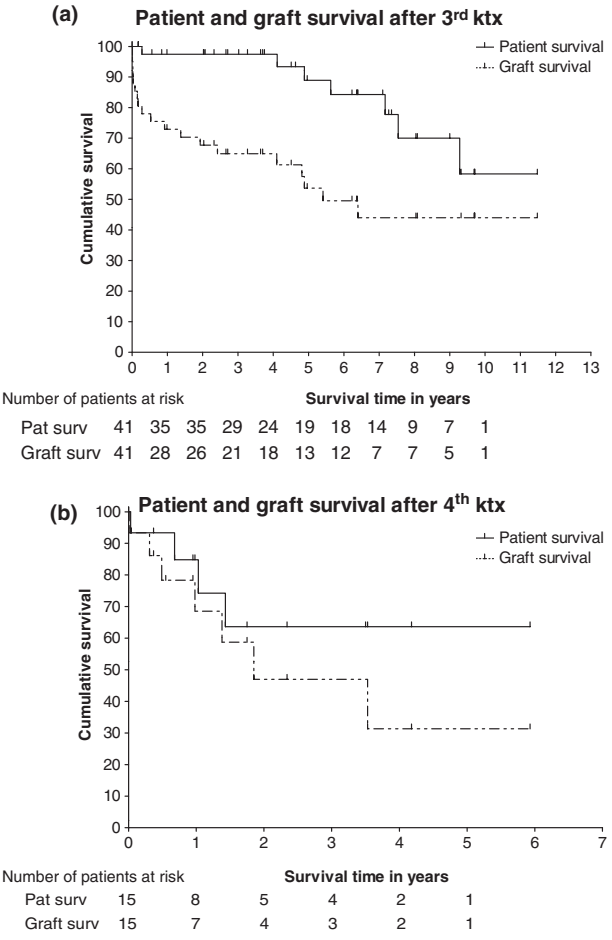

Figure 1 Long-term patient and graft survival. Kaplan–Meier survival curve for (a) patient and graft survival after third kidney transplantation (n = 41) and (b) patient and graft survival after fourth kidney transplantation (n = 15) performed between January 1997 and July 2008.

Table 4. Outcome after third and fourth kidney transplantation.

	Third transplant (n = 41)	Fourth transplant (n = 15)
Patient survival rate (%)		
1 year	97.4	84.8
2 year	97.4	63.6
3 year	97.4	–
5 year	88.9	–
Graft survival rate (%)		
1 year	72.9	68.5
2 year	67.7	47.0
3 year	64.9	–
5 year	53.6	–
Acute rejection episodes	22	8
Antibody-mediated	14*	6†
T-cell mediated	8‡	2§
Delayed graft function (%)	20 (49)	9 (60)

*Rejection was biopsy proven in 12/14 cases, 4 of which staining C4d+ and 1 staining C4d– (immunohistochemistry not available in seven cases). All specimens showed abundant presence of neutrophils in peritubular and glomerular capillaries. In 2/14 cases diagnosis of rejection was based on clinical findings.

†C4d+ staining was observed in concert with intracapillary granulocytes (1/6 specimens); 3/6 rejection episodes occurred in a single patient with the diagnosis of antibody-mediated rejection set upon the third biopsy with corresponding (immuno)histological features of humoral rejection; In 2/6 cases, rejection was diagnosed clinically.

‡Rejection episodes were biopsy proven in 5/8 cases showing Banff grade Ib (n = 1) and Banff II (n = 4) rejection. In 3/8 cases, rejection was clinically apparent.

§One rejection episode was diagnosed clinically and one biopsy was available showing Banff Ib rejection upon histology.

Fourth renal transplantation

Patient survival at 1 and 2 years was 84.8% and 63.6%, respectively. Four patients died during the observation period. Causes of death were sepsis 12 days (n = 1) and 1 year post-transplant (n = 1), and acute myocardial infarction 8 months post-transplant following graft loss (n = 1). One fourth renal allograft recipient died of acute liver failure because of sepsis 1.5 years after transplantation. This patient had developed multiple non-specific colonic ulcers that could not be attributed to either CMV, EBV or other intestinal pathogens. Graft survival in fourth graft recipients was 68.5% at 1 year and 47% at 2 years post-transplant. Delayed graft function was observed in 60% of patients. Five patients experienced a total of eight rejection episodes, the majority of which were antibody-mediated (six out of eight). Graft loss occurred in 7/15 patients. The patient in this group receiving a combined liver–fourth-kidney transplant is alive with a functioning graft and has not experienced any rejection of the kidney.

Surgical, infectious and drug-related complications

Surgical complications comprised wound dehiscence, hydronephrosis, postoperative or postbiopsy hematoma and development of lymphocele (Table 5). Among severe complications, intestinal perforation was noted in two cases. Perforation of the cecum was diagnosed in a fourth kidney graft recipient during the first postoperative week. Cause was segmental intestinal hypoperfusion associated with congestive heart failure and severe atherosclerosis. Despite emergency surgery with ileocoecal resection and ileostomy the patient died of septic multiorgan failure 12 days post-transplant. In another patient intestinal perforation occurred accidentally during third kidney transplantation because of massive scarring from multiple

Table 5. Complications. Surgical, infectious and drug-related complications after third and fourth kidney transplantation.

Complications	
Surgical complications	
Hydronephrosis	4
Wound dehiscence	4
Hematoma (postbioptic, retroperitoneal)	4
Lymphocele	2
Perforation of small intestine/cecum	2
Necrotizing appendicitis	1
Rupture of anastomosis (infectious)	1
Intravesical bleeding (tamponade)	1
Torsion of transplant with consecutive stenosis of ureter	1
Damage of femoral nerve	1
Infectious complications	
Pneumonia	4
CMV	2
Esophagitis (HSV, *Candida*)	2
EBV	1
Herpes genitalis	1
Herpes zoster	1
Colitis	1
Sepsis after hip fracture	1
Rhino-cerebral Mucor mycosis	1
Endocarditis (*Aspergillus*)	1
Drug-related complications	
Osteonecrosis	2
Leukoencephalopathy	1

laparotomies in the pretransplant course. After partial resection of the ileum and fashioning an ileo-ileostomy initial graft function was good. However, anastomotic leakage required graft nephrectomy on day 4 to avoid infection of the vascular anastomoses. Other surgical complications included damage to the femoral nerve, bladder tamponade and stenosis of the ureter 2 years post-transplant requiring surgical intervention.

Infectious complications consisted of bacterial pneumonia and infection with herpes viruses (CMV, EBV, HSV, and VZV). One third graft recipient experienced rhino-cerebral mucor mycosis requiring craniotomy and resection of the right temporal lobe. Another patient developed sepsis because of pulmonary aspergillosis and endocarditis requiring aortic valve replacement (Table 5).

Drug-related toxicity included osteonecrosis because of steroid treatment in two cases and FK506-associated leukoencephalopathy in one case (Table 5).

Discussion

Despite tremendous advances in the field of transplantation and transplant immunology, renal allograft survival is still limited [1]. Therefore, most transplant recipients will face graft loss and return to dialysis long-term. In this context, kidney retransplantation as a viable option for most of these patients may reduce mortality compared with remaining on dialysis [4] and improve quality of life. Kidney retransplantation has become a standard procedure and accounts for about 25% of all transplants performed in our center. Whereas outcome data and survival benefit of renal retransplantation have been extensively studied, data on subsequent – i.e. third and fourth – kidney transplantation are rare.

In this study, all third and fourth kidney transplantats performed at our center since 1997 were retrospectively analyzed with regard to patient and graft survival. Published data on graft survival after third kidney transplantation range from 61% to 91% at 1 year [7,10,15–18], which is in line with our 1-year graft survival of 73%. Scant data on 5-year graft survival rates range from 62% to 76% [7,11,15,16,18], which is slightly superior to the results presented here with a 5-year allograft survival rate of 54%. Concerning patient survival, the largest cohorts of third graft recipients published in the literature so far by Hagan *et al.* [11], Loupy *et al.* [15,16] and Izquierdo *et al.* [18] report a 1-year actuarial patient survival rate of 100%, 98% and 92.7%, respectively, and a 5-year patient survival of 97%, 96% and 90.6%, respectively, which is slightly superior to our 5-year survival rate of 89%. However, the leading causes of death in their population, namely cardiovascular events and sepsis, correlate very well with our findings.

After fourth kidney transplantation, 1-year graft survival rates between 50% and 87% [10,11,17,18] have been reported in study populations of not more than nine patients. In our series of 15 fourth kidney transplants, patient and allograft survival reached 84.8% and 68.5% at 1 year.

Third and subsequent kidney transplants still represent a certain surgical challenge. Technical difficulties arise from the fact that the allograft has to be positioned in previously manipulated fossae iliacae with restricted access to the iliac vessels because of prior transplantation and, in many cases, vascular anastomoses are technically demanding because of atherosclerotic changes resulting from the usually long lasting underlying disease. Regarding vascular anastomotic site, grafts were anastomosed to the external iliac vessels in the majority of cases. For technical reasons, only three grafts had to be anastomosed to the common iliac artery and external iliac vein ($n = 2$) and the common iliac artery and inferior vena cava ($n = 1$). Hagan *et al.* [11] and Loupy *et al.* [15,16], however, reported non-standard anastomotic sites in half of their recipients.

Dissection of the bladder for ureteroneocystostomy may be difficult because of scarring. Therefore, a transperitoneal approach through midline incision has been proposed for better vascular access, thus avoiding

redissection of the obliterated extraperitoneal pouch. Hagan *et al.* [11] used this transperitoneal access in 13 of 38 third kidney transplants. In another report extraperitoneal access was not feasible in 41% of patients [15,16]. In our series a transperitoneal approach was chosen in only two patients undergoing third transplantation (4%). However, multiple previous laparotomies may increase surgical risk, as reflected by the clinical course of one of our third transplant recipients. Massive scarring complicated the extraperitoneal approach by accidental perforation of the small intestine. Although the intestinal lesion was immediately oversewn, the affected intestinal portion had to be resected second-stage because of leakage. Consecutively, the kidney graft had to be removed despite good initial function because of local inflammation and the risk of infectious rupture of vascular anastomoses. Concerning urinary reconstruction, a standard ureteroneocystostomy using the Liche-Gregoire or Leadbetter-Politano technique was accomplished in all cases without the need for more extensive reconstruction [12].

In our experience, simultaneous graft nephrectomy is not necessary for implantation of a third or fourth transplant, as the non-functioning renal grafts are usually shrunken and do not restrict space for placement of the subsequent graft. Interestingly, Loupy *et al.* [15] observed that recipients undergoing graft removal between the second and third transplant had significantly higher PRAs than did recipients without graft nephrectomy.

Only one graft was lost because of surgical problems, which is in agreement with observations by Hagan *et al.* [11] and Mazzucchi *et al.* [10]. The predominant cause of graft loss in our cohort was rejection. Consistent with the literature [10,11,15,16], the high grade of sensitization in these patients causes significantly higher rates of delayed graft function than in primary graft recipients, with 49% to 60% of third and fourth graft recipients requiring postoperative dialysis. Despite the use of induction therapy, the incidence of acute rejection has markedly exceeded rejection rates for primary kidney transplants in this setting. In our series, a significant proportion of rejection episodes has proven to be antibody-mediated. Successful treatment of acute rejection seems to require profound immunosuppression including extensive plasma exchange and B-cell-depleting antibodies. Nevertheless, in six of our third graft recipients rejection led to graft loss within 6 months post-transplant. Thus, in our patient population, graft loss occurred as the result of either early rejection or chronic allograft dysfunction, which is in agreement with the observations by Horovitz *et al.* [7].

With regard to patient selection for repeat renal transplantation, the side-effects of long-term immunosuppression have to be taken into consideration. In particular, induction therapy upon retransplantation may trigger infectious complications, as seen in one of our third graft recipients. Despite intense induction therapy, this patient developed an episode of acute Banff II rejection that was treated with bolused steroids. The postoperative course was further complicated by necrotizing appendicitis and central venous line-associated MRSA (methicillin-resistant *Staphylococcus aureus*) sepsis followed by pulmonary aspergillosis. Immunosuppression was discontinued and graft nephrectomy was performed, which was complicated by intraperitoneal abscess formation. Subsequent infectious rupture of the arterial patch required ligature of the common iliac artery. An arterial crossover-bypass had to be performed to save the leg. Furthermore, the patient developed mycotic endocarditis which required aortic valve replacement and mitral valve reconstruction. Unfortunately, the patient died from multiorgan failure in the immediate postoperative course. This sensitized patient population usually requires profound immunosuppression which puts it at particular risk for severe infectious complications. In concert with cardiovascular comorbidities, these factors may extensively affect the outcome of repeat kidney transplantation.

As evident from the cardiovascular risk profile of our third and fourth graft recipients, meticulous patient selection is mandatory with a view to reducing morbidity and mortality post-transplantation. At our center, all patients with two or more cardiovascular risk factors are subjected to echocardiography and exercise stress test or myocardial szintigraphy pretransplant. All patients with a history of myocardial infarction or coronary heart disease as well as all patients with abnormal findings in non-invasive tests must undergo coronary angiography pretransplant. According to these criteria, coronary angiography was required in 14 persons in our study population, with three patients suffering from significant coronary artery stenosis. Two patients had coronary bypass surgery; the other one underwent successful endoluminal revascularization prior to kidney transplantation.

In their study, Ahmed *et al.* [17] failed to find a linear relationship between the number of retransplants and graft survival. This observation may have been influenced by the rather small study population of 24 third, eight fourth and one fifth transplant. Nevertheless, their observation supports our finding that the number of a patient's retransplants does not reliably predict outcome following repeat renal transplantation. In this context, three fifth kidney transplants (one heart–fifth kidney, one liver–fifth kidney and one fifth kidney alone transplantation), one sixth kidney transplantation and one seventh kidney transplantation have been successfully performed at our center. One of these patients died 10 days postoperatively because of sepsis of unknown origin. Especially in younger patients repeated kidney transplantation

may represent a prerequisite for complete medical but also social recovery reflected by return to work after successful transplantation. In our cohort, we have analyzed a subgroup of patients ($n = 9$) aged <50 years at the time of hospital discharge with functioning graft. Five patients could return to work after their third or fourth kidney transplantation and four patients had retired but recovered in a way that they succeeded in daily life experiencing only minor restrictions upon severe physical activity.

Retrospective data collection and the various types of immunosuppression applied are shortcomings of this analysis. However, this study constitutes the largest series of fourth renal allograft recipients published so far and the third largest series of third transplants. Therefore, it might provide valuable additional data on this difficult patient population.

In conclusion, our data show satisfactory patient and graft survival after third and fourth kidney transplantation. Therefore, loss of two or three previous renal grafts should not preclude recipients from being considered for further transplantation.

Authorship

KK-W: study design, collection and analysis of data, writing of the manuscript. WM: study design, writing of the manuscript. MM: contributed to data collection. GB and RÖ: participated in study design. RM and JP: participated in study design, critically revised the manuscript. CB: participated in data collection and analysis.

Funding

No funding.

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