Kidney Transplantation

Optimizing Surgical Outcome

Liselotte S.S. Ooms

The studies described in this thesis were performed at the department of Surgery, Erasmus University Medical Center, Rotterdam, The Netherlands
Printing of this thesis has been financially supported by:

Erasmus MC
Erasmus MC- Heelkunde
Nederlandse Transplantatie Vereniging
Nierstichting
Astellas Pharma B.V.
Chiesi Pharmaceuticals B.V.
ChipSoft

Cover Design: Lenne van Oijen, Studio Ketchup

ISBN 978-94-6295-760-2

Lay-out and print by: ProefschriftMaken // www.proefschriftmaken.nl

Kidney Transplantation

Optimizing Surgical Outcome

Het optimaliseren van de chirurgische resultaten na niertransplantatie

Proefschrift

Ter verkrijging van de graad van doctor aan de
Erasmus Universiteit Rotterdam
op gezag van de
rector magnificus

Prof.dr. H.A.P. Pols

en volgens het besluit van het College voor Promoties.

De openbare verdediging zal plaatsvinden op

woensdag 29 november 2017 om 09.30 uur

door

Liselotte Susanne Sophie Ooms
geboren te Wageningen

Erasmus University Rotterdam

PROMOTIECOMMISSIE

Promotor	Prof.dr. J.N.M. Ijzermans
Overige leden	Prof.dr. R. Zietse Prof.dr. I. Alwayn Prof.dr. L.B. Hilbrands
Copromotor	Dr. T. Terkivatan

TABLE OF CONTENTS

CHAPTER 1

General introduction

The kidneys are essential in maintaining the body's internal balance of water, acid metabolism, hormones and minerals. Many diseases can result in kidney failure, requiring short term or long lasting kidney replacement therapy, like dialyses.

Kidney transplantation is the best treatment for irreversible end stage renal disease (1). The first unsuccessful deceased donor kidney transplantation was performed by a Russian surgeon Yuri Voronoy in 1933, using the femoral artery and vein of the recipient. In the 1950s a group of French transplant surgeons (René Küss, Charles Dubost and Marceau Servelle) were the first who used the extraperitoneal renal transplantation procedure which is commonly used nowadays - called the 'Küss-procedure'.

From the 1970s adequate immunosuppressive therapy evolved and this enabled kidney transplantation on a larger scale. Since then many studies demonstrated a clear benefit for transplant recipients and in addition, kidney transplantation also results in a financial benefit for society (2). Nowadays, an average of 950 kidney transplantations are performed in the Netherlands each year, leading to a decrease on the Dutch waiting list from 883 patients in 2011 to 576 patients in 2015.

The success of kidney transplantation may be hampered by immunological problems, including vascular or cellular rejection, and recurrence of disease in the transplant. Of course, a patient may also be confronted with surgical complications that may lead to morbidity, graft loss and even mortality (3, 4). Preventing these surgical complications is a prerequisite for long term success and minimizing their incidence is one of the challenges in kidney transplantation.

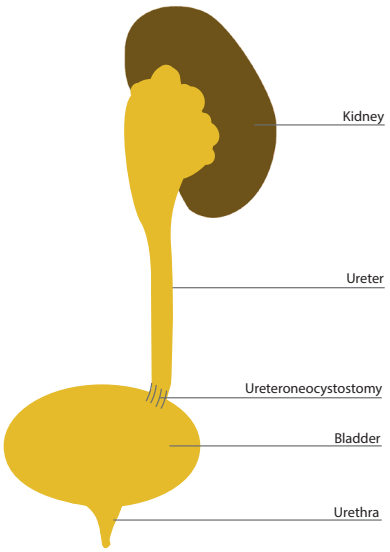
Therefore, the aim of the studies presented in this thesis is to optimize outcome of kidney transplantation by reducing surgical complications.

Urological complications

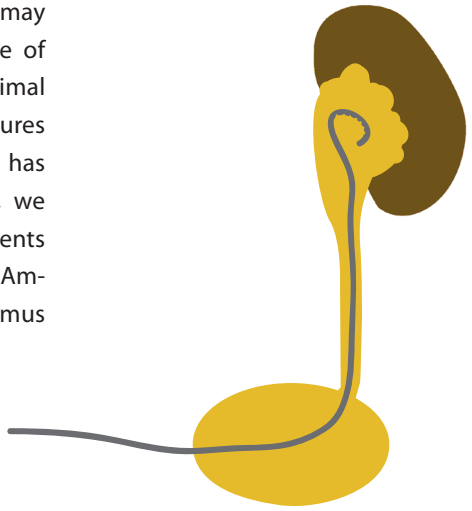
After the vascular anastomoses of the renal artery and vein on the external iliac vessels the ureteroneocystostomy is performed. This anastomosis between transplant ureter and bladder may be complicated by urinary leakage or ureteral stenosis (5). There are two types of ureteroneocystostomies (intravesical and extravesical). A previously conducted randomized controlled trial performed at the Erasmus MC has proven that both techniques are alike in the overall number of urological complications. However, the extravesical technique is associated with fewer urinary tract infections and therefore recommended (6). As the use of a ureteral stent is still under debate (7) we studied in chapter 2 the benefits of the use or non-use of ureteral stents in a randomized controlled

trial. In addition, in chapter 3 the outcome of two different external ureteral stents are compared as measured by the number of complications.

Several risk factors related to the development of urological complications after transplantation have been well established, including male gender for donor or recipient, pre-emptive transplantation and arterial reconstructions of multiple arteries of the kidney graft (8, 9). The influence of ureteral length of the graft on the number of urological complications is still unknown and subject of research in chapter 4.



Percutaneous nephrostomy placement (PCN) is the initial step in the treatment of urological complications, either due to leakage or stenosis. The urinary flow is deviated from the ureteroneocystostomy and anastomotic healing may be supported. If the anastomosis fails to heal the next step in the treatment schedule may include surgical re-intervention, or in case of stenosis antegrade balloon dilatation, a minimal invasive treatment option for ureteral strictures (10). The outcome of this latter technique has not been studied in detail. In chapter 5, we present a case series of 50 transplant recipients who are treated by balloon dilatation in the Amsterdam Medical Center (AMC) and the Erasmus Medical Center.



Infections are a common problem in patients receiving immunosuppressive treatment after transplantation. Urinary tract infections (UTI) after kidney transplantation are reported up to 38% (11). Analysis of risk factors associated with the development of UTI may help to reduce urinary tract related complications. Therefore, in chapter 6 we conducted a detailed study of 417 kidney transplant recipients and tried to define the risk factors related to UTI.

Guided by the outcome of the studies performed we will propose a new protocol for external vs. internal (double J) stenting in chapter 7.

Other surgical complications

In addition to urological complications, other surgical problems may occur after kidney transplantation, such as bleeding, vascular thrombosis and wound infections. A less common complication after kidney transplantation is incisional hernia, although it is one of the most frequent postoperative complications after regular abdominal surgery. The incidence in regular abdominal surgery varies between 11 and 20% in the general population and has great impact on the health related quality of life and body image (12-16). Known risk factors for development of incisional hernia are obesity, aneurysm of the abdominal aorta, wound infections and immunosuppressive therapy (15-17). Hence, it is suggested that transplant recipients may have an increased risk to develop incisional hernia due to the use of postoperative immunosuppressive therapy. In chapter 8, the incidence, risk factors and treatment options of incisional hernia after kidney transplantation are documented.

Retransplantation may be considered if a kidney transplant fails. In 2015, 152 out of 576 patients (26%) on the Dutch kidney transplant waiting list, awaited a retransplant. If a retransplantation must be performed, the use of the contralateral iliac fossa is advocated. However, in case of a third or even fourth retransplant, it is unavoidable to explore an iliac fossa that has already been dissected for the previous implantation and for removal of the non-functioning graft. In chapter 9, the surgical challenges of a retransplantation in the ipsilateral fossa are described.

References

1. Hornberger JC, Best JH, Garrison LP, Jr. Cost-effectiveness of repeat medical procedures: kidney transplantation as an example. Med Decis Making. 1997;17(4):363-72.
2. Rosselli D, Rueda JD, Diaz CE. Cost-effectiveness of kidney transplantation compared with chronic dialysis in end-stage renal disease. Saudi J Kidney Dis Transpl. 2015;26(4):733-8.
3. Ammi M, Daligault M, Sayegh J, Abraham P, Papon X, Enon B, et al. Evaluation of the Vascular Surgical Complications of Renal Transplantation. Ann Vasc Surg. 2016;33:23-30.
4. Rigg KM, Proud G, Taylor RM. Urological complications following renal transplantation. A study of 1016 consecutive transplants from a single centre. Transpl Int. 1994;7(2):120-6.
5. Zavos G, Pappas P, Karatzas T, Karidis NP, Bokos J, Stravodimos K, et al. Urological complications: analysis and management of 1525 consecutive renal transplantations. Transplant Proc. 2008;40(5):1386-90.
6. Slagt IK, Dor FJ, Tran TC, Kimenai HJ, Weimar W, Ijzermans JN, et al. A randomized controlled trial comparing intravesical to extravesical ureteroneocystostomy in living donor kidney transplantation recipients. Kidney Int. 2014;85(2):471-7.
7. Wilson CH, Rix DA, Manas DM. Routine intraoperative ureteric stenting for kidney transplant recipients. Cochrane Database Syst Rev. 2013;6:CD004925.
8. Slagt IK, Ijzermans JN, Visser LJ, Weimar W, Roodnat JI, Terkivatan T. Independent risk factors for urological complications after deceased donor kidney transplantation. PLoS One. 2014;9(3):e91211.
9. Neri F, Tsivian M, Coccolini F, Bertelli R, Cavallari G, Nardo B, et al. Urological complications after kidney transplantation: experience of more than 1,000 transplantations. Transplant Proc. 2009;41(4):1224-6.
10. Uflacker A, Sheeran D, Khaja M, Patrie J, Elias G, Saad W. Outcomes of Percutaneous Management of Anastomotic Ureteral Strictures in Renal Transplantation: Chronic Nephroureteral Stent Placement with and without Balloon Dilatation. Cardiovasc Intervent Radiol. 2015;38(3):693-701.
11. Wu X, Dong Y, Liu Y, Li Y, Sun Y, Wang J, et al. The prevalence and predictive factors of urinary tract infection in patients undergoing renal transplantation: A meta-analysis. Am J Infect Control. 2016.
12. Bevis PM, Windhaber RA, Lear PA, Poskitt KR, Earnshaw JJ, Mitchell DC. Randomized clinical trial of mesh versus sutured wound closure after open abdominal aortic aneurysm surgery. Br J Surg. 2010;97(10):1497-502.
13. Burger JW, Luijendijk RW, Hop WC, Halm JA, Verdaasdonk EG, Jeekel J. Long-term follow-up of a randomized controlled trial of suture versus mesh repair of incisional hernia. Ann Surg. 2004;240(4):578-83; discussion 83-5.
14. van 't Riet M, Steyerberg EW, Nellensteyn J, Bonjer HJ, Jeekel J. Meta-analysis of techniques for closure of midline abdominal incisions. Br J Surg. 2002;89(11):1350-6.
15. van Ramshorst GH, Eker HH, Hop WC, Jeekel J, Lange JF. Impact of incisional hernia on health-related quality of life and body image: a prospective cohort study. Am J Surg. 2012;204(2):144-50.
16. de Goede B, Eker HH, Klitsie PJ, van Kempen BJ, Polak WG, Hop WC, et al. Incisional hernia after liver transplantation: risk factors and health-related quality of life. Clin Transplant. 2014;28(7):829-36.
17. Smith CT, Katz MG, Foley D, Welch B, Leverson GE, Funk LM, et al. Incidence and risk factors of incisional hernia formation following abdominal organ transplantation. Surg Endosc. 2015;29(2):398-404.

CHAPTER 2

Stenting the ureteral anastomosis reduces urological complications in kidney transplantation: a randomized controlled trial, SPLINT-trial

L.S.S. Ooms[1], J. van de Wetering[2], H.J.A.N Kimenai[1], R.C. Minnee[1], T.C.K. Tran[1], H. Hartog[1], J.N.M. IJzermans[1], T. Terkivatan[1]

1. Department of Surgery, Erasmus University Medical Center, Rotterdam, The Netherlands
2. Department of Nephrology, Erasmus University Medical Center, Rotterdam, The Netherlands

Manuscript in preparation

Abstract

Stenting of the ureteral anastomosis in kidney transplantation is still open for discussion. In living donor kidney transplantation, we tested the hypothesis if omitting a stent is as effective as the use of a stent regarding urological complications. In this randomized controlled trial (SPLINT), eligible patients who received a living donor kidney transplantation in the Erasmus University Medical Center were included consecutively between April 2014 and March 2017. Exclusion criteria were lack of informed consent, age (< 18years), abnormalities of the urinary tract system, primary focal segmental glomerulosclerosis (FSGS) and participation in another ongoing clinical trial. Two-hundred patients were randomized for suprapubic externalized single J stent placement (N=100) or no stent placement (N=100). Primary outcome was defined as the number of percutaneous nephrostomy placements (PCN) up to 1 month postoperatively. In total 124 males and 76 females were included, with a mean age of 54 years; 101 patients were randomized in the stent group and 99 patients in the no stent group. Baseline characteristics were comparable in both groups. In the no stent group, there were significantly more PCN placements, 18% vs 4%, P=0.001, more urinary leakages, 12% vs 0%, P<0.001 and surgical re-interventions due to urological complications 7% vs 1%, P=0.028. In the stent group, there were more patients with haematuria, 76% vs 49%, P<0.001, graft rejection, 36% vs 21%, P=0.024 and prolonged hospital stay, 13 vs 10 days, P<0.001. Mean GFR at day 7, 14, 21 and 1 month after transplantation was equal in both groups. In multivariate risk factor analyses, the variables that were independently related to PCN placement, were no stent placement (OR 7.67, 95%CI 2.33-25.20), history of smoking (OR 3.37, 95%CI 1.05-10.81) and first warm ischemia time (OR 0.56, 95%CI 0.34-0.93). Although stent placement may increase postoperative hematuria and prolong hospital stay, stenting should be advocated in living donor kidney transplantation. Stent placement significantly reduced the number of PCN placements, urinary leakages and surgical re-interventions due to urological complications.

Introduction

Kidney transplantation is the only treatment offering long-term benefit to patients with chronic kidney failure. Urological complications after kidney transplantation, such as urinary leakage and ureteral strictures, are associated with significant morbidity, surgical and radiological interventions, prolonged hospital stay and even mortality. Most urological complications are related to the ureteroneocystostomy and are treated by percutaneous nephrostomy (PCN) placement[1,2].

It has been suggested that standard use of a ureteral stent in kidney transplantation may diminish the risk of urological complications. However, stent placement has disadvantages as well and the role of ureteral stents in living donor kidney transplantation is still not well defined. Stent related complications may include infection, obstruction, stent migration, breakage, stone formation, haematuria, and secondary ureter obstruction[3,4]. Currently, there are no well-defined evidence based arguments that favour stent placement.

In this SPLINT-trial (Stent PLacement IN living donor kidney Transplantation) the hypothesis will be tested if omitting a ureteral stent in kidney transplantation is as effective or even reduces the number of urological complications without stent related problems. This study has a follow up of 1 year, including analyses concerning cost-effectiveness and quality of life. This is a preliminary report with only the clinical outcome of events that occurred within 1 month after transplantation.

Methods

Study design

In this randomized controlled trial, we included all patients who received a living donor kidney transplantation in the Erasmus University Medical Center, Rotterdam, the Netherlands, between April 2014 and March 2017. Exclusion criteria were no informed consent, age (< 18years), duplicated ureter system of the donor kidney, patients with a reconstructed urinary tract or conduit after total or partial cystectomy, patients with bladder dysfunction that requires continuous or intermittent catheterization. Patients with primary focal segmental glomerulosclerosis (FSGS) and residual urine production were also excluded. Because FSGS is known for its quick recurrence in the kidney graft and a first sign is proteinuria. With an externalized stent, we can distinguish between proteinuria of the transplant kidney and the native kidneys. Furthermore, we excluded recipients that were included into another ongoing clinical trial. After intubation in

the operating room, we randomized 200 recipients for either stent placement (N=100, Teleflex, suprapubic externalized single J stent, 7fr) or no stent placement (N=100). Randomization was performed after intubation in the operation room by a envelop system, randomized by an independent statistician at the Erasmus Medical Center. Due to the use of an externalized stent, blinding was not possible. The Medical Ethical Committee of the Erasmus University Medical Center approved the trial protocol (MEC-2013-196) and the study was registered at the (Dutch) Netherlands Trial Register (NTR4498).

Surgical technique

Donor nephrectomy was performed with either a fully laparoscopic, a robot assisted of hand assisted approach. In recipients, an extraperitoneal approach of the iliac fossa was performed in all patients. Firstly, the renal artery was anastomosed to the external iliac artery and the renal vein to external iliac vein, followed by an extravesical ureteroneocystostomy described by Lich-Gregoir[5,6]. The detrusor muscle was closed over the anastomosis by one or two interrupted absorbable sutures to create a sub-mucosal tunnel with an anti-reflux mechanism. When randomized to stent placement, a 7fr suprapubic externalized single J stent (Teleflex) was used and removed 9 days postoperatively. A transurethral urinary bladder catheter was standard care in all patients and was removed after 7 days.

Power calculation

The SPLINT-trial was designed as a non-inferiority study and powered to demonstrate that omitting a stent does not lead to a relevant increased complications rate, i.e. rate of required PCN drainage. To show that the increase of patients without a stent requiring a PCN is at most 5% (non-inferiority margin), 96 patients per arm were required (one-side alpha= 0.025, power=90%). In this calculation, it was assumed that in case of stent placement, 20% of the patients need a PCN[1], while in case of no stent placement this percentage equals 9%[2]. To allow for a few non-evaluable cases, 100 patients per arm were randomized.

Definitions

Baseline data of the recipients included gender, age, ASA classification, number of previous transplantations, body mass index (BMI), warm and cold ischemia time, duration of surgery, per-operative blood loss, pre-emptive transplantation (prior to start dialysis), rejection <1 month, surgical re-interventions < 1 month after kidney transplantation (KT) and length of hospital stay. Our primary outcome was PCN placement within 1 month. Urinary leakage, (detected by a MAG-3 scan or proven by chemistry samples in case of extensive fluid production of the wound or by the drain) or a rise in serum creatinine level combined with a hydronephrosis on ultrasound, indicated PCN place-

ment. Our secondary outcome was graft function measured using Glomerular filtration rate (GFR), haematuria (defined as macroscopic haematuria during hospital admission), urinary tract infection (UTI) and rejection. UTI was scored when there as a urinary culture with a bacterium of ≥ 10^5 CFU/mL which was treated with antibiotics. Rejection was scored if patients received anti-rejection treatment (methylprednisolone intravenous, IVIG, alemtuzumab, r-ATG). History of smoking included current or past smokers.

Immunosuppressive treatment

Immunosuppressive treatment consisted of basiliximab intravenous on the day of surgery and day 4 after transplantation. Postoperative immunosuppression consisted of tacrolimus, mycophenolate mofetil and prednisolone. The prednisone was tapered off to be discontinued at 4 months after transplantation.

Statistical analysis

All analyses were conducted using IBM SPSS Statistics for Windows (version 21.0. Armonk, NY: IBM Corp, USA). A p-value of <0.05 (two-sided) was considered statistically significant. Continuous variables with normal distribution are presented as means with standard deviation and analyzed using the independent *t* test. Skewed distributed variables are presented as median (range) and analyzed using the Mann-Whitney *U* test. Categorical variables were presented as numbers with percentages and were analysed using Chi-square test. We performed multivariate analysis using logistic regression and included covariates with p-values <0.1 in univariate analysis. The analysis was two-tailed and results were presented as odds-ratios (OR) with 95% confidence intervals (95% CI).

Results

Baseline characteristics

Between April 2014 and March 2017, 200 patients were included in the SPLINT-trial. In one patient, the randomisation was overruled by the surgeon, since he judged it as necessary to place a stent because of difficulties perioperative. We included 99 patients in the no stent group and 101 patients in the stent group. In total 124 males and 76 females were included, mean age was 54 years. Baseline characteristics were comparable in both groups (gender, age, ASA classification, number of previous KT, donor nephrectomy technique, BMI, history of smoking, pre-emptive transplantation, ischemia times, ureteral length and residual urinary production of recipients). Table 1.

Table 1. Baseline characteristics

Characteristic	Total (200)	No Stent (99)	Stent (101)	P-value
Gender recipient N (%)				0.857
M	124 (62)	62 (63)	62 (61)	
F	76 (38)	37 (37)	39 (39)	
Age recipient in years mean ± SD	54±13	55±13	52±14	0.174
Gender donor N (%)				0.158
M	81 (41)	45 (45)	36 (36)	
F	119 (59)	54 (54)	65 (64)	
Age donor in years mean ± SD	54±12	54±12	53±13	0.599
ASA N (%)				0.371
2	28 (14)	11 (11)	17 (17)	
3	164 (82)	85 (86)	79 (78)	
4	8 (4)	3 (3)	5 (5)	
Number KT N (%)				0.259
1	173 (86)	89 (90)	84 (83)	
2	19 (10)	6 (6)	13 (13)	
3	8 (4)	4 (4)	4 (4)	
Technique laparoscopic N (%)	123 (62)	60 (61)	63 (62)	0.797
BMI recipient mean ± SD	27±5	28±5	27±5	0.368
History of smoking N (%)	123 (61)	59 (60)	64 (63)	0.584
Pre-emptive KT N (%)	102 (51)	47 (47)	55 (55)	0.323
Residual urinary production N (%)	172 (86)	82 (83)	90 (89)	0.201
Ureteral length in cm; mean ± SD	9±2	9±2	9±2	0.285
First warm ischemia time in minutes; mean ± SD	3±1	3±1	3±2	0.190
Cold ischemia time in minutes; mean ± SD	140±29	142±31	139±27	0.374
Second warm ischemia time in minutes; mean ± SD	20±7	20±7	20±8	0.885

M, male; F, female; KT, kidney transplantation; SD, standard deviation; BMI, body mass index; N, number.

Urological complications

In the no stent group, 18 patients received a PCN within 1 month after transplantation. Of this group, 11 patients received a PCN due to urinary leakage. Six urinary leakages resolved without further interventions, 3 patients needed a surgical re-intervention due to the urinary leakage and 2 patients underwent both antegrade balloon dilatation, as well as a surgical re-intervention. Note that 1 patient in the no stent group with urinary leakage did not receive a PCN, but underwent direct surgical repair. In the no stent group, 7 patients received a PCN due to hydronephrosis. One of these patients underwent balloon dilatation, the others resolved without any intervention. One patient in the no stent group with hydronephrosis due to a blood clot in the ureter also did not receive a PCN and underwent direct surgical repair. In the stent group, 4 patients

received a PCN within 1 month after transplantation, all due to hydronephrosis. One patient underwent balloon dilatation and another patient balloon dilatation followed by a surgical re-intervention. There were significantly more PCN placement in the no stent group, 18% vs 4% (P=0.001). There were significantly more urinary leakages in the no stent group, 12% vs 0% (P<0.001) and significantly more surgical re-interventions due to urological complications 7% vs 1 %, (P=0.028). The number of PCN placed due to hydronephrosis was not different. Details are depicted in figure 1 and table 2.

Figure 1. Flowchart SPLINT-trial

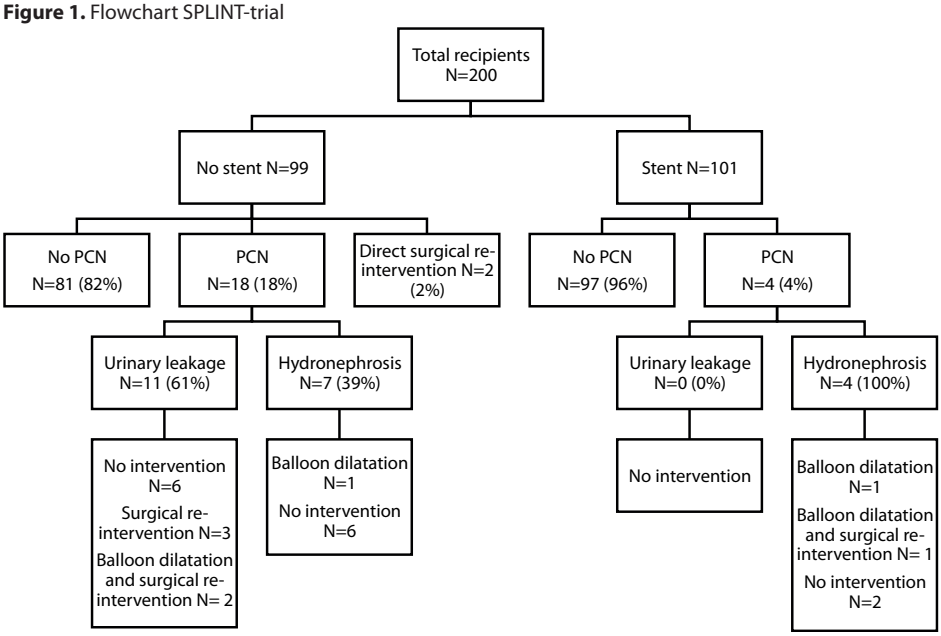


Table 2. Urological complications

Characteristic	Total (200)	No Stent (99)	Stent (101)	P-value
PCN placement < 1 month N (%)	22 (11)	18 (18)	4 (4)	**0.001**
Urinary leakage < 1 month N (%)	11 (6)	12 (12)	0 (0)	**<0.001**
Hydronephrosis < 1 month N (%)	12 (6)	8 (8)	4 (4)	0.220
Surgical re-intervention due to urological complications N (%)	8 (4)	7 (7)	1 (1)	**0.028**
Antegrade balloon dilatation N (%)	5 (3)	3 (3)	2 (2)	0.634

PCN, percutaneous nephrostomy placement; N, number.

Overall outcome

There were no differences between the stent and no stent group regarding duration of surgery, blood loss, overall surgical re-intervention within 1 months, urinary tract infections, urosepsis, wound infections and readmissions within 1 month after transplantation. Duration of ureteral anastomosis with stent placement was 17 min vs 12 minutes in the no stent group (P<0.001). In the stent group, there were significantly more patients with macroscopic haematuria, 76% vs 49% (P<0.001). In addition, in the stent group there were more patients treated because of graft rejection within 1 month after transplantation, 36% vs 21%, (P=0.024) and the total length of hospital stay was significantly higher with a mean of 13 vs 10 days (P<0.001). Table 3.

Table 3. Overall outcome

Characteristic	Total (200)	No Stent (99)	Stent (101)	P-value
Duration of surgery in minutes; mean ± SD	116±36	113±39	119±33	0.281
Blood loss in mL; median (range)	150 (0-2000)	150 (0-2000)	150 (0-1300)	0.352
Surgical re-intervention < 1 month N (%)	20 (10)	10 (10)	10 (10)	0.962
Hematuria N (%)	126 (63)	49 (49)	77 (76)	**<0.001**
UTI N (%)	45 (23)	25 (25)	20 (20)	0.356
Urosepsis N (%)	8 (4)	4 (4)	4 (4)	0.977
Wound infection N (%)	22 (11)	14 (14)	8 (8)	0.160
Rejection <1-month N (%)	57 (29)	21 (21)	36 (36)	**0.024**
Biopsy proven rejection < 1-month N (%)	47 (23)	13 (13)	34 (34)	**0.001**
Total length of hospital stay (days) mean ± SD	11±5	10±4	13±6	**<0.001**
Readmission <1-month N (%)	34 (17)	21 (21)	13 (13)	0.116

SD, standard deviation; N, number; UTI, urinary tract infection

Graft outcome

Mean GFR at day 7, day 14, day 21 and 1 month after transplantation was equal in both groups as depicted in table 4.

Table 4. Graft outcome

Characteristic	No stent (99)	Stent (101)	P-value
GFR mL/min 7 days after KT mean ± SD	41 ± 15	42 ± 19	0.880
GFR mL/min 14 days after KT mean ± SD	46 ± 15	46 ± 17	0.493
GFR mL/min 21 days after KT mean ± SD	48 ± 14	47 ± 16	0.814
GFR mL/min 1 month after KT mean ± SD	47 ± 14	47 ± 16	0.342

GFR, Glomerular Filtration Rate; KT, kidney transplantation; SD, standard deviation

Risk factor analyses PCN placement

In a univariate risk factor analysis for PCN placement, stent placement, history of smoking and the first warm ischemia time had P-values <0.1. Table 5. These variables were included in our multivariate analysis, which showed that no stent placement (OR 7.67, 95%CI 2.33-25.20), history of smoking (OR 3.37, 95%CI 1.05-10.81) and first warm ischemia time (OR 0.56, 95%CI 0.34-0.93) were independently related to PCN placements. Table 6.

Table 5. Risk factors for PCN placement

Characteristic	No PCN (178)	PCN (22)	P-value
Gender recipient N (%)			0.527
M	109 (61)	15 (68)	
F	69 (39)	7 (32)	
Stent placement N (%)	97 (55)	4 (18)	**0.001**
Age recipient in years mean ± SD	53±13	56±16	0.357
Gender donor N (%)			0.675
M	73 (41)	8 (36)	
F	105 (59)	14 (64)	
Age donor in years mean ± SD	53±12	56±14	0.330
ASA N (%)			0.778
2	26 (15)	2 (9)	
3	145 (81)	19 (86)	
4	7 (4)	1 (5)	
Number KT N (%)			0.592
1	153 (86)	20 (91)	
2	17 (10)	2 (9)	
3	8 (4)	0 (0)	
Technique laparoscopic N (%)	107 (60)	16 (73)	0.251
BMI recipient; mean ± SD	27±5	28±6	0.238
History of smoking N (%)	105 (59)	18 (82)	**0.038**
Pre-emptive KT N (%)	92 (52)	10 (46)	0.581
Residual urinary production N (%)	155 (87)	17 (77)	0.211
Ureteral length in cm; mean ± SD	9±2	9±2	0.794
First warm ischemia in minutes; mean ± SD	3.2±1.4	2.7±0.7	0.084
Rejection <1month N (%)	52 (29)	5 (23)	0.525
Cold ischemia time in minutes; mean ± SD	140±29	142±28	0.797
Second warm ischemia time in minutes; mean ± SD	19.4±7.4	20.9±5.8	0.350
Duration of surgery in minutes; mean ± SD	116±37	116±28	0.974
Blood loss in mL; median (range)	150 (0-2000)	200 (20-575)	0.161

M, male; F, female; KT, kidney transplantation; SD, standard deviation; BMI, body mass index; N, number; PCN, percutaneous nephrostomy placement.

Table 6. Multivariate risk factor analysis

Risk factor	Odds ratio	95% CI	P-value
History of smoking	3.37	1.05-10.81	**0.041**
No stent	7.67	2.33-25.20	**0.001**
First warm ischemia time	0.56	0.34-0.93	**0.024**

CI, 95% Confidence Intervals

Discussion

These are the preliminary data of the SPLINT trial, a randomized controlled trial in living donor kidney transplantation, which investigated the influence of stent vs no stent placement on the number of urological complications. There were significantly more PCN placements, urinary leakages and surgical re-interventions due to urological complications in the no stent group. In the stent group, there was significantly more haematuria and graft rejection. Furthermore, the total length of hospital stay was higher in the stent group with a mean of 13 vs 10 days. The variables that were independently related to PCN placement, were no stent placement (OR 7.67), history of smoking (OR 3.37) and first warm ischemia time (OR 0.56).

Before conducting this trial, there were no well-defined evidence based arguments that favoured stent placement. In total 5 randomized controlled trials[7-11] on stent placement have been reported previously. These studies differ in study design regarding living and deceased donation, intravesical or extravesical anastomosis and type of stent. Stenting seemed to be in favour, but it remained open for discussion whether this should be on routine basis or only on strictly defined criteria. A Cochrane review on this topic supports the use of ureteral stents in selected recipients, but without a statement on routine stenting, type of stent and timing of stent removal[12].

We first studied if the type of anastomosis (extravesical vs intravesical) was a risk factor for PCN placement [13]. There was no difference in the number of PCN placement between the intra and extravesical anastomosis (20% vs 20%), however the number of urinary tract infections was lower in the extravesical group. The extravesical anastomosis has its place in our standard care nowadays.

With these preliminary results of the SPLINT trial, we are convinced that stent placement with an extravesical anastomosis does reduce the number of urological complications significantly. Within 1 month after transplantation, there were 4% PCN placements in the stented extravesical anastomosis group. This seems to be considerably lower compared to the previously published data (20%) of the INEX trial. Of course, we cannot state yet

whether this difference can be explained by the follow up of 3 months in the INEX vs 1 month in this preliminary report of the SPLINT trial.

Although stent placement significantly increases the duration of ureteral anastomosis with 5 minutes, it did not influence the total duration of surgery. The total length of hospital stay is significantly higher in the stent group. However, there were 21 patients who needed to be readmitted within 1 month in the no stent group and only 13 in the stent group (P=0.116). The analysis of readmissions within 1 year will provide more information concerning this subject.

A remarkable finding was the significantly higher number of rejections in the stent group, 36% vs 21%, P=0.024. These were the patient who received anti-rejection treatment (methylprednisolone intravenous, IVIG, alemtuzumab, r-ATG) within 1 month after transplantation. We did not find any explanation for this finding other than coincidence. Patients with stents are hospitalized longer, maybe rejections are detected faster during clinical stay than in outpatient visits. Also, urine production can be monitored accurately with the external stent, possibly inducing a low threshold for biopsy. However, the number of biopsy proven rejections were significantly higher in the stent group as well, 34% vs 13% (P=0.001). We do not believe that the material used in stents induces more rejection.

We identified three risk factors for PCN placement; no stent placement, history of smoking and the first warm ischemia time. The risk factor of the first warm ischemia time should be interpreted with caution, as the difference between both groups is only 0.5 minute (30 seconds) and is not significant in univariate analyse. Furthermore, if warm ischemia time would influence outcome, a significant P-value for the second warm ischemia time would also have been expected.

There are a few limitations to this study. These are the preliminary results of a trial with a total follow up of 1 year after transplantation. We have only included events (PCN, readmissions and re-interventions) which occurred within 1 month after transplantation. Late events are not included yet and can still change the definitive outcome of this trial. Furthermore, the results concerning the cost-effectiveness and quality of life analyses are left out now as well. Besides, the suprapubic externalized type of stent used in this trial is not a commonly used stent. Most transplant centers use a double J stent and in literature the double J stent also has minor urological complications. A retrospective study by Vogel et al. including 76 patients with 43 externalized stents and 33 double J stents have reported an incidence of leakage of the ureteroneocystostomy of 13.9% in the externalized stent group compared to 0% in the double J group. Furthermore,

they found a 2 day reduction of hospital stay with an internal stent [14]. Gomes et al. also retrospectively reviewed the use of external, internal stents and no stent in 2061 kidney transplant recipients. In their cohort, urological complications occurred in 17.3% in the group with external stents, 8.4% in patients that did not receive a stent, and 5.4% in kidney transplant recipients in whom a double J stent was placed ($P < .0005$)[15]. The authors even state: "use of an external catheter which was associated with a high rate of UC, should be avoided". Guleria et al. also reduced their urological complications by changing their technique from a non-stented (7.7%) to a double J stented (for a period of 6 weeks) ureteroneocystostomy (3.8%) [16]. Unfortunately, all these studies have a retrospective design and no prospective randomized controlled trials are available. Therefore, we suggest a new trial that will investigate whether single J or double J stenting is superior in reducing the number of urological complications.

We conclude that although stent placement increases postoperative hematuria and total length of hospital stay, it should be advocated during living donor kidney transplantation based on these preliminary data. Stent placement significantly reduced the number of PCN placements, urinary leakage and surgical re-interventions due to urological complications. Further research concerning the type of stent should be conducted.

References

1. Dols LF, Terkivatan T, Kok NF, et al. Use of stenting in living donor kidney transplantation: does it reduce vesicoureteral complications? *Transplant Proc.* 2011;43(5):1623-1626.
2. Miraglia R, Caruso S, Milazzo M, Salis P, Luca A, Gridelli B. Efficacy of interventional radiology procedures for the treatment of early ureteral complications after kidney transplantation. *Transplant Proc.* 2006;38(9):2919-2920.
3. Sarier M, Demir M, Duman I, Yuksel Y, Demirbas A. Evaluation of Ureteral Stent Colonization in Live-Donor Renal Transplant Recipients. *Transplant Proc.* 2017;49(3):415-419.
4. Veltman Y, Shields JM, Ciancio G, Bird VG. Percutaneous nephrolithotomy and cystolithalapaxy for a "forgotten" stent in a transplant kidney: case report and literature review. *Clin Transplant.* 2010;24(1):112-117.
5. Gregoir W. [the Surgical Treatment of Congenital Vesico-Ureteral Reflux] Le Traitement Chirurgical Du Reflux V'esico-Ur'et'eral Cong'enital. *Acta Chir Belg.* 1964;63:431-439.
6. Lich R, Jr., Howerton LW, Davis LA. Childhood urosepsis. *J Ky Med Assoc.* 1961;59:1177-1179.
7. Bassiri A, Amiransari B, Yazdani M, Sesavar Y, Gol S. Renal transplantation using ureteral stents. *Transplant Proc.* 1995;27(5):2593-2594.
8. Benoit G, Blanchet P, Eschwege P, Alexandre L, Bensadoun H, Charpentier B. Insertion of a double pigtail ureteral stent for the prevention of urological complications in renal transplantation: a prospective randomized study. *J Urol.* 1996;156(3):881-884.
9. Dominguez J, Clase CM, Mahalati K, et al. Is routine ureteric stenting needed in kidney transplantation? A randomized trial. *Transplantation.* 2000;70(4):597-601.
10. Kumar A, Kumar R, Bhandari M. Significance of routine JJ stenting in living related renal transplantation: a prospective randomised study. *Transplant Proc.* 1998;30(7):2995-2997.
11. Pleass HC, Clark KR, Rigg KM, et al. Urologic complications after renal transplantation: a prospective randomized trial comparing different techniques of ureteric anastomosis and the use of prophylactic ureteric stents. *Transplant Proc.* 1995;27(1):1091-1092.
12. Wilson CH, Bhatti AA, Rix DA, Manas DM. Routine intraoperative ureteric stenting for kidney transplant recipients. *Cochrane Database Syst Rev.* 2005(4):CD004925.
13. Slagt IK, Dor FJ, Tran TC, et al. A randomized controlled trial comparing intravesical to extravesical ureteroneocystostomy in living donor kidney transplantation recipients. *Kidney Int.* 2014;85(2):471-477.
14. Vogel T, Utech M, Schmidt F, et al. Double-J Versus External Ureteral Stents in Kidney Transplantation: A Retrospective Analysis. *Nephrourol Mon.* 2015;7(4):e27820.
15. Gomes G, Nunes P, Castelo D, et al. Ureteric stent in renal transplantation. *Transplant Proc.* 2013;45(3):1099-1101.
16. Guleria S, Chahal R, Madaan S, et al. Ureteric complications of renal transplantation: the impact of the double J stent and the anterior extravesical ureteroneocystostomy. *Transplant Proc.* 2005;37(2):1054-1056.

CHAPTER 3

Minimizing the number of urological complications after kidney transplantation: a comparative study of two types of external ureteral stents

L.S.S. Ooms[1], L.G. Spaans[1], M.G.H. Betjes[2], J.N.M. IJzermans[1], T. Terkivatan[1]

1. Department of Surgery, Erasmus University Medical Center, Rotterdam, The Netherlands
2. Department of Nephrology, Erasmus University Medical Center, Rotterdam, The Netherlands

Experimental and Clinical Transplantation, 2016 Apr;15(2):143-149

Abstract

The aim of this study was to evaluate the effects of 2 types of external ureteral stents on the number of urological complications after kidney transplant. Data were retrospectively collected from 366 consecutive transplants performed between January 2013 and January 2015 in our hospital, in which an external ureteral stent was placed during surgery and removed after 9 days. Urological complications were defined as urinary leakage or ureteral stenosis requiring percutaneous nephrostomy placement. A total of 197 patients received a straight stent with 2 larger side holes (type A; 8F "Covidien" tube, Covidien, Dublin, Ireland) and 169 patients received a single J stent with 7 smaller side holes (type B; 7F "Teleflex" single J stent; Teleflex Medical, Athlone, Ireland). We found a significantly higher number of percutaneous nephrostomy placements with type A stents, with 34 (17%) versus 16 (9%) in type B ($P = 0.030$). Reason for percutaneous nephrostomy placement, occurrence of stent dysfunction, and need for early removal (< 8 days) were equal in both groups ($P = 0.397$), whereas incidence of rejection and urinary tract infection were higher in type B stent group. Patient and graft survival did not differ between the groups. Use of the type B stent was associated with less urological complications compared with the type A stent.

Introduction

Kidney transplant is the best and most cost-effective treatment for patients with end-stage renal disease, improving both quantity and quality of life for recipients.[1] Urological complications, such as urinary leakage and ureteral strictures, can compromise graft function and are associated with patient morbidity, mortality, prolonged hospital stay, and reinterventions.[2,3] Complication rates due to failure of the ureteroneocystostomy are reported to be up to 30% and usually occur within the first 3 months after transplant.[4,5] Radiological or surgical reinterventions are often needed if urological complications do not dissolve spontaneously. A previously conducted randomized controlled trial showed that 20% of all kidney recipients required placement of a percutaneous nephrostomy (PCN) drain.[6] Moreover, 5% of this cohort needed ureteral reintervention, including balloon dilatation or surgical revision of the ureteroneocystostomy.[6]

Several factors are presumed to influence the number of urological complications after kidney transplant, including preemptive transplants, male sex of recipient and donor, and the presence of multiple renal arteries.[7,8] Furthermore, ureteric stenting in renal transplant is still debated. Some studies suggest that prophylactic ureteral stent insertion may reduce the risk of urological complications such as ureteral strictures and leakages.[4,9,10] However, concerns have been raised regarding potential stent-related complications, such as urinary tract infections (UTI), stent breakage or migration, reflux, stone formation, hematuria, and secondary ureter obstruction.[4,11,12] Some centers, including ours, have a prophylactic stenting policy; however, in most centers, surgeons base their choice on earlier experiences, training, and personal preferences. The Cochrane review from Wilson and associates debates which stent caliber and stent duration is best to avoid urological complications. Although the type of stent was mostly similar (double J stent was used in all but 1 study), the time until stent removal diverged from 7 days until 3 months and stent caliber varied from 5F to 7F between all studies.[4] To our knowledge, no studies have been published that compared the influence of different externalized ureteric stents on the number of urological complications in kidney transplant recipients.

In our center, we prefer the use of external stents over double J stents because of several advantages, such as the possibility of monitoring urine production and the simplicity of stent removal without a cystoscopy. Furthermore, we have no double J-related complications such as "the forgotten stent" or stent encrustation.[13,14] We have used 2 different types of external ureteral stents as standard care in the past years. As guidelines in literature are not equivocal, we conducted a database analysis to evaluate the outcomes of these 2 kinds of stents used during kidney transplant.

Methods

We included all patients who received a kidney transplant with an externalized stent from January 2013 to January 2015. We considered bilateral kidney transplants and pediatric kidney transplants as exclusion criteria. From January 2013 until January 2014, patients were treated with type A stents, and the following year until January 2015 patients were treated with type B stents. Type A stents refers to a 8F "Covidien" polyvinyl chloride tubes (Covidien, Dublin, Ireland) and type B stents refers to a 7F polyurethane "Teleflex" single J stent (Teleflex Medical, Athlone, Ireland) (Figures 1 and 2). Kidney donors were either deceased or living. Recipient characteristics, clinical information, and follow-up data were retrospectively obtained from electronic patient records. Data regarding graft function were limited to 6 months after transplant. Data regarding rejection episodes, PCN placement, and patient and graft survival were reviewed during complete follow-up (until July 2015). Graft failure was defined as patient's return to hemo- or peritoneal dialysis, if graft nephrectomy was performed, or if the patients received a new preemptive kidney transplant. This study received approval from our center's medical ethics committee.

Definitions

A UTI was defined as *an infection of the urinary tract with a positive bacterial culture of the urine sample for which treatment with antibiotic therapy was given*. Only UTIs within the first 3 months after surgery were considered. A urological complication was defined as *urinary leakage or ureteral stricture requiring PCN placement*; PCN placement is considered to be the first step in the treatment of urological complications. Percutaneous nephrostomy placement was indicated when postoperative ultrasonography revealed hydronephrosis in combination with a rising serum creatinine level or a perirenal urinoma indicating urine leakage, confirmed by ultrasonography or renal MAG-3 (radioisotope renography) scanning. Stents removed before day 8 were registered as dysfunctional.

Surgical procedure

If a kidney graft had multiple renal arteries, an arterial reconstruction was made. In the recipient, the renal vein was anastomosed to the external iliac vein and the renal artery to the external iliac artery. All patients underwent an extravesical Lich-Gregoir anastomosis of the ureter with the introduction of a suprapubic externalized stent. The stent was removed manually on postoperative day 9. A transurethral catheter in the bladder was left in situ until postoperative day 7. A wound drain was placed and removed after 1 or 2 days, depending on the amount of drain production.

Figure 1. Type A 8F Stent (Left) and Type B Single J 7F Stent (Right)

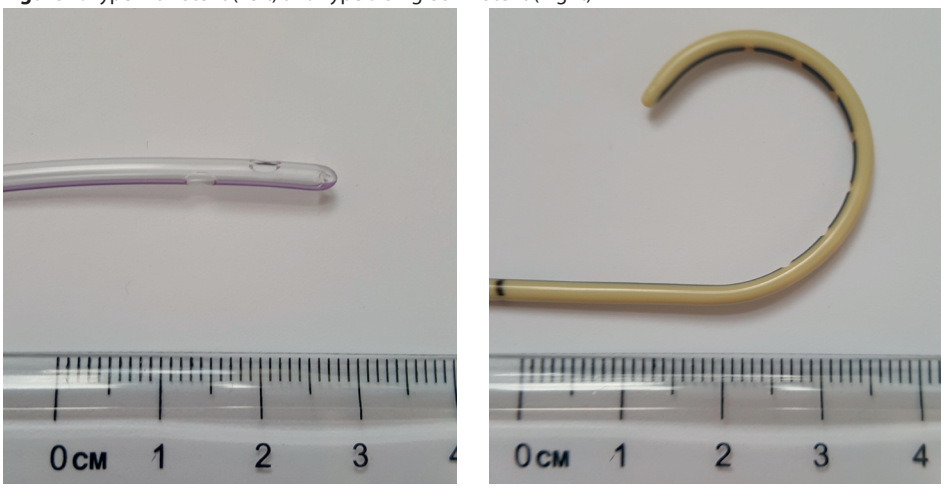
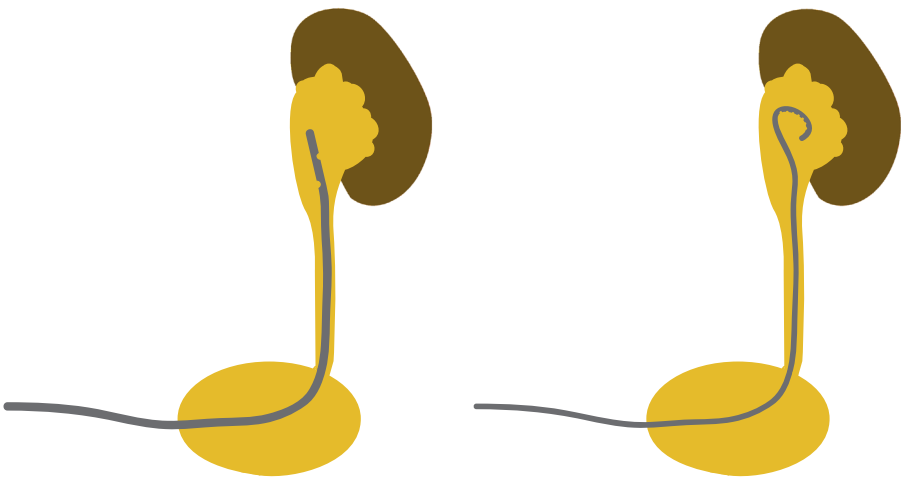


Figure 2. Type A 8F Stent (Left) and Type B Single J 7F Stent (Right)



Immunosuppressive regimen

Almost all patients received a similar immunosuppressive regimen. This included induction therapy with basiliximab (Simulect®, Novartis Pharmaceuticals, Basel, Switzerland) and maintenance therapy with tacrolimus (Prograft®, Astellas Pharma, Tokyo, Japan), mycophenolate mofetil (Cellcept®, Roche, Basel, Switzerland), and glucocorticoids. On indication, a conversion of aforementioned immunosuppressive medications was performed in individual patients, such as additional antithymocyte globulin induction therapy or belatacept **(**Nulojix®, Bristol Myers-Squibb, New York City, NY, USA) instead of tacrolimus.

Statistical analyses

All statistical analyses were performed with SPSS software (SPSS: An IBM Company, version 21.0, IBM Corporation, Armonk, NY, USA). Categorical variables are presented as numbers with percentages and analyzed using chi-squared test. Continuous variables with normal distribution are presented as means with standard deviation and analyzed using the independent *t* test. Skewed distributed variables are presented as median (range) and analyzed using the Mann-Whitney *U* test. Graft survival was analyzed using the Kaplan-Meier method, and a log-rank test was conducted to compare survival curves. Two-tailed *P* values of < 0.05 were considered statistically significant.

Results

Baseline characteristics

Between January 2013 and January 2015, 370 patients received kidney transplants with external stenting at our hospital. Four patients were excluded from our study: 3 patients because of bilateral kidney transplant and 1 because of a pediatric kidney graft. Our cohort consisted of 197/366 patients (54%) receiving type A stenting and 169/366 patients (46%) receiving type B stenting. Our patient group comprised 230 male patients and 136 female patients. The mean age of recipients was 55 ± 15 years. Demographic details of kidney recipients, kidney grafts, and transplants are presented in Table 1. There were no significant differences between both groups, except for the length of follow-up.

Urological complications

In our patient group, 50/366 patients (14%) required PCN placement, in which 37 patients (10%) underwent a PCN placement due to hydronephrosis and 13 patients (4%) due to urinary leakage (Table 2).

The incidence of PCN placement was significantly higher with type A stenting (17% vs 9%; $P = 0.030$). Median time between transplant and PCN placement was 17 days (range, 2-190 d) and did not differ significantly between groups; reason for PCN placement also did not differ. Urinary tract infections within the first 3 months after transplant occurred more often in patients who received type B stenting (37% vs 26%; $P = 0.034$). Three patients with type A stenting and 2 patients with type B stenting underwent balloon dilatation of the strictured segment of the ureter. Open ureter revision was performed in 7 patients with PCN in type A stenting, with 5 due to hydronephrosis and 2 due to persistent urine leakage. Only 1 patient who had type B stenting underwent surgical ureter revision. This patient was clinically suspected to have an anastomotic leak and was not treated with PCN but underwent immediate ureter revision.

Table 1. Baseline Characteristics

	Total Group (n = 366)	Ureteric Type A Stent (n = 197)	Ureteric Type B Stent (n = 169)	P-value
Recipient age (y), mean ± SD	55 ± 15	55 ± 14	56 ± 15	0.378
Recipient sex				
Male N (%)	230 (63)	119 (60)	111 (66)	0.298
Female N (%)	136 (37)	78 (40)	58 (34)	
Type of donor				
Deceased N (%)	128 (35)	66 (33.5)	62 (37)	0.524
Living N (%)	238 (65)	131 (66.5)	107 (63)	
Multiple transplants N (%)	69 (19)	43 (22)	26 (15)	0.116
Preemptive transplant N (%)	132 (36)	76 (39)	56 (33)	0.280
Body mass index (kg/m^2), mean ± SD	27 ± 5	26 ± 5	27 ± 5	0.848
Multiple arteries N (%)	94 (26)	46 (23)	48 (28)	0.270
Implantation side				
Left N (%)	74 (20)	41 (21)	33 (20)	0.760
Right N (%)	292 (80)	156 (79)	136 (80)	
Operating time (min), mean ± SD	141 ± 40	140 ± 39	143 ± 41	0.546
Warm ischemic time (min), median (range)	20 (10-149)	20 (10-149)	20 (11-43)	0.839
Cold ischemic time (min), median (range)	164 (95-1440)	162 (95-1410)	170.5 (100-1440)	0.569
Blood loss during surgery (mL), median (range)	200 (0-18 000)	200 (0-3600)	200 (0-18 000)	0.274
Hospital admission (d), median (range)	14 (9-142)	14 (9-123)	14 (9-142)	0.332
Stent duration (d), median (range)	9 (1-12)	9 (1-12)	9 (1-12)	0.227
Follow- up duration (mo), median (range)	14 (0-34)	20 (0-34)	10 (0-17)	**<0.001**

SD, standard deviation; Y, years; Min, minutes; d, days; mo, months

In Table 3, the baseline characteristics of the patients who received a PCN are documented. As shown, there were significantly more patients who were transplanted in the left fossa and more patients who received a retransplant in the patient group with type A stent who received a PCN.

Stent-related complications

Ureteric stents were removed after a median of 9 days (range, 1-12 d) in patients with type A and type B stents (Table 2). Stents were equally often removed prematurely (< 8 d) in both groups (17% vs 13%; $P = 0.261$). No significant differences were found between the 2 groups regarding reason for early stent removal (hydronephrosis, obstruction, migration, spontaneously, early graft nephrectomy or other) ($P = 0.397$).

Overall complications

Graft rejection occurred significantly more often in patients who received the type B stent than in patients who received the type A stent (37% vs. 22%; $P = 0.002$) (Table 2). Surgical reinterventions regarding the transplant were performed in 33 patients (including the previously mentioned 8 patients who underwent ureter revision) and occurred equally often in both groups (6% vs 3%; $P = 0.055$). Reasons for surgical reinterventions in the type A stenting group were graft nephrectomy, postoperative bleeding, venous thrombectomy, abdominal wall abscess, and retransplant. Reasons for surgical reinterventions in the type B stenting group were graft nephrectomy, postoperative bleeding, suspected necrotizing fasciitis, fascial dehiscence, abdominal wall hematoma, and incisional hernia. The incidence of surgical procedures not related to transplant, performed in the first year after transplant, was not significantly different for both groups (11% vs 6%; $P = 0.116$).

Table 2. Urinary, Overall, and Stent-Related Complications

	Total Group (n = 366)	**Ureteric Type A Stent (n = 197)**	**Ureteric Type B Stent (n = 169)**	**P-value**
Urinary complications				
PCN placement N (%)	50 (14)	34 (17)	16 (9)	**0.030**
Time to PCN placement (d), median (range)	17 (2-190)	15.5 (4-159)	33 (2-190)	0.588
Reason for PCN placement				
Urinary leakage N (%)	13 (4)	10 (5)	3 (2)	0.089
Hydronephrosis N (%)	37 (10)	24 (12)	13 (8)	0.155
Radiological balloon dilatation N (%)	5 (1)	3 (2)	2 (1)	0.780
Ureter reconstruction/reimplant N (%)	8 (2)	7 (4)	1 (1)	0.053
Urinary tract infection N (%)	114 (31)	52 (26)	62 (37)	**0.034**
Stent-related complications				
Early stent removal N (%)	56 (15)	34 (17)	22 (13)	0.261
Reason for early stent removal (< 8 d)				
Spontaneously N (%)	15 (4)	9 (5)	6 (4)	
Hydronephrosis N (%)	4 (1)	2 (1)	2 (1)	
Obstruction N (%)	18 (5)	13 (7)	5 (3)	
Migration N (%)	4 (1)	2 (1)	2 (1)	
Early transplantectomy N (%)	3 (1)	3 (2)	0 (0)	
Other N (%)	12 (3)	5 (3)	7 (4)	
Overall complications				
Wound infection ≤ 3 mo N (%)	21 (6)	12 (6)	9 (5)	0.753
Surgical reinterventions regarding transplant N (%)	33 (9)	23 (6)	10 (3)	0.055
Other surgical procedures ≤ 12 mo N (%)	62 (17)	39 (11)	23 (6)	0.116
Rejection therapy N (%)	105 (29)	43 (22)	62 (37)	**0.002**
Time to rejection therapy (mo), median (range)	0 (0-16)	0 (0-16)	0 (0-10)	0.490

Table 3. Baseline Characteristics of Patients With Percutaneous Nephrostomy

	Total Group (n = 50)	Ureteric Type A Stent (n = 34)	Ureteric Type B Stent (n = 16)	P-value
Recipient age, mean ± SD	55 ± 15	55.5 ± 14	57 ± 16	0.700
Recipient sex				
Male N (%)	30 (60)	20 (59)	10 (63)	0.804
Female N (%)	20 (40)	14 (41)	6 (37)	
Type of donor				
Deceased N (%)	17 (34)	9 (27)	8 (50)	0.101
Living N (%)	33 (66)	25 (73)	8 (50)	
Multiple transplants N (%)	7 (14)	7 (21)	0 (0)	0.050
Preemptive transplant N (%)	14 (28)	10 (29)	4 (25)	0.746
Body mass index (kg/m^2), mean ± SD	27 ± 5	27 ± 5	27 ± 4	0.961
Multiple arteries N (%)	11 (22)	10 (29)	1 (6)	0.065
Implant side				
Left N (%)	8 (16)	8 (23)	0 (0)	**0.034**
Right N (%)	42 (84)	26 (77)	16 (100)	
Operating time (min), mean ± SD	138 ± 35	136 ± 31	142 ± 42	0.606
Warm ischemic time (min), median (range)	19 (13-43)	19 (13-32)	19 (13-43)	0.676
Cold ischemic time (min), median (range)	159 (104-1440)	153 (110-1263)	215.5 (104-1440)	0.149
Blood loss during surgery (mL), median (range)	250 (0-3100)	200 (0-1600)	325 (0-3100)	0.500
Hospital admission (d), median (range)	16 (10-123)	17 (11-123)	15.5 (10-29)	0.453
Stent duration (d), median (range)	9 (1-10)	8 (1-9)	9 (6-10)	0.191
Follow- up duration (mo), median (range)	16.5 (2-27)	19.5 (3-27)	9 (0-15)	**<0.001**

SD, standard deviation; Y, years; Min, minutes; d, days; mo, months

Graft function and survival

Glomerular filtration rate and serum creatinine levels were not significantly different between the groups, except for month 6, which showed higher serum creatinine levels in the type B stenting group (median 135 vs 126 µmol/L; $P = 0.030$) (Table 4). As shown by the Kaplan-Meier curve, kidney graft survival did not differ significantly between the groups ($P = 0.781$) (Figure 3). The 3-month, 6-month, and 1-year graft survival rates in the type A stenting group were 97%, 96%, and 95%, with corresponding rates in the type B stenting group of 98%, 97%, and 95% ($P = 0.781$). The 3-month, 6-month, and 1-year patient survival rates in the type A stenting group were 99%, 98%, and 98%, with corresponding rates in the type B stenting group of 99%, 98%, and 95% ($P = 0.093$).

Table 4. Graft Function

	Total Group (n = 366)	Ureteric Type A Stent (n = 197)	Ureteric Type B Stent (n = 169)	P-value
GFR after transplant (ml/min), mean ± SD				
Day 1	20 ± 14	20 ± 14	20 ± 14	0.963
Day 2	30 ± 21	30 ± 21	30 ± 22	0.721
Day 3	32 ± 22	32 ± 22	33 ± 22	0.914
Day 7	35 ± 21	35 ± 20	36 ± 22	0.421
Month 1	46 ± 16	47 ± 16	45 ± 17	0.352
Month 3	47 ± 15	47 ± 15	46 ± 16	0.330
Month 6	48 ± 16	49 ± 16	46 ± 16	0.079
Serum creatinine after transplant(μmol/L) median (range)				
Day 1	319.5 (67-1810)	307 (67-1810)	334 (81-1745)	0.858
Day 2	205 (54-1619)	203 (54-1619)	219 (68-1462)	0.712
Day 3	186 (51-1765)	183.5 (51-1765)	188 (64-1327)	0.888
Day 7	166 (50-1213)	166.5 (58-1091)	163 (50-1213)	0.728
Month 1	132 (59-652)	129 (64-652)	135 (59-562)	0.125
Month 3	132 (64-419)	131 (64-419)	134 (64-272)	0.102
Month 6	130 (47-301)	126 (47-293)	135 (61-301)	**0.030**

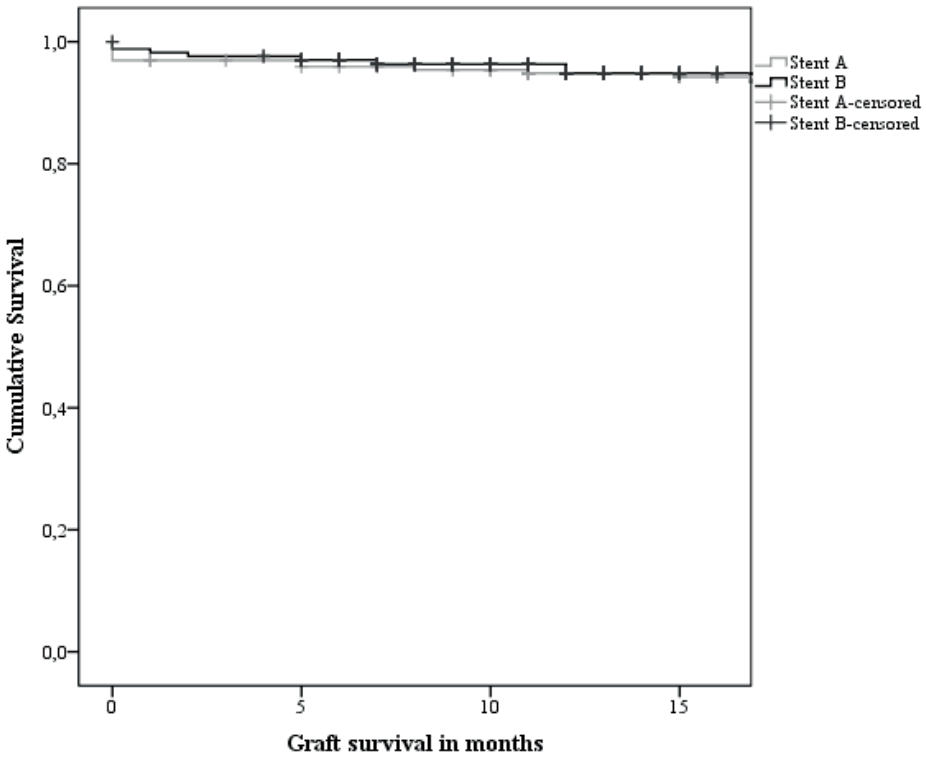
GFR, glomerular filtration rate; SD, standard deviation

Discussion

The aim of this retrospective study was to evaluate the influence of 2 different types of externalized ureteric stents (type A was an 8F polyvinyl chloride tube and type B was a 7F polyurethane single J stent) on the incidence of urological complications. We found a significantly higher incidence of PCN placements in patients who received the type A stent and a higher incidence of rejection and UTI in patients who received the type B stent. There were no significant differences in the reason for PCN placement or for patient or graft survival between both groups.

An explanation for the higher number of PCN placements in the type A stent group may be that this stent has fewer drainage holes and may therefore obstruct relatively easier. Obstructed stents can potentially cause a hydronephrosis of the kidney graft, necessitating PCN placement. However, as the median time between transplant and PCN placement was 17 days, stents were mostly already removed at the time of PCN placement. Furthermore, we found no differences between the groups regarding early stent removal due to stent obstruction. Another likely explanation for the higher number of PCN placements with type A stents could be its wider 8F caliber. This could potentially cause edema of the ureter after stent removal, which could explain several temporally

Figure 3. Kaplan-Meier Graft Survival Curve



PCN placements due to passing hydronephrosis without demanding an additional invention such as surgical reconstruction or balloon dilatation. It is possible that this larger caliber stent also caused transient ischemia of the ureter due to higher pressure on the ureteral wall, resulting in more ureteral stenosis requiring reinterventions. Although the number of surgical and balloon reinterventions was not significantly higher in type A stenting ($P = 0.053$), a trend can be detected in favor of type B stenting.

Urinary tract infections are common complications after kidney transplant with a reported incidence of 26% to 98%.[15-17] Although lower UTIs are often thought to be of a mild nature, some studies suggest that UTIs can contribute to the development of acute allograft rejection and possibly even compromise graft function in the short term.[18,19] The incidence of UTIs within the first 3 months after transplant in our study was higher in the type B stent group. This could not be explained by the type of stent material, as a study of Lopez and associates found that polyurethane catheters (stent type B) had lower *Staphylococcus aureus*, *Staphylococcus epidermidis*, *Escherichia coli*, and *Pseudomonas aeruginosa* adherence compared with polyvinyl chloride catheters (our type A stent).[20]

Another explanation for the higher number of UTIs could be the higher rejection rate shown in the group B stent patients. Acute rejection episodes are treated with high-dose immunosuppressive therapy, leading to increased risk of infections.[21] Incidences of graft rejection might be increased during the past few years because of shifting boundaries for donor acceptance and because increasingly more ABO-incompatible transplants are being performed in our center.[22] A causal association between stent material and rejection episodes seems highly unlikely.

One important limitation of this study was its retrospective design. Another drawback was the limited follow-up period, especially in patients who received the type B stent. However, the protective effects of the stent are expected to be the most significant during the first weeks after transplant.

To our knowledge, no other study has compared 2 different types of externalized ureteral stents used in kidney transplant. There are some studies available that have compared double J versus external ureteral stents. Vogel and associates retrospectively compared these 2 stents and concluded that the external stent had significantly more urinary leakage (14% vs 0%) and more hospitalization days for patients without immunological complications (13 vs 11 days).[23] Gomes and associates also found more urological complications with external stenting compared with double J stenting (17% vs 5%); however, this was also a retrospective study.[24] Another way of stenting the ureteroneocystostomy is by using an internal stent tied to a Foley catheter. This way, the stent is removed simultaneous during Foley catheter removal. This technique was described by Taghizadeh-Afshari and associates in 2014. They randomized 90 patients into 2 study groups, with 1 group having the stent attached to the Foley catheter and the group having these separated. They reported a urinary leakage rate of 3.3%, with all of these occurring in the separated stent group. Furthermore, they report 0% stent crustation in the attached group. However, a drawback of their study was the small sample size.[25] More prospective research is necessary to compare other ureteral stents types and to clarify which type of stent establishes the least number of urological complications and best renal outcome.

In conclusion, we found a significantly higher PCN placement rate in patients who received the type A stent versus that shown in patients who received the type B stent. The type B stent was associated with more UTIs and higher rejection rate compared with the type A stent, without influencing patient and graft survival.

References

1. Hornberger JC, Best JH, Garrison LP, Jr. Cost-effectiveness of repeat medical procedures: kidney transplantation as an example. *Med Decis Making.* 1997;17(4):363-372.
2. Rigg KM, Proud G, Taylor RM. Urological complications following renal transplantation. A study of 1016 consecutive transplants from a single centre. *Transpl Int.* 1994;7(2):120-126.
3. Thomalla JV, Leapman SB, Filo RS. The use of internalised ureteric stents in renal transplant recipients. *Br J Urol.* 1990;66(4):363-368.
4. Wilson CH, Rix DA, Manas DM. Routine intraoperative ureteric stenting for kidney transplant recipients. *Cochrane Database Syst Rev.* 2013;6:CD004925. doi: 10.1002/14651858.CD004925.pub3.
5. Zavos G, Pappas P, Karatzas T, et al. Urological complications: analysis and management of 1525 consecutive renal transplantations. *Transplant Proc.* 2008;40(5):1386-1390. doi: 10.1016/j.transproceed.2008.03.103.
6. Slagt IK, Dor FJ, Tran TC, et al. A randomized controlled trial comparing intravesical to extravesical ureteroneocystostomy in living donor kidney transplantation recipients. *Kidney Int.* 2014;85(2):471-477. doi: 10.1038/ki.2013.464.
7. Neri F, Tsivian M, Coccolini F, et al. Urological complications after kidney transplantation: experience of more than 1000 transplantations. *Transplant Proc.* 2009;41(4):1224-1226. doi: 10.1016/j.transproceed.2009.03.044.
8. Slagt IKB, IJzermans JNM, Visser LJ, Weimar W, Roodnat JI, Terkivatan T. Independent risk factors for urological complications after deceased donor kidney transplantation. *PLoS One.* 2014;9(3). doi: 10.1371/journal.pone.0091211.
9. Benoit G, Blanchet P, Eschwege P, Alexandre L, Bensadoun H, Charpentier B. Insertion of a double pigtail ureteral stent for the prevention of urological complications in renal transplantation: a prospective randomized study. *J Urol.* 1996;156(3):881-884.
10. Mangus RS, Haag BW. Stented versus nonstented extravesical ureteroneocystostomy in renal transplantation: a metaanalysis. *Am J Transplant.* 2004;4(11):1889-1896.
11. Osman Y, Ali-El-Dein B, Shokeir AA, Kamal M, El-Din AB. Routine insertion of ureteral stent in live-donor renal transplantation: is it worthwhile? *Urology.* 2005;65(5):867-871. doi: 10.1016/j.urology.2004.11.050.
12. Ranganathan M, Akbar M, Ilham MA, Chavez R, Kumar N, Asderakis A. Infective complications associated with ureteral stents in renal transplant recipients. *Transplant Proc.* 2009;41(1):162-164. doi: 10.1016/j.transproceed.2008.10.022.
13. Karabicak M, Ipekci T, Isoglu CS, et al. A rare complication after renal transplantation: Forgotten stent. *Arch Ital Urol Androl.* 2015;87(2):175-176. doi: 10.4081/aiua.2015.2.175.
14. Veltman Y, Shields JM, Ciancio G, Bird VG. Percutaneous nephrolithotomy and cystolithalapaxy for a "forgotten" stent in a transplant kidney: case report and literature review. *Clin Transplant.* 2010;24(1):112-117. doi: 10.1111/j.1399-0012.2009.01133.x.
15. Takai K, Aoki A, Suga A, et al. Urinary tract infections following renal transplantation. *Transpl P.* 1998;30(7):3140-3141.
16. Chuang P, Parikh CR, Langone A. Urinary tract infections after renal transplantation: a retrospective review at two US transplant centers. *Clin Transplant.* 2005;19(2):230-235. doi: 10.1111/j.1399-0012.2005.00327.x.
17. Martinezmarcos F, Cisneros J, Gentil M, et al. Prospective study of renal-transplant infections in 50 consecutive patients. *Eur J Clin Microbiol.* 1994;13(12):1023-1028.

18. Rice JC, Peng T, Kuo YF, et al. Renal allograft injury is associated with urinary tract infection caused by *Escherichia coli* bearing adherence factors. *Am J Transplant.* 2006;6(10):2375-2383. doi: 10.1111/j.1600-6143.2006.01471.x.
19. Pelle G, Vimont S, Levy PP, et al. Acute pyelonephritis represents a risk factor impairing long-term kidney graft function. *Am J Transplant.* 2007;7(4):899-907.
20. Lopez-Lopez G, Pascual A, Perea EJ. Effect of plastic catheter material on bacterial adherence and viability. *J Med Microbiol.* 1991;34(6):349-353.
21. Schmaldienst S, Dittrich E, Horl WH. Urinary tract infections after renal transplantation. *Current Opinion in Urology.* 2002;12(2):125-130.
22. de Weerd AE, van Agteren M, Ijzermans JN, Weimar W, Betjes MG. Post-Transplantation immunoadsorption can be withheld in ABO-incompatible kidney transplant recipients. *Ther Apher Dial.* 2015;19(5):513-517. doi: 10.1111/1744-9987.
23. Vogel T, Utech M, Schmidt F, et al. Double-J versus external ureteral stents in kidney transplantation: a retrospective analysis. *Nephrourol Mon.* 2015;7(4):e27820. doi: 10.5812/numonthly.27820.
24. Gomes G, Nunes P, Castelo D, et al. Ureteric stent in renal transplantation. *Transplant Proc.* 2013;45(3):1099-1101. doi: 10.1016/j.transproceed.2013.02.086.
25. Taghizadeh-Afshari A, Alizadeh M, Farshid S. Comparison of complications and short term results of conventional technique versus new technique during graft ureteral stent insertion in bari technique at Emam Khomeini Hospital, Urmia. *Glob J Health Sci.* 2014;6(7 Spec No):31-37. doi: 10.5539/gjhs.v6n7p31.

CHAPTER 4

Ureteral length in living donor kidney transplantation: does size matter?

L.S.S. Ooms[1], I.K.B Slagt[1], F.J.M.F. Dor[1], T.C.K. Tran[1], H.J.A.N. Kimenai[1], J.N.M. Ijzermans[1], M.G.H. Betjes[2], T. Terkivatan[1]

1. Department of Surgery, Erasmus University Medical Center, Rotterdam, The Netherlands
2. Department of Nephrology, Erasmus University Medical Center, Rotterdam, The Netherlands

Transplant International, 2015 Nov;28(11):1326-31

Abstract

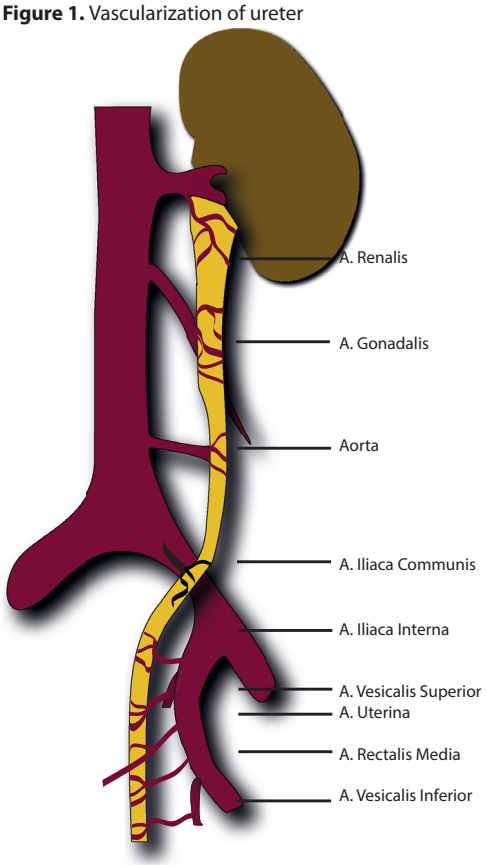
The aim of this study is to evaluate the role of ureteral length on urological complications. Data were retrospective collected from the INEX-trial database, a RCT to compare the intravesical to the extravesical ureteroneocystostomy. Ureteral length was measured in 198 recipients and used to divide recipients into 3 categories based on interquartile ranges: Short (≤8.5cm), medium (8.6-10.9cm) and long ureters (≥11cm). Urological complications were defined as the number of percutaneous nephrostomy placements (PCN). Fifty recipients fell into the short, 98 into the medium and 50 recipients into the long ureter category. Median follow-up was 26 (range 2-45) months. There was no significant difference in number of PCN placements between the categories. There were 9 (18%) PCN placement in the short ureter category, 21 (20%) in medium ureter category and 10 (21%) PCN placements in the long ureter category, p=0.886. Risk factor analysis for gender, arterial multiplicity and type of ureteroneocystostomy showed no differences in PCN placements between the three ureteral length categories. We conclude that ureteral length alone does not seem to influence the number of urological complications.

Introduction

Reducing ureter-related complications remains one of the challenges in kidney transplantation. Major urological complications, such as urinary leakage and ureter strictures, may lead to increased morbidity and prolonged hospital stay (1, 2) and are reported with an incidence of overall urological complications has been reported between 4.8-20% (3, 4). Multiple factors are presumed to contribute to the development of urological complications. The influence of donor and recipient factors are being discussed in literature and include: male gender of recipient and donor, arterial multiplicity and pre-emptive transplantation as possible risk factors for urological complication (5).

Some other factors that may contribute to the development of urological complications after kidney transplantation are graft related, such as ureteral vascularization and arterial multiplicity (6). Diminished blood supply of the ureter can cause ischemia of the most distal part of the ureter, resulting in urinary leakage or ureter strictures. The native vascularization of the ureter is by segmental arteries derived from the renal, vesicle, gonadal, common iliac or internal iliac vessels or directly from the abdominal aorta (Figure 1). During living donor nephrectomy most of these segmental branches are dissected, resulting in the renal artery as the main blood supply of the ureter. Therefore, it is assumed that a shorter ureteral length is accommodated with better vascularization and may possibly cause less urological complications.

Figure 1. Vascularization of ureter



Because of the limited knowledge about the influence of ureteral length on urological complications after kidney transplantation, we have conducted this study using the available data of the recently published randomized controlled INEX-trail (7).

Methods

Study population and data selection

Between October 2010 and December 2012 a randomized controlled trial, referred to as the INEX-study, was conducted in our center (7). In this study, 200 consecutive recipients of a living donor kidney transplant were randomized to either an intravesical or extravesical ureteroneocystostomy. Exclusion criteria were age <18years, a double ureter system of the donor kidney, robot-assisted donor nephrectomy using the DaVinci Surgical System or an absent native bladder of the recipient. During this trial ureteral length was measured and documented prospectively in all kidney transplant recipients.

Baseline characteristics included; recipient gender, age, body mass index (BMI), warm and cold ischemia time, duration of operation, number of donor renal arteries and median follow-up in months. Total ureteral length was measured intra-operatively from the center of the pyelum to the most distal part of the ureter. After the vascular anastomoses had been performed, the ureter was prepared for the ureteroneocystostomy. The kidney was placed in its preferred position before cutting the excess length of the ureter. The length of a ureter is ideal when a tension free anastomosis can be made and the risk of ureteral rotation or kinking is minimalized. The length of the removed segment was measured and then subtracted from the total ureteral length, representing the remaining ureteral length in the recipient for this study. Recipients were divided into 3 categories based on the interquartile ranges of ureteral length. Patients with a ureteral length at or below the 25th percentile were placed in the lowest category (short ureter category), the ureteral lengths above the 75th percentile in the highest category (long ureter category) and the middle 50 percent in the moderate category (medium ureter category).

Percutaneous nephrostomy (PCN) placement during complete follow-up was used as a primary outcome for urological complications, since PCN placement is considered to be the initial treatment for major urological complications, like urinary leakage or ureteral stenosis. The reason for PCN placement and the consecutive treatment were documented. Urinary leakage, (detected by a MAG-3 scan or proven by chemistry samples in case of extensive fluid production of the wound or by the drain) or a rise in serum creatinine level combined a hydronephrosis on ultrasound, indicated PCN placement.

Risk factor analysis

A risk factor analysis was performed to determine the relationship between the numbers of PCN placements in the three ureteral length categories by analysing each potential risk factor separately. Based on available literature, we selected: recipient gender, arte-

rial multiplicity of the kidney graft and type of ureteroneocystostomy as potential risk factors (5, 8).

Surgical technique in the recipient

The extraperitoneal approach in the iliac fossa was performed in all recipients. All kidney grafts with multiple arteries had an arterial reconstruction prior to transplantation. This was either side to end or side to side on the main renal artery. After the (end-to-side) vascular anastomoses on the external iliac vessels, a consultant transplant surgeon performed either an intravesical anastomosis described by Politano-Leadbetter (9) or an extravesical anastomosis described by Lich-Gregoir (10, 11) as determined by randomization to create continuity of the urinary tract. A ureterovesical 8- French stent was used as part of our standard care and was externalized suprapubically. The stent was removed 9 days postoperatively. An urinary bladder catheter was placed and removed after 7 days.

Immunosuppressive treatment

Immunosuppressive treatment consisted of basiliximab intravenous on the day of surgery and day 4 after transplantation. Postoperative immunosuppression consisted of tacrolimus, mycophenolate mofetil and prednisolone. The prednisolone was tapered off to be discontinued at 4 months after transplantation.

Statistical analysis

Categorical variables were presented as numbers (percentage). Continuous variables were presented as means with standard deviation if normally distributed or as median with range if not normally distributed. Continuous variables were analysed using the one-way ANOVA or Kruskal-Wallis test. Categorical variables were analysed using Chi-square test. Risk factor analysis was performed using logistic regression with PCN as outcome and the interaction of ureteral length categories and gender, type of ureteroneocystostomy and arterial multiplicity as predictors. All analyses were conducted using IBM SPSS Statistics for Windows (version 21.0. Armonk, NY: IBM Corp, USA). A p-value of <0.05 (two-sided) will be considered statistically significant.

Results

Baseline characteristics

Between October 2010 and December 2012, a total of 200 recipients were included in the INEX trial (7). Ureteral length was measured in 198 recipients. Mean ureteral length of all recipients was 9.6cm ± 1.6cm. Recipients were divided into three different catego-

ries. Fifty recipients were allocated to the short ureter category (≤8.5cm), with a mean ureteral length of 7.5cm ±0.9cm. Nighty-eight recipients were allocated to the medium ureter category (8.6cm-10.9cm), mean ureteral length was 9.7cm ±0.6cm and 50 recipients were allocated to the long ureter category (≥11cm), mean ureteral length was 11.7cm ±0.6cm. All ureters were shortened during surgery; the removed segment size had a mean of 4.7cm ± 2.1cm. Table 1 provides an overview of baseline characteristics of the three categories. No significant differences were found between recipient gender and age, BMI, ischemia time, duration of operation or follow-up in months. The median follow-up of all recipients was 26 (2-45) months.

Table 1. Baseline characteristics

Variable	Short ureter (n=50)	Medium ureter (n=98)	Long ureter (n=50)	P-value
Recipient age in years mean ± SD	52 ± 14	55 ± 13	55 ± 14	0.514
Recipients gender				
- Male N (%)	29 (58)	66 (67)	34 (68)	0.469
- Female N (%)	21 (42)	32 (33)	16 (32)	
Recipients BMI mean ± SD	26 ± 5	26 ± 5	27 ± 4	0.583
Warm ischemia in minutes mean ± SD	26 ± 7	26 ± 6	27 ± 14	0.498
Cold ischemia in minutes mean ± SD	147 ± 25	150 ± 29	149 ± 32	0.773
Duration operation in minutes mean ± SD	131 ± 25	133 ± 29	135 ± 31	0.808
Follow-up in months median (range)	29 (3-44)	25.5 (2-45)	25 (11-44)	0.235
Ureteral length in cm mean ± SD	7.5 ± 0.9	9.7 ± 0.6	11.7 ± 0.6	**<0.001**

SD, standard deviation; M, Male; F, Female; BMI; body mass index

Urological outcome

There was no significant difference in the number of PCN placements between the three categories (Table 2 and Figure 2).

In the short ureter category (≤8.5cm), 9 recipients (18%) were treated with a PCN. Eight recipients received a PCN due to hydronephrosis, and 1 recipient had urinary leakage. Median time between transplantation and PCN placement was 9 days (range 3-182 days). The recipient with urinary leakage recovered from the leakage without any other intervention. However, this recipient developed a ureter stricture one year after transplantation for which a ureter reconstruction was performed. Of the 8 recipients with a PCN placement due to hydronephrosis, one had immediately surgical ureter reconstruction and another recipient underwent an unsuccessful percutaneous balloon dilatation of a ureter stricture followed by surgical ureter reconstruction. In 6 recipients, the hydronephrosis resolved without any other intervention (Table 2 and Figure 2).

Table 2. Urological complications

Variable	Short ureter (n=50)	Medium ureter (n=98)	Long ureter (n=50)	P-value
PCN N (%)	9 (18)	21 (21)	10 (20)	0.886
Days between KT-PCN median (range)	9 (3-182)	12 (2-86)	7 (3-29)	0.367
Reason PCN	**N=9**	**N=21**	**N=10**	
- Hydronephrosis N (%)	8 (89)	17 (81)	8 (80)	0.847
- Urinary leakage N (%)	1 (11)	4 (19)	2 (20)	
Treatment PCN	**N=9**	**N=21**	**N=10**	
- No N (%)	6 (67)	14 (67)	9 (90)	0.493
- Balloon dilatation N (%)	1 (failed)	2 (9)	1 (10)	
- Ureteral revision N (%)	3 (33)	4 (19)	-	
- Nephrolithotomy N (%)	-	1 (5)	-	

KT, Kidney transplantation; PCN, percutaneous nephrostomy

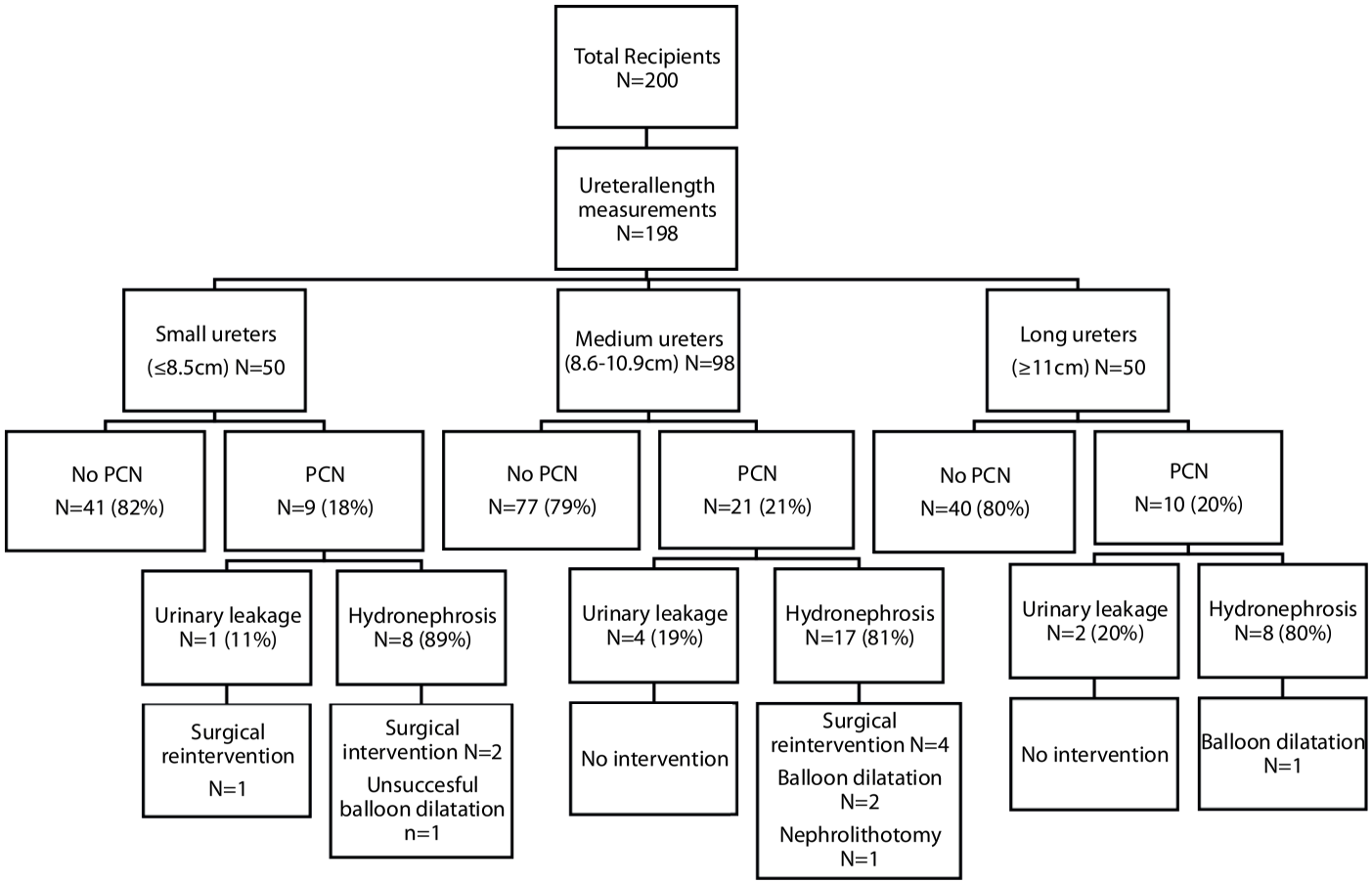
In the medium ureter category (8.6-10.9cm), 21 recipients (21%) had a PCN placement. In 17 recipients (81%) it was because of hydronephrosis and in 4 recipients (19%) due to urinary leakage. Median time between transplantation and PCN placement was 12 days (range 2-86 days). All 4 recipients with urinary leakage recovered without any other intervention. Of the 17 recipients with PCN placement due to hydronephrosis, 4 recipients underwent surgical re-intervention because of a ureter stricture, 2 underwent successful percutaneous balloon dilatation and in 10 recipients, the hydronephrosis resolved without any other intervention. In 1 recipient, the hydronephrosis was due to obstruction due to nephrolithiasis in the kidney graft 9 months after transplantation. This recipient underwent percutaneous nephrolithotomy and the PCN could be removed successfully afterwards (Table 2 and figure 2).

In the long ureter category (≥11cm) 10 recipients (20%) were treated with a PCN. Eight recipients had hydronephrosis (80%) and 2 recipients (20%) urinary leakage. Median time between transplantation and PCN placement was 7 days (range 3-29 days). There was no need for any re-intervention for the recipients with urinary leakage. In 8 recipients with a hydronephrosis, one recipient with a ureter stricture underwent successful percutaneous balloon dilatation. In the other 7 recipients, hydronephrosis resolved without additional intervention (Table 2 and Figure 2).

Risk factor analysis

In total 31/129 (24%) males and 9/69 (13%) females received PCN placement. Thirty-six out of 198 patients had arterial multiplicity of the kidney graft of whom 9/36 (25%) received a PCN. This group contained 19/36 kidneys with a lower pole artery, of whom 6/19 (32%) received a PCN and 17/36 kidneys with an additional (non-lower pole) artery,

Figure 2. Flow chart



of whom 3/17 (18%) received a PCN. Furthermore, in 20/100 (20%) patients with an extravesical ureteroneocystostomy a PCN was placed and 20/98 (20%) patients with an intravesical anastomosis. Risk factor analysis was performed using logistic regression with PCN as outcome and the interaction of ureteral length categories and gender, type of ureteroneocystostomy and arterial multiplicity as predictors. The interaction between gender and ureteral length category was not significant (p=0.355), neither was the interaction for arterial multiplicity (p=0.152), nor the interaction for the type of ureteroneocystostomy (intra- vs extravesical)(p=0.239). Therefore, we cannot conclude differential effects of the risk factors in the three categories.

Discussion

Based on the available anatomical knowledge of the ureteral vascularization, it is presumed that a shorter ureteral length is preferable to a longer ureter in kidney transplantation. However, in this study, we found that ureteral length alone does not seem to contribute to the number of urological complications. We performed a risk factor analysis for recipient gender, arterial multiplicity and for type of ureteroneocystostomy. There were no differential effects of these risk factors in the three ureteral length categories.

In a study by Ali-Asgari et al. the complication rate, long term survival and hospitalization days were not significantly different between ureters less or more than 5,5cm. However, no information could be found on the technique of ureteral length measurement (12).

Slagt et al. previously analyzed risk factors for urological complications in deceased donor kidney transplantation. Multivariate analysis showed that male recipients and arterial reconstructions were independent risk factors for urological complications (5). Carter et al. also stated that arterial multiplicity increases the risk of urological complications after living kidney transplantation, confirming the earlier findings by Kok et al. (6, 8). Unfortunately, analysis of the influence of a lower pole artery could not be performed adequately due to the limited number of patients with a lower pole artery in this series.

There are some limitations to this study. The measurements of the ureteral length were part of the earlier published INEX-trial. In this randomized controlled trial, the intravesical vs. extravesical ureteroneocystostomy were compared. Therefore, our study population is not uniform. However, in the INEX-trial the number of urological complications were the same in both groups (7). Furthermore, different transplant surgeons measured the ureteral length and inter-observer bias of a few millimeters could not be excluded.

Our number of urological complications, defined by PCN placements, is high compared to literature. We have a relatively large number of patients who received a PCN due to hydronephrosis, which resolved without any treatment 23/40 (58%). This is probably because in our center PCN placement is considered to be a minimal invasive intervention and we therefore maintain a low threshold to place a PCN. A bit hydronephrosis leads to PCN placement either for therapeutic benefit but also as a diagnostic tool. If we would exclude these PCN placements due to hydronephrosis which needed no additional intervention, the short ureter category would include 3/50 (6%) PCN placements, the medium ureter 11/98 (11%) and the long ureter 3/50 (6%), p=0.423. Therefore, still ureteral length does not seem to influence the number of PCN placements.

If neither the ureteral length, nor the technique for ureteroneocystostomy are factors that contribute to urological complications, the use of a ureteral stent may be questioned. In our institute, a ureterovesical stent is placed routinely. The Cochrane review of Wilson et al. report a urological complication rate of 0-4% in the stented group vs. 0-17.3% in the non-stented group. However, the number of urinary tract infections is significantly higher in the stented group and stent-related complications, like obstruction, migration and stone formation, should not be neglected. We agree with the authors of the Cochrane review that a well-designed study of stenting versus selective stenting should be executed (13).

Additionally, more insight should be established in the microcirculation and perfusion of the ureteral blood flow. To our knowledge, only 1 animal study has been published about the effect of ureteral access sheath on microcirculation of the ureter. Lallas et al. demonstrated that the use of the access sheath can cause a transient decrease in ureteral blood flow (14). This raises the question whether the use of a ureterovesical stent in kidney transplantation also influences the microcirculation of the ureter.

We conclude that ureteral length alone does not seem to influence the number of urological complications after kidney transplantation. Risk factor analysis for recipient gender, arterial multiplicity and for type of ureteroneocystostomy provided no differential effects between the three categories. Further research on the microvascular blood flow of the ureter and the use of a ureterovesical stent is warranted to answer more questions about risk factors for urological complications in living donor kidney transplantation.

References

1. Pleass HC, Clark KR, Rigg KM, Reddy KS, Forsythe JL, Proud G, et al. Urologic complications after renal transplantation: a prospective randomized trial comparing different techniques of ureteric anastomosis and the use of prophylactic ureteric stents. Transplant Proc. 1995;27(1):1091-2.
2. Neri F, Tsivian M, Coccolini F, Bertelli R, Cavallari G, Nardo B, et al. Urological complications after kidney transplantation: experience of more than 1,000 transplantations. Transplant Proc. 2009;41(4):1224-6.
3. Dols LF, Terkivatan T, Kok NF, Tran TC, Weimar W, JN IJzermans, et al. Use of stenting in living donor kidney transplantation: does it reduce vesicoureteral complications? Transplant Proc. 2011;43(5):1623-6.
4. Buresley S, Samhan M, Moniri S, Codaj J, Al-Mousawi M. Postrenal transplantation urologic complications. Transplant Proc. 2008;40(7):2345-6.
5. Slagt IK, Ijzermans JN, Visser LJ, Weimar W, Roodnat JI, Terkivatan T. Independent risk factors for urological complications after deceased donor kidney transplantation. PLoS One. 2014;9(3):e91211.
6. Kok NF, Dols LF, Hunink MG, Alwayn IP, Tran KT, Weimar W, et al. Complex vascular anatomy in live kidney donation: imaging and consequences for clinical outcome. Transplantation. 2008;85(12):1760-5.
7. Slagt IK, Dor FJ, Tran TC, Kimenai HJ, Weimar W, Ijzermans JN, et al. A randomized controlled trial comparing intravesical to extravesical ureteroneocystostomy in living donor kidney transplantation recipients. Kidney Int. 2014;85(2):471-7.
8. Carter JT, Freise CE, McTaggart RA, Mahanty HD, Kang SM, Chan SH, et al. Laparoscopic procurement of kidneys with multiple renal arteries is associated with increased ureteral complications in the recipient. Am J Transplant. 2005;5(6):1312-8.
9. Politano VA, Leadbetter WF. An operative technique for the correction of vesicoureteral reflux. J Urol. 1958;79(6):932-41.
10. Gregoir W. [the Surgical Treatment of Congenital Vesico-Ureteral Reflux] Le Traitement Chirurgical Du Reflux V'esico-Ur'et'eral Cong'enital. Acta Chir Belg. 1964;63:431-9.
11. Lich R, Jr., Howerton LW, Davis LA. Childhood urosepsis. J Ky Med Assoc. 1961;59:1177-9.
12. Ali-Asgari M, Dadkhah F, Ghadian A, Nourbala MH. Impact of ureteral length on urological complications and patient survival after kidney transplantation. Nephrourol Mon. 2013;5(4):878-83.
13. Wilson CH, Rix DA, Manas DM. Routine intraoperative ureteric stenting for kidney transplant recipients. Cochrane Database Syst Rev. 2013;6:CD004925.
14. Lallas CD, Auge BK, Raj GV, Santa-Cruz R, Madden JF, Preminger GM. Laser Doppler flowmetric determination of ureteral blood flow after ureteral access sheath placement. J Endourol. 2002;16(8):583-90.

CHAPTER 5

Antegrade balloon dilatation for post-transplantation ureteral strictures: case series

L.S.S. Ooms[1], A. Moelker[2], J.I. Roodnat[3], M. Idu[4], J.N.M. Ijzermans[1], T. Terkivatan[1]

1. Department of Surgery, Erasmus University Medical Center, Rotterdam, The Netherlands
2. Department of Radiology, Erasmus University Medical Center, Rotterdam, The Netherlands
3. Department of Nephrology, Erasmus University Medical Center, Rotterdam, The Netherlands
4. Department of Surgery, Amsterdam Medical Center, Amsterdam, The Netherlands

Accepted for publication in Experimental and Clinical Transplantation

Abstract

The aim of this study was to investigate the effect of antegrade balloon dilatation on ureteral strictures that developed after kidney transplantation (KT). Hospital database of the Erasmus Medical Center (EMC), Rotterdam, and the Academic Medical Center (AMC), Amsterdam, were retrospectively screened for patients that underwent balloon dilatation after KT. Balloon dilatation was technically successful whenever it was able to pass the strictured segment with the guidewire followed by balloon inflation, and it was clinically successful if no further interventions, for instance surgical revision of the ureteroneocystostomy or prolonged double J placement, were necessary. Fifty patients (2.4%) out of 2075 kidney transplantations underwent antegrade balloon dilatation because of urinary outflow obstruction. Median time between KT and balloon dilatation was 3 (0-139) months. In 43/50 (86%) patients balloon dilatation was technically successful and in 7 (14%) patients it was impossible to pass the strictured segment with the guidewire. In 20/43(47%) technically successful patients, the procedure was also clinically successful, with median follow up after balloon dilatation of 35.5 months (0-102). We did not identify patient or stricture characteristics that influenced the outcome of treatment. Balloon dilatation is a good option for ureter stricture treatment after KT as its minimal invasive and can prevent surgical exploration in almost half of the cases.

Introduction

Major urological complications after kidney transplantation (KT), including urinary leakage and ureter strictures, are reported with an incidence between 2.3-20% [1-3]. Ureteral strictures are the most commonly reported urological complication and can cause significant morbidity after KT with prolonged hospital stay and repetitive interventions.

A ureteral outflow obstruction is characterized by elevated serum creatinine in combination with hydronephrosis on ultrasound examination and is generally treated with a percutaneous nephrostomy (PCN). In several cases the obstruction will resolve spontaneously, but in a few cases additional treatment is necessary to guarantee adequate outflow.

Treatment options for ureteral strictures include long term double J catheter insertion, balloon dilatation or surgical revision of the ureteroneocystostomy. In the literature, only a few studies are available that report on the success-rate of these treatments. Helfand et al. report on their experience with surgical management of ureteral strictures after KT and proposed an algorithm for the management of strictures [4]. The algorithm is based on size of the stricture (<3cm) and the time between transplantation and diagnosis of the stricture (<3 months). However, the study population was small (n=13) [4].

Balloon dilatation has proven its efficacy in the treatment of the ureterovesical junction for an obstructive mega-ureter and in uretero-ileal strictures of 1cm or less in patients after surgical urinary diversion [5-7].

The primary objective of this study is to present a case series of balloon dilation treatment for post-transplantation ureteral strictures and to determine its success-rate. The secondary objective is to determine which factors might be of influence on the outcome of balloon dilatation.

Methods

Patients

The Medical Ethical Committee approved the trial protocol (MEC-2015-119).The hospital database of the Erasmus Medical Center (EMC), Rotterdam, and the Academic Medical Center(AMC), Amsterdam, were screened for patients that underwent radiological balloon dilatation of the ureter after KT. Baseline characteristics included recipient gender and age, type of donor (deceased vs. living), second warm ischemic time (WIT), cold

ischemic time (CIT), technique for ureteroneocystostomy (intravesical vs. extravesical), number of prior transplantations, months between KT and balloon dilatation, stricture characteristics, readmissions within 1 month after balloon dilatation and follow up in months after balloon dilatation. Balloon dilatation was considered technically successful if the interventional radiologist could pass the strictured segment with the guidewire and the balloon could be inflated. Balloon dilatation was clinically successful if no further interventions, for instance surgical revision of the ureterneocystostomy or later prolonged double J placement, were necessary. Graft survival was based on the date a patient returned to hemo- or peritoneal dialysis or received a pre-emptive new transplant. All complications that occurred within 30 days after balloon dilatation and lead to a readmission, were documented.

Diagnosing ureteral stricture

For all patients presented with increased serum creatinine and hydronephrosis on ultrasound, percutaneous nephrostomy (PCN) placement was the first step in treatment. Using anterograde pyelography, the diagnosis of ureteral stricture was confirmed. For this study, all pyelograms were analyzed retrospectively for location of the ureter stricture (proximal, mid-ureteral, distal, total or multiple) and length of the stricture by 1 interventional radiologist (AM) with over 8 years of experience in urogenital interventions. If the ureter had multiple strictured segments the length of the longest stricture was documented.

Balloon dilatation procedure

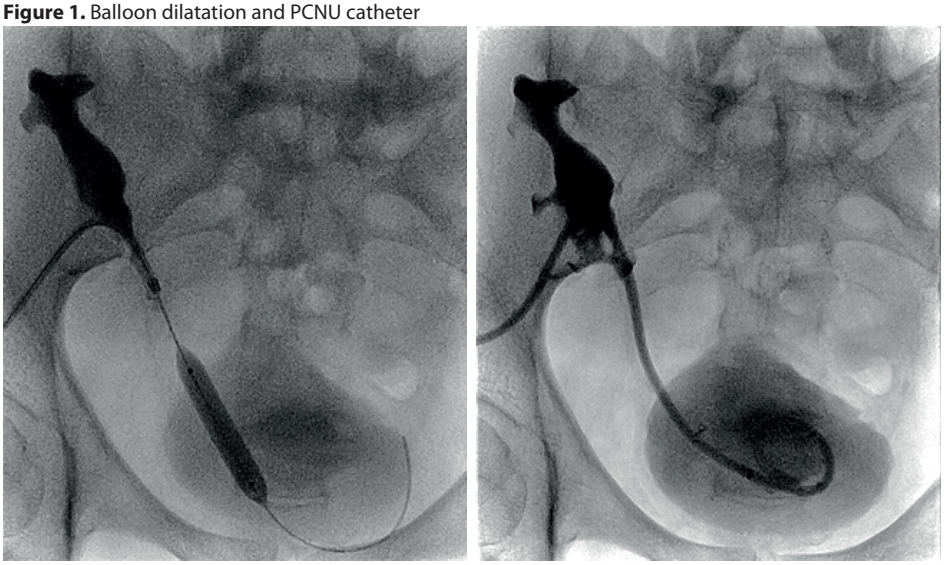
The nephrostomy tube was replaced by a 8 French vascular sheath and a 4 French catheter with a hydrophilic 0.035" guidewire (Terumo, Belgium) was introduced through the sheath into the renal pelvis and ureter in antegrade fashion. The guidewire was then passed through the strictured segment of the ureter into the bladder and a 3 to 8 mm diameter balloon was advanced over the guidewire and inflated during several minutes. In cases where traversing the stricture was difficult, smaller diameter wires (0.014") and balloons could be used. The type of balloon varied over time between a regular and a cutting balloon up to the discretion of the treating interventional radiologist. The cutting balloon has three or four microsurgical blades. These blades are fixed longitudinally on the outer surface of the balloon, expand radially and deliver longitudinal incisions in the strictured segment of the ureter. After deflation of the balloon, either a PCN, a nephroureterostomy catheter (PCNU, figure 1) or a double J catheter was placed.

Statistical analyses

Categorical variables are presented as numbers (percentage). Continuous variables are presented as median (range) if not normally distributed; continuous variables with nor-

mal distribution are presented as means with standard deviation. Normality was based on the shape of the histogram plot and tested with the Shapiro-Wilk test. Categorical variables are analyzed using the Chi-square test. Continuous variables are analyzed using the Mann-Whitney-U test or an independent T-test. Graft survival is analyzed using a log rank test and is censored for death. For graft survival we did not distinguish between technically or clinically successful balloon dilatations. All technically and clinically unsuccessful balloon dilatations were considered as unsuccessful. All analyses were conducted using IBM SPSS Statistics for Windows (version 21.0. Armonk, NY: IBM Corp, USA). A p-value <0.05 (two-sided) was considered statistically significant.

Figure 1. Balloon dilatation and PCNU catheter



Results

Baseline characteristics

A total of 50 patients underwent antegrade balloon dilatation (table 1). This included 37 (2.5 %) patients of 1496 kidney transplants that were performed in the Erasmus MC between August 2007 and September 2015. Thirteen (2.2%) patients underwent balloon dilatation out of the total of 579 kidney transplantations performed in the AMC. The AMC included patients for this study within a shorter period, being from March 2011 until June 2015. Median time between KT and balloon dilatation treatment was 3 months (range, 0-139). The median length of the total strictured segment was 2 (0.5-5) cm and median follow up after balloon dilatation was 35.5 (0-102) months.

Table 1. Baseline characteristics

Characteristic	Total patients N=50
Gender: Male N (%)	30 (60)
Age at KT mean ± SD years	48 ± 16
Type donor: Living N (%)	35 (70)
WIT 2 in minutes median (range)	26.5 (13-80)
CIT in minutes median (range)	169 (96-2520)
Type anastomose	
Intra N (%)	10 (20)
Extra N (%)	34 (68)
Not documented N (%)	6 (12)
Primary reason PCN	
Hydronephrosis N (%)	43 (86)
Urinary leakage N (%)	7 (14)
Number transplant median (range)	1 (1-4)
Months between KT and BD median (range)	3 (0-139)
Length longest stricture in cm median (range)	1.5 (0.5-5)
Length total stricture in cm median (range)	2 (0.5-5)
Location stricture	
Distal N (%)	33 (66)
Proximal N (%)	3 (6)
Mid-ureteral N (%)	2 (4)
Total N (%)	6 (12)
Multiple N (%)	6 (12)
Number of BD median (range)	1 (1-4)
Technical successful balloon dilatation N (%)	43 (86)
Clinical successful (of technically successful) BD N (%)	20 (47)
Follow up in months after BD median (range)	35.5 (0-102)

N, number; KT, kidney transplantation; cm, centimeter; SD, standard deviation; BD, balloon dilatation; WIT, Warm Ischemic Time; CIT, Cold Ischemic Time; Intra, intravesical; Extra, extravesical

Balloon dilatation

In 43 of 50 (86%) patients balloon dilatation was performed successfully from a technical point of view, whereas in 7 (14%) patients it was impossible to pass the strictured segment with the guidewire. Out of the 7 patients of whom the stricture was impossible to pass, two patients had a second and even a third attempt for balloon dilatation. These all remained technically unsuccessful. In 20 of the 43 (47%) patients who underwent a technically successful balloon dilatation, the procedure was also clinically successful. Median follow up after balloon dilatation was 35.5 months (0-102). In 12 patients balloon dilatation was clinically successful after one attempt, 7 patients needed a second

treatment and one patient needed 4 balloon dilatation treatments before success was reached. These additional balloon dilatation were during a repeat procedure and not in the same procedure.

One patient with a technically successful dilatation died from a pneumosepsis (pneumocystis jiroveci) 1 month after balloon dilatation. This was prior to stent removal; therefore, we were not able to determine whether balloon dilatation was successful. Another patient had a severe graft rejection after balloon dilatation and graft nephrectomy was necessary. In this case, we were also not able to determine the success of balloon dilatation. Therefore, in these two patients the success was scored as missing. One patient had a kidney infarction after balloon dilatation and this was scored as unsuccessful. This event will be discussed further below in the complications section.

Two patients underwent a surgical revision of the ureterocystostomy prior to a successful balloon dilatation. One of these patients received her transplant in 2003 and had a surgical revision of the ureteroneocystostomy in 2004. During this period, we did not carry out balloon dilatations yet in our hospital. In 2014, this patient had a recurrent stricture and underwent successful balloon dilatation. The other patient had urinary leakage primarily followed by a surgical ureteral reconstruction 2 days after transplantation. This patient developed a stricture which was successfully treated with balloon dilatation.

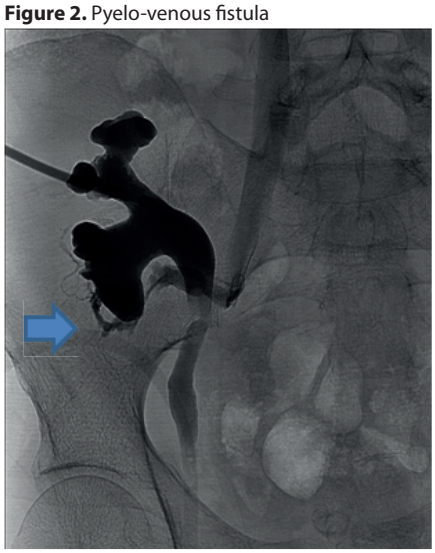
Of the patients who underwent technical successful balloon dilatation (n=43) a regular balloon was used in 36 patients and a cutting balloon in 7 patients. In 40 patients the strictured segment was stented post-balloon dilatation with a PCNU catheter or a double J catheter and in 3 patients a regular PCN was placed and therefore scored as non-stented.

Twenty-six patients underwent surgical repair after a balloon dilatation attempt. In 16 patients the strictured segment was resected and a new ureteroneocystostomy was made. In 4 patients the native ureter was attached to the transplant pyelum, 3 patients had a pyelocystostomy and in 1 patient the native ureter was attached to the transplant ureter. During surgical exploration in 1 patient the total ureter was strictured and no further surgical options were available. This patient remained nephrostomy dependent. In the last patient no ureteral obstruction was objectified during surgical exploration, however a very limited bladder capacity was detected and this patient was treated with a suprapubic catheter.

Complications

In one patient a kidney infarction was diagnosed 22 days after balloon dilatation treatment and 13 days after PCN replacement. As kidney function deteriorated, a biopsy was performed to exclude rejection. Renal failure was attributed to loss of parenchymal tissue secondary to infarction due to vascular damage. The complication was not attributed to balloon dilatation as such. However, the intervention procedure was scored as clinically unsuccessful in this case series.

Figure 2. Pyelo-venous fistula



One patient developed a ureter stricture of 1,5cm in the distal part of the ureter 3 months after transplantation. A PCN was placed and a pyelogram was made to visualize the pyelo-ureteral anastomosis. During this procedure, a fistula between the pyelum and iliac vein was visualized (Figure 2). It is unknown whether it was present before or caused by the intervention. The antegrade balloon dilatation procedure was ended prematurely, i.e. before entering the bladder with the guidewire; no ureteral dilatation was performed. In the hours following the procedure the patient developed a septic shock and died despite antibiotic treatment. The cause of death was explained by bacteremia due to direct circulatory contamination with a multi-resistant E.coli in an immunocompromised patient.

There were 23 patients without complications that lead to readmission. Eighteen patients were readmitted within one month because of urosepsis. These readmissions could also cohere with chronic contamination due to continue PCNU or PCN placement requiring a replacement of the PCNU or PCN. One patient was readmitted because of the previously mentioned kidney infarction, 1 patient was readmitted because of hematuria with creatinine rise caused by an obstructive blood cloth, 1 patient was readmitted with a deep venous thrombosis, 2 patients were readmitted in order to treat additional rejection, 3 patients were admitted because of PCN related complications (urinary leakage or dislocation) and 1 for diarrhea followed by urosepsis and surgical revision of the ureteroneocystostomy, again all within the 30 days period. In this last patient a perforation of the ureter occurred while the radiologist tried to pass the strictured segment with

the guidewire. It was impossible to pass the strictured segment and the procedure was ended prematurely.

Graft survival

Graft survival after successful balloon dilatation was 100% at 12 months and 75% at 24 months after balloon dilatation. For the unsuccessful procedures graft survival was 92% at 12 and 24 months after attempting the balloon dilatation, P=0.937 (Figure 3). Grafts failed due to several causes, such as 3 chronic failures followed by pre-emptive retransplantation in 2 patients, 2 acute rejections, the previously mentioned kidney infarction, 1 recurrent primary disease (focal segmental glomerulosclerosis), 1 glomerulosclerosis and interstitial fibrosis, 1 cardiac shock with subsequent contrast overload lead to acute tubulus necrosis and in 1 patient due to urosepsis.

Figure 3. Graft survival after balloon dilatation

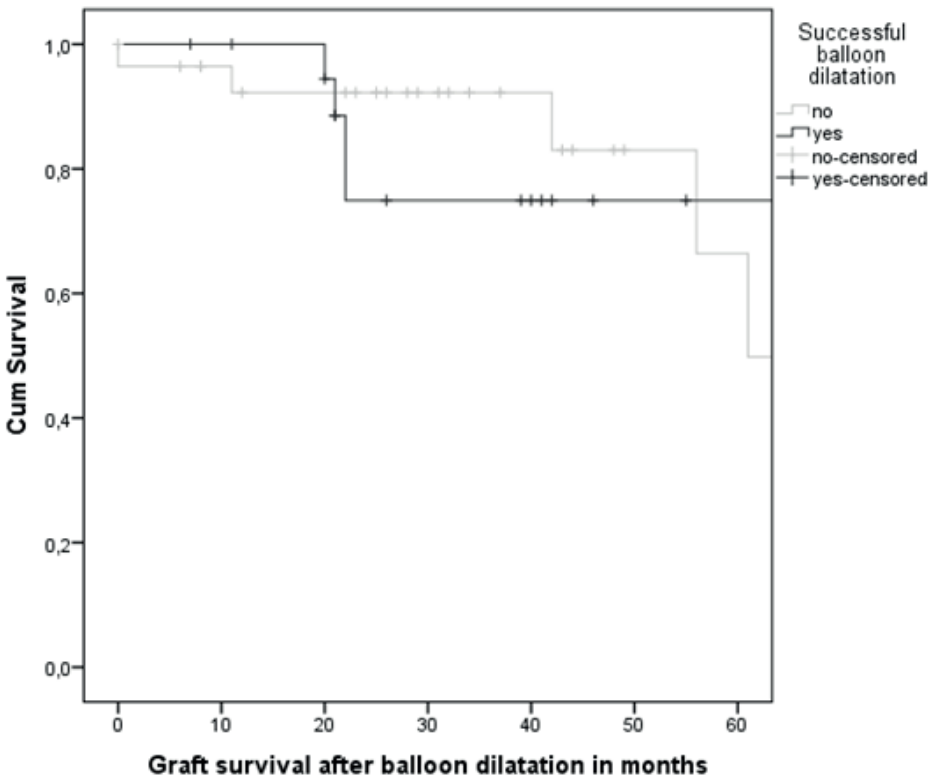


Table 2. Factors that might contribute to clinical success of technically successful balloon dilatation (N=2 outcome is missing)

Factor	Unsuccessful clinical balloon dilatation (N=21)	Successful clinical balloon dilatation (N=20)	P-value
Extravesical technique ureteroneocystostomy N (%)	16 (84)	12 (71)	0.326
Gender recipients Male (N%)	14 (67)	10 (50)	0.279
Type of donor living N (%)	14 (67)	16 (80)	0.335
WIT 2 in minutes median (range)	24 (14-80)	25.5 (13-56)	0.886
CIT in minutes median (range)	180 (96-1860)	156 (114-1260)	1.000
Length longest stricture in cm median (range)	1.7 (0.5-5)	1.5 (0.5-5)	0.439
Longest stricture > 3cm N (%)	5 (24)	2 (10)	0.240
Months between KT and BD median (range)	3 (0-139)	3 (0-135)	0.484
>3months between KT and BD N (%)	8 (38)	8 (40)	0.901
Location stricture			
- Total N (%)	2 (10)	1 (5)	0.562
- Proximal N (%)	2 (10)	1 (5)	
- Distal N (%)	12 (57)	15 (75)	
- Mid-ureteral N (%)	2 (10)	0 (0)	
- Multiple (%)	3 (13)	3 (15)	
Type balloon			
- Cutting N (%)	4 (19)	3 (15)	0.731
- Regular N (%)	17 (81)	17 (85)	
Diameter balloon			
- 3-4 mm N (%)	4 (19)	3 (15)	0.942
- 5-6 mm N (%)	7 (33)	7 (35)	
- 7-8 mm N (%)	10 (48)	10 (50)	
Stented post dilatation N (%)	20 (95)	18 (90)	0.520

Univariate analysis. Cm, centimeters; KT, kidney transplantation; BD, balloon dilatation; SD, standard deviation; WIT, Warm Ischemic Time; CIT, Cold Ischemic Time

Risk factor analysis

In univariate analysis, we found that neither donor characteristics (type donor, WIT, CIT), type of ureteroneocystostomy technique, recipients gender, months between KT and balloon dilatation, type and diameter of the balloon used, stricture length, stricture location nor the use of a stent after balloon dilatation were factors that could influence the outcome of the treatment (table 2).

Discussion

Urological complications as urinary leakage and ureteral strictures may occur as early as well as late complications after kidney transplantation. In this study, we analyzed the outcome of balloon dilatation as treatment for ureter strictures after kidney transplantation. The technical success-rate was 86% and the subsequent clinical success-rate of balloon dilatation treatment was 47%. We could not identify any factors that may have contributed to a (non)successful outcome of a balloon dilatation.

Several other studies report on the outcome of balloon dilatation. Asadpour et al. report on 24 patients with ureteral strictures of whom 11(46%) had a successful outcome after balloon dilatation and PCN treatment [8] and there results are comparable to the outcome of the present study. Aytekin et al. report a balloon dilatation success-rate of 90% in their cohort of 10 patients with late obstructions due to strictures, which is a higher success-rate than our cohort. Four patients had a recurrence of the stricture, and therefore repeated balloon dilatation was necessary. In 2 of these patients a metallic stent was placed. In only 1 patient surgical revision of the ureterocystostomy after balloon dilatation was necessary. It should be noted that in this study a 7-Fr double J catheter was inserted as standard care after balloon dilatation. This might have increased their success-rate [9]. On the other hand Juaneda et al. report on 45 patients with ureteral strictures with a 45% success-rate while placing a double J catheter after all balloon dilatations as well [10].

He et al. tried to define a management strategy for kidney transplant recipients who developed a ureteral obstruction. In their study they define 3 grades of ureteral strictures; Grade 1) hydronephrosis without an evidently strictured segment, Grade 2) hydronephrosis with ≤1 cm strictured segment, and Grade 3) hydronephrosis with >1 cm strictured segment [11]. They propose the following treatment options; Grade 1) prolonged stent insertion for 6 weeks, Grade 2) cystoscopy with incision or balloon dilatation followed by stent insertion for 6 weeks, Grade 3) Surgery. When we apply this classification and management strategy on our cohort, 17 patients would fit the grade 2 classification, in 9 of these patients balloon dilatation was successful. In our cohort 33 patients have a stricture that can be classified as grade 3 and would therefore benefit from surgical treatment. However, 11 of these patients had successful balloon dilatation and would have been subjected to unnecessary surgical intervention when following this classification [11]. Based on our cohort we would advise to perform a balloon dilatation prior to surgical revision, as it is less invasive, irrespective of the proposed grading system.

There are some limitations to this study. Even though our study includes the highest number of balloon dilatations reported until now, the number of 50 patients remains low. Therefore, analyses for factors that could contribute to the success-rate of balloon dilatation treatment cannot be performed reliably or maybe none of the factors does influence the outcome. Furthermore, our post-balloon dilatation treatment was different in our patients. In some of them the PCN drain was left in situ and in others the PCN was removed and a single pigtail in PCNU position or a double J catheter was placed instead. Based on the available literature double J catheter placement has a favorable outcome, however this would indicate an additional cystoscopy would be necessary to remove the double J catheter [9,11]. A drain in PCNU position would give the benefit of a stented stricture post-dilatation treatment and would lack the risks of an additional cystoscopy.

We believe that balloon dilatation should be advocated as the first treatment for ureter strictures. It is clinical successful in 47% of the patients and it is less invasive than open surgical ureter reconstruction.

References

1. Bachar GN, Mor E, Bartal G, Atar E, Goldberg N, Belenky A. Percutaneous balloon dilatation for the treatment of early and late ureteral strictures after renal transplantation: long-term follow-up. *Cardiovasc Intervent Radiol.* 2004;27(4):335-338.
2. Lojanapiwat B, Mital D, Fallon L, et al. Management of ureteral stenosis after renal transplantation. *J Am Coll Surg.* 1994;179(1):21-24.
3. Slagt IK, Dor FJ, Tran TC, et al. A randomized controlled trial comparing intravesical to extravesical ureteroneocystostomy in living donor kidney transplantation recipients. *Kidney Int.* 2014;85(2):471-477.
4. Helfand BT, Newman JP, Mongiu AK, Modi P, Meeks JJ, Gonzalez CM. Reconstruction of late-onset transplant ureteral stricture disease. *BJU Int.* 2011;107(6):982-987.
5. Garcia-Aparicio L, Blazquez-Gomez E, Martin O, et al. Use of high-pressure balloon dilatation of the ureterovesical junction instead of ureteral reimplantation to treat primary obstructive megaureter: is it justified? *J Pediatr Urol.* 2013;9(6 Pt B):1229-1233.
6. Schondorf D, Meierhans-Ruf S, Kiss B, et al. Ureteroileal strictures after urinary diversion with an ileal segment-is there a place for endourological treatment at all? *J Urol.* 2013;190(2):585-590.
7. Boylu U, Oommen M, Raynor M, Lee BR, Blank B, Thomas R. Ureteroenteric anastomotic stricture: novel use of a cutting balloon dilator. *J Endourol.* 2010;24(7):1175-1178.
8. Asadpour A, Molaei M, Yaghoobi S. Management of ureteral complications in renal transplantation: prevention and treatment. *Saudi J Kidney Dis Transpl.* 2011;22(1):72-74.
9. Aytekin C, Boyvat F, Harman A, Ozyer U, Colak T, Haberal M. Percutaneous therapy of ureteral obstructions and leak after renal transplantation: long-term results. *Cardiovasc Intervent Radiol.* 2007;30(6):1178-1184.
10. Juaneda B, Alcaraz A, Bujons A, et al. Endourological management is better in early-onset ureteral stenosis in kidney transplantation. *Transplant Proc.* 2005;37(9):3825-3827.
11. He B, Bremner A, Han Y. Classification of ureteral stenosis and associated strategy for treatment after kidney transplant. *Exp Clin Transplant.* 2013;11(2):122-127.

CHAPTER 6

Urinary tract infections after kidney transplantation: a risk factor analysis of 417 patients

L.S.S. Ooms[1], J.N.M. Ijzermans[1], A.F. Voor in t Holt[2], M.G.H. Betjes[3], M.C. Vos[2], T.Terkivatan[1]

1. Department of Surgery, Erasmus University Medical Center, Rotterdam, The Netherlands
2. Department of Microbiology, Erasmus University Medical Center, Rotterdam, The Netherlands
3. Department of Nephrology, Erasmus University Medical Center, Rotterdam, The Netherlands

Annals of Transplantation, 2017 Jun 30;22:402-408

Abstract

The aim of this study was to evaluate the number of urinary tract infections (UTI) that occur after kidney transplantation (KT) and to identify possible risk factors for development of a UTI. For this study, we retrospectively analysed all KTs that were performed between January 2012 and December 2013 in the Erasmus University Medical Center, Rotterdam. UTI was scored if: a patient had a urine culture with no more than two species of microorganisms, second, with at least one of which was a bacterium of ≥ 10^5 CFU/mL, third which was treated with antibiotics and fourth, which occurred within 3 months after KT. A total of 417 patients were transplanted from January 2012 until December 2013. One hundred and fifteen (28%) developed a UTI, after a median of 13 days from transplantation (range: 3-82). The most common causative agent was *Escherichia coli*, followed by *Enterococcus faecalis, Enterococcus faecium* and *Klebsiella pneumoniae*. The variables that were independently related to a UTI were female gender (OR 3.58, 95%CI 2.16-5.91), recipients age >60y (OR 2.12, 95%CI 1.28-3.48), percutaneous nephrostomy placements (OR 6.29, 95%CI 3.35-11.85) and surgical re-interventions (OR 2.12, 95%CI 1.04-4.32). Mean glomerular filtration rate was significantly lower in the group of patients with a UTI at 3, 6, 9 and 12 months postoperatively compared to those patients who did not have a UTI. We conclude that a UTI after KT is a common problem. We identified independent risk factors for the development of a UTI. UTI is associated with a GFR decrease postoperatively.

Introduction

Kidney transplantation (KT) is the best and most cost-effective treatment for patients with end stage renal disease. It improves overall survival rates and quality of life of patients compared to patients on chronic dialysis (1). Preventing complications that comprise graft outcome remains a challenge in KT.

Infections are a common problem in patients receiving immunosuppressive treatment after transplantation (2). Urinary tract infections (UTI) after KT are reported up to 38% (3). For example, Bodro et al. reported an incidence of 184 UTI (21%) out of 867 KT recipients with a median of 18 days from transplantation (4). Furthermore, acute graft pyelonephritis is mentioned up to 15% and an association with kidney graft impairment and graft loss has been reported (4, 5).

Risk factors for the development of a UTI after KT are prolonged hospital stay and a high body mass index (BMI) (6). Furthermore, independent risk factors are shown to be female gender, recurrent UTI before transplantation, acute rejection, induction therapy (either anti-thymocyte globulin or basiliximab) and cytomegalovirus infection (7).

In this study, we retrospectively analyzed the data of 417 KTs performed in our center between January 2012 and December 2013, to evaluate the number of UTI in the first 3 months after transplantation. Additionally, we aimed to identify risk factors that were related to the development of UTI and we investigated whether a UTI in the first 3 months after transplantation compromised graft function within the first 12 months after transplantation.

Methods

Study population and data selection

In this study we included all KT recipients (>18yrs) operated at the Erasmus University Medical Center between January 2012 and December 2013, independent of a reconstructed urinary tract (i.e. Bricker bladder) or UTI prior to transplantation. Pediatric KT recipients were excluded from this study. Baseline data of the recipients included gender, age, ethnicity, ASA classification, type of donor, number of previous transplantations, HLA-mismatches, ABO-incompatible KT, BMI, diabetes, technique for ureteroneocystostomy (intra- vs. extravesical), warm and cold ischemia time, duration of surgery, per-operative blood loss, pre-emptive transplantation (prior to start dialysis), use of ureterovesical stent, percutaneous nephrostomy placements (PCN) < 3 months after KT,

biopsy proven rejection en subsequent treatment <3 months, surgical re-intervention < 3 months after KT and hospital admittance days of initial admission. Follow-up for our primary outcome (UTI) was performed until 3 months after KT. For our secondary outcome (graft function) follow up was performed until 12 months after KT. The medical ethical committee of the Erasmus University medical center approved this study protocol (MEC-2016-279).

Urinary tract infection

For the definition for UTI we used adjusted Center of Disease Control (CDC) definitions (8). UTI was scored if firstly a patient had a urine culture with no more than two species of microorganisms (CDC). Second, with at least one of which was a bacterium of ≥ 10^5 CFU/mL (CDC), third which was treated with antibiotics (non-CDC) and fourth, which occurred within 3 months after KT (non-CDC). Antibiotic treatment was started when the patient had one of the following symptoms: fever>38°C, suprapubic tenderness, urinary urgency/frequency, transplant tenderness and dysuria. During the primary admission for the transplantation, urinary cultures were collected every Monday, Wednesday and Friday. After discharge, urinary cultures were not collected in a standardized manner and frequency, as they were only taken by the above mentioned clinical indications. All first UTI that arose within 3 months after transplantation were included in this study, all recurrent UTI in the same patient were not scored as separate events. All patients received a surgical prophylaxis with cefazolin 3*1000mg intravenous on the day of surgery. Postoperatively a prophylaxis to prevent a *Pneumocystis carinii* pneumonia of 480mg trimethoprim/sulfamethoxazole was given orally once a day until 3 months after KT. To prevent cytomegalovirus (CMV) infections, a prophylaxis of valganciclovir was given the first 6 months after transplantation, unless both the donor and recipient were CMV negative. Dosage of valganciclovir was dependent on GFR: 1) if GFR> 40 ml/min: 450mg once a day 2) if GFR: 25-39ml/min: 450mg every other day 3) if GFR <25ml/min : 450mg twice a week.

Surgical technique

During surgery, the kidney was placed in the extra peritoneal iliac fossa. After the vascular anastomoses on the external iliac vessels, the surgeon performed either an intravesical anastomosis described by Politano-Leadbetter (9) or an extravesical anastomosis described by Lich-Gregoir (10, 11). An externalized ureterovesical stent was placed as standard care (excluding some patients with residual native urine production, about 7%) and it was removed 9 days postoperatively. A transurethral urinary bladder catheter was removed after 7 days. In the cause of a urinary leakage or a ureter stenosis (resulting in hydronephrosis) a PCN was placed postoperatively.

Immunosuppressive treatment

Immunosuppressive treatment consisted of basiliximab intravenous on the day of surgery and day 4 after transplantation. Postoperative immunosuppression consisted of tacrolimus, mycophenolate mofetil and prednisolone. The prednisolone was tapered off to be discontinued at 4 months after transplantation.

Statistical analysis

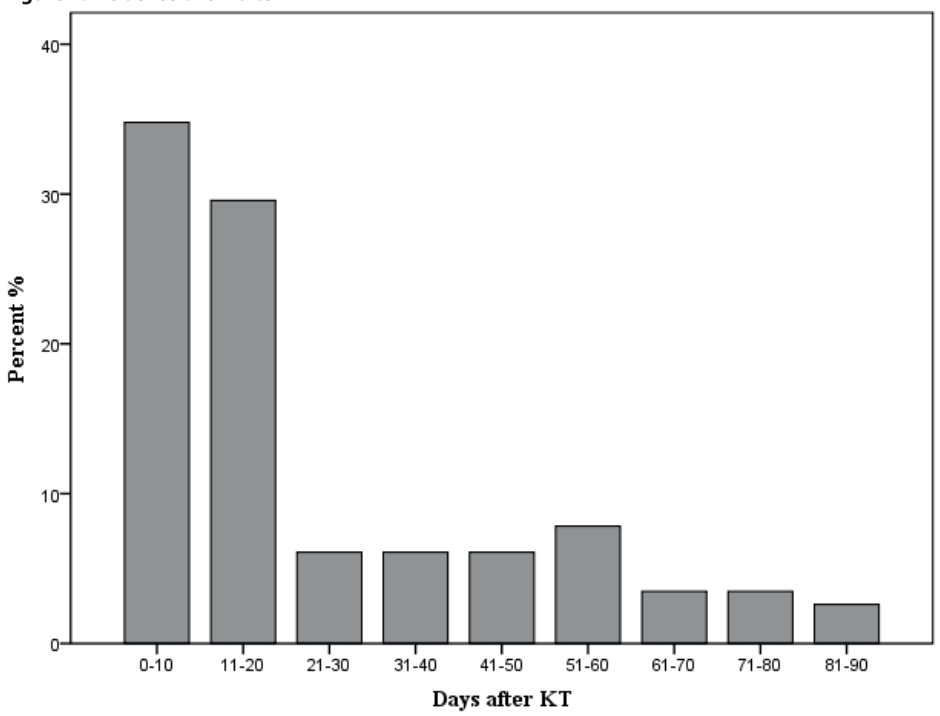
All analyses were conducted using IBM SPSS Statistics for Windows (version 21.0. Armonk, NY: IBM Corp, USA). A p-value of <0.05 (two-sided) was considered statistically significant. Continuous variables were presented as means with standard deviations if normally distributed or as median with range if not normally distributed. These variables were analysed using the independent T-test or the Mann-Whitney U test. Categorical variables were presented as numbers with percentages and were analysed using Chi-square test. We performed multivariate analysis using logistic regression and included covariates with p-values <0.05 in univariate analysis. The analysis was two-tailed and results were presented as odds-ratios (OR) with 95% confidence intervals (95% CI).

Results

Baseline characteristics

Between January 2012 and December 2013 417 adult (>18yr) KT were performed in our center. Mean age of this cohort was 55±14 years and included 261 (63%) males and 156 (37%) females. The most common ethnicity was caucasian (79%), most KT involved living donors (67%) with a median cold ischemia time of 158 (89-1576) minutes and a warm ischemia time of mean 23±8 minutes. One hundred and fifteen patients out of a total of 417 patients (28%) developed UTI, after a median of 13 days from transplantation (range: 3-82). Most UTI occurred within the first 20 days after KT, N=74 out of 417 (18%) (figure 1). There were no differences in recipients with UTI and those without UTI with respect to ASA-classification, type of donor, number of transplant, HLA mismatches, ABO-incompatible transplantation, BMI, pre-emptive transplantation, diabetes, technique for ureteroneocystostomy (intra vs extra), stent usage, warm and cold ischemia time, duration of surgery, per-operative blood loss, and biopsy proven rejection within 3 months after transplantation. Then again, univariate analysis did show that UTI was related to female gender, higher age, age>60y, non-caucasian ethnicity (i.e. Asian/African-American) PCN placements < 3 months after KT, more surgical re-interventions and prolonged initial hospital stay (Table 1). Thirty-seven out of 60 patients with a PCN placed within 3 months after KT developed a UTI < 3 months after KT. Eleven of these developed a UTI prior to PCN placement and 26 patients developed a UTI after PCN placement.

Figure 1. Incidence of UTI after KT



Causative agent

Out of 417 patients a total of 4559 urinary cultures were taken within 3 months after KT. This implies that in individual patients a mean of 11±6 urinary cultures were collected. From the urinary cultures of the 115 patients with a UTI, the microorganism most commonly identified was *Escherichia coli* (n=50), followed by *Enterococcus faecalis* (n=28), *Enterococcus faecium* (n=8), *Klebsiella pneumoniae* (n=8), *Pseudomonas aeruginosa* (n=6), *Klebsiella oxytoca* (n=4), *Proteus mirabilis* (n=3), *Acinetobacter* spp. (n=3), *Citrobacter* spp (n=3), *Pseudomonas fluorescens* (n=2), *Pseudomonas putida* (n=2), *Enterobacter cloacae* (n=2), *Morganella morganii* (n=2), and single cases of *Aeromonas caviae*, *Candida krusei*, *Escherichia* spp, *Pseudomonas* spp, *Staphylococcus epidermidis*, *Staphylococcus aureus*, and *Streptococcus agalactiae*. In urinary cultures of 13 out of 115 patients (11.3%), 2 different microorganisms were identified.

Risk factor analyses

In univariate analyses female gender, age, number of PCN, surgical re-interventions, non-caucasian ethnicity and initial hospitalisations days were different between patients who developed a UTI with P values <0.05. We included these variables in the multivariate analysis. The variables that were independently related to a UTI were female gender,

Table 1. Demographic and clinical characteristics

Characteristic	No UTI (302)	UTI (115)	P-value
Gender recipient male N (%)	210 (70)	51 (44)	**<0.001**
Age recipient in years mean ± SD	54±14	58±13	**0.007**
Age > 60y N (%)	111 (37)	61 (53)	**0.003**
Ethnicity N (%)			
Caucasian	245 (81)	83 (72)	**0.046**
Non-caucasian	57 (19)	32 (28)	
ASA N (%)			0.700
2	56 (19)	26 (23)	
3	237 (80)	88 (76)	
4	3 (1)	1 (1)	
Living Donor N (%)	205 (68)	76 (66)	0.727
Number transplant N (%)	1 247 (82)	1 91 (79)	0.680
	2 40 (13)	2 19 (17)	
	≥3 15 (5)	≥3 5 (4)	
HLA-MM median (range)	3 (0-6)	4 (0-6)	0.950
ABO incompatible N (%)	14 (5)	7 (6)	0.545
BMI recipient mean ± SD	26±5	27±5	0.144
Pre-emptive KT N (%)	109 (36)	37 (32)	0.453
Diabetes N (%)	74 (25)	33 (29)	0.381
Extravesical technique N (%)	225 (87)	81 (80)	0.076
Stent Yes N (%)	281 (93)	106 (92)	0.672
Biopsy proven rejection <3 months N (%)	39 (13)	15 (13)	0.972
Cold ischemia minutes time median (range)	157 (89-1576)	159 (110-1380)	0.751
Warm ischemia 2 minutes time mean ± SD	23±8	22±7	0.837
Duration of surgery minutes mean ± SD	141±38	141±45	0.972
Blood loss in mL median (range)	250 (0-3600)	300 (0-3000)	0.053
PCN placement < 3 months N (%)	23 (8)	37 (32)	**<0.001**
Surgical re-intervention < 3 months N (%)	24 (8)	23 (20)	**0.001**
Initial hospital admittance days median (range)	12 (5-65)	15 (7-122)	**<0.001**

UTI; urinary tract infection; N, number; SD, standard deviation; KT, kidney transplantation; BMI, body mass index; PCN, percutaneous nephrostomy; ASA, American Society of Anesthesiologist physical status classification

recipients age >60y, PCN placements and surgical re-interventions (Table 2). Excluding patients who already had a UTI prior to PCN placement (N=11) in the same multivariate model, would still result in a significant OR of 4.52 (95%CI 2.31-8.83, p<0.001) for PCN placement as an independent risk for UTI.

Table 2. Multivariate risk factor analysis

Risk factor	Odds ratio	95% CI	P-value
Female gender	3.58	2.16-5.91	**<0.001**
Age > 60y	2.12	1.28-3.48	**0.003**
PCN < 3 months after KT	6.29	3.35-11.85	**<0.001**
Surgical re-intervention < 3 months	2.12	1.04-4.32	**0.038**
Initial hospitalisation days	1.02	0.99-1.05	0.148
Non-caucasian ethnicity	1.75	0.99-3.08	0.051

CI, 95% confidence intervals; PCN, percutaneous nephrostomy; KT; kidney transplantation

Graft function

Mean glomerular filtration rate (GFR) was significantly lower in patients who developed a UTI at 3, 6, 9 and 12 months after transplantation compared to patients who did not develop a UTI (Table 3).

Table 3. Graft function

Characteristic	Total (417)	No UTI (302)	UTI (115)	P-value
GFR mL/min 1 month after KT mean ± SD	46± 17	47± 17	43 ±18	0.061
GFR mL/min 3 months after KT mean ± SD	47± 15	48± 15	43± 16	**0.005**
GFR mL/min 6 months after KT mean ± SD	48± 16	49± 16	44± 17	**0.005**
GFR mL/min 9 months after KT mean ± SD	48± 16	49±16	45± 17	**0.010**
GFR mL/min 12 months after KT mean ± SD	48± 16	50±16	43± 16	**<0.001**

GFR, glomerular filtration rate; UTI, urinary tract infection; KT, kidney transplantation; SD, standard deviation

Discussion

In this analysis, we identified 115 out of 417 patients (28%) who developed a UTI after KT. In multivariate analysis, variables that were independently related to the development of UTI were female gender, recipients' age>60y, PCN placement and surgical re-interventions within 3 months after transplantation. Mean GFR at 3, 6, 9 and 12 months after transplantation was significantly lower in patients who had a UTI compared to those who did not have a UTI.

Female gender has previously been associated with the development of UTI, both in the normal population as in kidney recipients (12). The risk for UTI after placement of a PCN could be explained due to the additional port d 'entrée. Incidence of UTI in non-transplant patients with PCN are reported by Kaskarelis et al. with 0.87% UTI in 341 patients (13). This number seems to be much higher in transplant patients as the total number of

PCN placed within 3 months after KT in our cohort was 60 patients of whom 26 patients (43%) developed a UTI after PCN placement. PCNs were placed if a urinary leakage or a stenosis of the ureter (resulting in hydronephrosis) occurred post-operatively. Instead of PCN placement, an alternative treatment option for these urological complications is direct surgical repair. However, in a previously conducted RCT at our center (INEX-trial) only 10 out of 40 patients with a PCN placement required a re-intervention (such as a surgical revision or a balloon dilatation) (14), saving 30 patients from revision. Therefore, direct surgical re-invention in case of urological complications would be excessive. Minimizing the number of urological complications and thus PCN placement remains one of the challenges in KT.

There was a significant decrease in mean GFR in patients after developing a UTI compared to those who did not. This finding is complimentary to the results of Bodro et al (4). In a review of Martin-Gandul et al. the impact of UTI on graft function appears to be different according to the period of the onset of the infection (early vs. late). They found that late and recurrent UTI only seem to be related to an increased risk of graft dysfunction, this is in contrast to our results (15). It should be noted that the GFR outcome on 6, 9 and 12 months can be influenced by several factors. In our analyses, we only included events (rejection, UTI) that occurred within the first 3 months after transplantation. Furthermore, there were more non-caucasian patients (28% vs 19%) in the UTI group. We have used GFR data without correcting for African-American origin. This could also contribute to a lower GFR in the UTI group. Therefore, we suggest that the association between UTI and decreased GFR should be taken with caution.

In a Cochrane review by Lusardi et al. the use of antibiotics prophylaxis for short term catheter bladder drainage (≤14 days) in adults was discussed (16). They conclude that antibiotic prophylaxis, compared to treatment with antibiotics when microbiologically indicated, reduced the rate of bacteriuria in general surgical patients when a urinary catheter is placed for at least 24 hours (16). As KT recipients receive high dose immunosuppression, the use of a prophylaxis is emphasized by Wolters et al.(17). They suggest 250mg of ciprofloxacin twice daily 1 day before and at the day of the removal of the urinary catheter (17). This finding is supported by a meta-analysis of Marschall et al. stating that patients admitted to the hospital who undergo short term urinary catheterization (< 14 days) might benefit from antimicrobial prophylaxis; a drawback of this article for our cohort is that the patients included were no KT recipients. Ciprofloxacin and trimethoprim/sulfamethoxazole were the most commonly used antibiotics for prophylaxis in their meta-analysis (18). In our cohort of KT recipients with a UTI, we found that 24% of tested Enterobacteriaceae were resistant to ciprofloxacin and 86% to trimethoprim/sulfamethoxazole; therefore, antibiotic prophylaxis using these two antibiotics is not

effective. Additionally, other microorganisms identified (e.g. Enterococci and Staphylococci) are intrinsically resistant to ciprofloxacin. Therefore, we purpose culture-based prophylaxis for KT recipients.

In our center an externalized stent and a urinary bladder catheter are placed during transplantation and removed on respectively day 9-10 and day 7 after transplantation, both without antibiotic prophylaxis. We identified age>60y and female gender as separate and independent risk factors for the development of a UTI. It may be advocated to remove the stent in patients with these risk factors with an antibiotic prophylaxis, although there is no strong evidence for this approach. A well-designed prospective randomized controlled trial in KT recipients with an externalized stent could provide the answer to this subject.

One of the limitations of our study is the fact that this is a retrospective study. The symptoms of UTI were not well documented and therefore we were not able to use the full CDC criteria and thus we choose to include those patients who received antibiotic treatment for UTI. Furthermore, there are a few symptoms included in the CDC criteria, such as costovertebral angle pain or tenderness and urinary urgency/frequency, which are not always relevant to transplant recipients. Since the kidney transplant is in the iliac fossa and some transplant recipients have no residual urine production and therefore have limited bladder capacity resulting in urinary urgency and frequency without a UTI. Another drawback of this study was that urinary cultures were not collected in a standardized manner and frequency after discharge, only during the primary admission every Monday, Wednesday and Friday standard urinary cultures were collected, after discharge they were only taken by clinical indication.

We conclude that UTI after KT is a common problem (28%). *E. coli* and *E. faecalis* are the most causative agents. We identified female gender, age>60y, PCN placement and surgical re-interventions as independent risk factors for the development of UTI after KT. UTI is associated with a decrease in mean GFR at 3, 6, 9 and 12 months postoperatively. Further studies are needed to resolve these severe complications in these high-risk patients. Studies on removing the catheter or stent under antibiotic prophylaxis are now urgently needed.

References

1. Rosselli D, Rueda JD, Diaz CE. Cost-effectiveness of kidney transplantation compared with chronic dialysis in end-stage renal disease. Saudi J Kidney Dis Transpl. 2015;26(4):733-8.
2. Anastasopoulos NA, Duni A, Peschos D, Agnantis N, Dounousi E. The Spectrum of Infectious Diseases in Kidney Transplantation: A Review of the Classification, Pathogens and Clinical Manifestations. In Vivo. 2015;29(4):415-22.
3. Wu X, Dong Y, Liu Y, Li Y, Sun Y, Wang J, et al. The prevalence and predictive factors of urinary tract infection in patients undergoing renal transplantation: A meta-analysis. Am J Infect Control. 2016.
4. Bodro M, Sanclemente G, Lipperheide I, Allali M, Marco F, Bosch J, et al. Impact of Urinary tract infections in short-term kidney graft outcome. Clin Microbiol Infect. 2015.
5. Ariza-Heredia EJ, Beam EN, Lesnick TG, Cosio FG, Kremers WK, Razonable RR. Impact of urinary tract infection on allograft function after kidney transplantation. Clin Transplant. 2014;28(6):683-90.
6. Galindo Sacristan P, Perez Marfil A, Osorio Moratalla JM, de Gracia Guindo C, Ruiz Fuentes C, Castilla Barbosa YA, et al. Predictive factors of infection in the first year after kidney transplantation. Transplant Proc. 2013;45(10):3620-3.
7. Golebiewska JE, Debska-Slizien A, Rutkowski B. Urinary tract infections during the first year after renal transplantation: one center's experience and a review of the literature. Clin Transplant. 2014;28(11):1263-70.
8. Prevention CfDCa. Urinary Tract infection (Catheter-Associated Urinary Tract Infection [CAUTI] and Non-Catheter-Associated Urinary Tract Infection [UTI]) and other Urinary System Infection [USI] Events January 2015 (modified april 2015).
9. Politano VA, Leadbetter WF. An operative technique for the correction of vesicoureteral reflux. J Urol. 1958;79(6):932-41.
10. Gregoir W. [the Surgical Treatment of Congenital Vesico-Ureteral Reflux] Le Traitement Chirurgical Du Reflux V'esico-Ur'et'eral Cong'enital. Acta Chir Belg. 1964;63:431-9.
11. Lich R, Jr., Howerton LW, Davis LA. Childhood urosepsis. J Ky Med Assoc. 1961;59:1177-9.
12. Capocasale E, De Vecchi E, Mazzoni MP, Dalla Valle R, Pellegrino C, Ferretti S, et al. Surgical site and early urinary tract infections in 1000 kidney transplants with antimicrobial perioperative prophylaxis. Transplant Proc. 2014;46(10):3455-8.
13. Kaskarelis IS, Papadaki MG, Malliaraki NE, Robotis ED, Malagari KS, Piperopoulos PN. Complications of percutaneous nephrostomy, percutaneous insertion of ureteral endoprosthesis, and replacement procedures. Cardiovasc Intervent Radiol. 2001;24(4):224-8.
14. Slagt IK, Dor FJ, Tran TC, Kimenai HJ, Weimar W, Ijzermans JN, et al. A randomized controlled trial comparing intravesical to extravesical ureteroneocystostomy in living donor kidney transplantation recipients. Kidney Int. 2014;85(2):471-7.
15. Martin-Gandul C, Mueller NJ, Pascual M, Manuel O. The Impact of Infection on Chronic Allograft Dysfunction and Allograft Survival After Solid Organ Transplantation. Am J Transplant. 2015;15(12):3024-40.
16. Lusardi G, Lipp A, Shaw C. Antibiotic prophylaxis for short-term catheter bladder drainage in adults. Cochrane Database Syst Rev. 2013;7:CD005428.
17. Wolters HH, Palmes D, Lordugin E, Bahde R, Senninger N, Holzen JP, et al. Antibiotic prophylaxis at urinary catheter removal prevents urinary tract infection after kidney transplantation. Transplant Proc. 2014;46(10):3463-5.
18. Marschall J, Carpenter CR, Fowler S, Trautner BW, Program CDCPE. Antibiotic prophylaxis for urinary tract infections after removal of urinary catheter: meta-analysis. BMJ. 2013;346:f3147.

CHAPTER 7

DUET-trial: DoUble j or External stenting during kidney Transplantation? Study-protocol

L.S.S. Ooms, J.N.M. Ijzermans, T. Terkivatan

Department of Surgery, Erasmus University Medical Center Rotterdam, The Netherlands

Manuscript in preparation

Abstract

Urological complications after kidney transplantation, such as urinary leakage and ureteral strictures, are associated with significant morbidity, surgical or radiological re-interventions, prolonged hospital stay and even mortality. It has been demonstrated that stent placement can minimize the number of urological complications. Two types of ureteral stents can be used; mainly divided in internal double J stents and external single J stents. It is unknown which kind of stent is superior in preventing urological complications. Therefore, in this study we will investigate whether double J stenting is superior to the use of an external stent in reducing the number of urological complications after kidney transplantation.

This will be a single-centre randomized controlled trial. Randomization will be performed after intubation in the operation room. All adult kidney transplant recipients that will be transplanted at the Erasmus University Medical Center (>18yrs) are invited to participate. Patients will be excluded if they do not understand the Dutch language sufficiently to sign the informed consent forms and to fill in the questionnaires, or if they have a reconstructed urinary tract or conduit after total or partial cystectomy, a bladder dysfunction that requires continuous or intermittent catheterization, or will receive a donor kidney with more than one ureter. In addition, patients with primary FSGS and residual urine production will be excluded. Nowadays, our clinical practice is the use of an external stent during kidney transplantation. Our "intervention" will be the use of an internal double J stent which will be removed by cystoscopy 3 weeks after transplantation. Our main study endpoint is the number of percutaneous nephrostomy (PCN) drainages. The secondary study parameters are urinary tract infections, macroscopic haematuria, radiological interventions, surgical re-interventions and stent obstruction or dysfunction. Furthermore, we will ask the recipients to fill in questionnaires to analyse the quality of life and make a cost-effectiveness analysis.

The DUET-trial will provide evidence about which type of stent (double J vs. external) should be used during kidney transplantation to minimize the number of urological complications.

Introduction

Kidney transplantation is the best treatment offering long-term benefit to patients with chronic kidney failure. Urological complications after kidney transplantation, such as urinary leakage and ureteral strictures, are associated with significant morbidity, surgical or radiological re-interventions, prolonged hospital stay and even mortality. Many urological complications are related to the ureteroneocystostomy and the first treatment for urinary leakage or ureteral stenosis is placement of a percutaneous nephrostomy (PCN) drain(1, 2). It has been demonstrated that stent placement can minimize the number of urological complications (3, 4). Two types of ureteral stents can be used; mainly divided in internal double J stents and external single J stents. In our center, we have used an external stent for several years and urological complications are reported up to 9% of the kidney transplant recipients (5). However, in literature several studies even report less urological complications using a double J stent. A retrospective study by Vogel et al. including 76 patients with 43 external stents and 33 double J stents have reported an incidence of leakage of the ureteroneocystostomy of 13.9% in the external stent group compared to 0% in the double J stent group. Furthermore, they found a 2 day reduction of hospital stay with a double J stent (6). Gomes et al. also retrospectively reviewed the use of external, double J stents and no stents in 2061 kidney transplant recipients. In their cohort, urological complications occurred in 17.3% in the group with external stents, 8.4% in patients that did not receive a stent, and 5.4% in kidney transplant recipients in whom a double J stent was placed ($P < .0005$)(7). The authors even state: "the use of an external stent which was associated with a high rate of urological complications, should be avoided". Guleria et al. also reduced their urological complications by changing their technique from a non-stented (7.7%) to a double J stented (for a period of 6 weeks) ureteroneocystostomy (3.8%)(8). Unfortunately, all these studies have a retrospective design and no prospective randomized controlled trials are available. Therefore, in the DUET-trial we will investigate whether double J stenting is indeed superior to the use of an external stent in reducing the number of urological complications after kidney transplantation, as measured by the number of PCN placements.

Methods

Study design

This will be a single-centre randomized controlled trial with a superiority design. Randomization by a computerized system will be performed after intubation in the operation room, stratified for type of donor (living/ deceased). Physicians participating in this study will be unaware of the randomization sequence thereby guaranteeing concealed

allocation. Since patients and physicians will notice post-operatively the presence of an external stent, the study cannot be blinded. Participants will be included during a period of 3 years, 100 recipients each year. Last follow-up moment of all questionnaires will 6 months after transplantation.

Participants

All adult kidney transplant recipients in the Erasmus University Medical Center (>18yrs) are invited to participate.

Exclusion criteria

- Patients who do not understand the Dutch language sufficiently to sign the informed consent forms and to fill in the questionnaires
- Patients with a reconstructed urinary tract or conduit after total or partial cystectomy
- Patients with bladder dysfunction that requires continuous or intermittent catheterization
- Donor kidneys with more than one ureter
- Patients with primary FSGS and residual urine production (because FSGS can progress rapidly in the new kidney graft and using an external stent gives the possibility of monitoring the transplants urine on proteinuria, i.e. a first sign of FSGS recurrence)

Withdrawal, dropout, and discontinuation

Subjects can leave the study at any time for any reason if they wish to do so without any consequences. The investigator can decide to withdraw a subject from the study for urgent medical reasons. These patients will not be replaced, as we have anticipated on some missing data in our power calculation.

Intervention

After the vascular anastomosis, the transplant surgeon will perform an extravesical anastomosis as described by Lich-Gregoir (9, 10). A myotomy of 2-3 cm on the anterolateral surface of the bladder dome is performed to expose the mucosa of the bladder wall. A small incision is made in the mucosa. The transplanted ureter is trimmed and spatulated posteriorly. The bladder mucosa is sutured to the ureter with a running absorbable suture. The detrusor muscle is closed over the anastomosis by one or two interrupted absorbable sutures to create a sub-mucosal tunnel with an antireflux mechanism. Participants who are randomized to external stenting will receive an externalised 7 French ureteric stent (Teleflex®). Participants who are randomized to double J stenting will receive a short (12cm) internal Double J 7 French stent (Teleflex®). The tip of both stents will be positioned in the pelvis of the transplanted kidney. The position of the stent will be verified during ultrasonography, which is being performed the day after surgery as

standard post-operative care. External stents will be removed 9 days post-operatively. Double J stents will be removed after 3 weeks by cystoscopy in the outpatient clinic of the department of urology. An antibiotic prophylaxis will be used during this procedure based on the latest urinary cultures. Recipients will be asked to fill in questionnaires at different time points (pre-operative, week 2, week 6 and 6 months after transplantation), including a Visual Analogue Score (VAS), quality of life questionnaire (SF-36), Euro-Qol (EQ-5D) and 'Werk en Zorg' questionnaires.

Outcomes and measures

Our main study endpoint is the number of percutaneous nephrostomy (PCN) drainages. The secondary study parameters are the number of urinary tract infections, macroscopic haematuria, radiological interventions, surgical re-interventions and stent obstruction or dysfunction. Additionally, a quality of life and cost effectiveness analysis will be performed by using questionnaires. Validated questionnaires for pain, quality of life, health state, work efforts and disabilities in daily life are measured by the VAS, Euro-Qol, SF-36 and 'Werk en Zorg'. Other study parameters are baseline values, which might intervene with the main study parameter: donor age and gender, recipient age and gender, body mass index, smoking, ASA classification, operation time and return to normal daily activities.

Adverse events

The sponsor will suspend the study if there is sufficient ground that continuation of the study will jeopardise subject health or safety. The sponsor will notify the accredited medical ethical board without undue delay of a temporary halt including the reason for such an action. The study will be suspended pending a further positive decision by the accredited medical ethical board. The investigator will take care that all subjects are kept informed. The sponsor will report serious adverse events (SAEs) to the accredited medical ethical board. A data safety monitoring board will be installed to evaluate this study after every 50 included patients.

Randomization and blinding

Randomization will be performed after intubation in the operation room by an electronic system, stratified for type of donor (living/deceased). Since patients and physicians will notice post-operatively the presence of an external stent, the study cannot be blinded.

Date entry and quality control of data

The coordinating investigator collects all data. Every patient is coded into numbers. The coordinating and principal investigators have access to the source data. Data will be stored for 15 years.

Sample size calculation

This study aims to show that a double J stent results in fewer PCN placements. Based on an two-sided alpha of 0.05, 149 patients are needed to have an 80% power to reject the null hypothesis of no effect when tested with Fisher's exact test when the double J stent in fact reduces the probability of PCN placement from 9% to 1.5% (3,5) To allow for a few non evaluable cases we randomize 150 patients per arm. (SAS Power and Sample Size 14.1)

Statistical analysis

The primary study outcome is PCN placement. This is a categorical variable and will be presented as number (percentage). Continuous variables will be presented as median (range) en mean with standard deviation, depending whether the variable is normally distributed. Categorical variables will be compared with the Chi-square test. Continuous variables will be compared with the Mann-Whitney-U test or independent T test. The questionnaires, filled out at different time points, will be analysed with a linear mixed model. All analyses will be conducted using IBM SPSS Statistics for Windows (version 20.0. Armonk, NY: IBM Corp, USA). A p-value <0.05 (two-sided) will be considered statistically significant.

Discussion

In this single center randomized controlled trial, we will investigate whether double J stenting is superior to single J (external) stenting in preventing urological complications after kidney transplantation.

It has been demonstrated that stent placement can minimize the number of urological complications (3, 4). In our center, we have used an external stent for several years and urological complications are reported up to 9% of the kidney transplant recipients (5). In literature, the double J stent even has less urological complications 0-5.4% and the use of a double J is associated with a 2-day reduction of hospital stay (6, 7). Unfortunately, all these studies are retrospective and no well-designed prospective randomized controlled trial is available on this matter.

Therefore, we present this study protocol of the DUET-trial. A randomized controlled trial, which will be conducted at the Erasmus University Medical Center, Rotterdam, The Netherlands.

References

1. Dols LF, Terkivatan T, Kok NF, Tran TC, Weimar W, JN IJ, et al. Use of stenting in living donor kidney transplantation: does it reduce vesicoureteral complications? Transplant Proc. 2011;43(5):1623-6.
2. Miraglia R, Caruso S, Milazzo M, Salis P, Luca A, Gridelli B. Efficacy of interventional radiology procedures for the treatment of early ureteral complications after kidney transplantation. Transplant Proc. 2006;38(9):2919-20.
3. Wilson CH, Rix DA, Manas DM. Routine intraoperative ureteric stenting for kidney transplant recipients. Cochrane Database Syst Rev. 2013;6:CD004925.
4. Mongha R, Kumar A. Transplant ureter should be stented routinely. Indian J Urol. 2010;26(3):450-3.
5. Ooms LS, Spaans LG, Betjes MG, Ijzermans JN, Terkivatan T. Minimizing the number of urological complications after kidney transplantation: A comparative study of two types of external ureteral stents. Exp Clin Transplant. 2016.
6. Vogel T, Utech M, Schmidt F, Holscher Keplin W, Diller R, Brockmann J, et al. Double-J Versus External Ureteral Stents in Kidney Transplantation: A Retrospective Analysis. Nephrourol Mon. 2015;7(4):e27820.
7. Gomes G, Nunes P, Castelo D, Parada B, Patrao R, Bastos C, et al. Ureteric stent in renal transplantation. Transplant Proc. 2013;45(3):1099-101.
8. Guleria S, Chahal R, Madaan S, Irving HC, Newstead CG, Pollard SG, et al. Ureteric complications of renal transplantation: the impact of the double J stent and the anterior extravesical ureteroneocystostomy. Transplant Proc. 2005;37(2):1054-6.
9. Gregoir W. [the Surgical Treatment of Congenital Vesico-Ureteral Reflux] Le Traitement Chirurgical Du Reflux V'esico-Ur'et'eral Cong'enital. Acta Chir Belg. 1964;63:431-9.
10. Gregoir W, Vanregemorter G. [Congenital Vesico-Ureteral Reflux] Le Reflux V'esico-Ur'et'eral Cong'enital. Urol Int. 1964;18:122-36.

CHAPTER 8

Incidence, risk factors and treatment of incisional hernia after kidney transplantation: an analysis of 1564 consecutive patients

L.S.S. Ooms[1*], J. Verhelst[1*], J. Jeekel[2], J.N.M. IJzermans[1], J.F. Lange[1], T. Terkivatan[1]

1. Department of Surgery, Erasmus University Medical Center, Rotterdam, The Netherlands
2. Department of Neuroscience, Erasmus University Medical Center, Rotterdam, The Netherlands

Surgery, 2016 May;159(5):1407-11

Abstract

The objective was to evaluate the incidence and treatment of incisional hernia following kidney transplantation, and to identify potential risk factors. A retrospective cohort study was performed. All kidney transplant recipients between 2002 and 2012 were included. Two groups were identified: patients with incisional hernia and patients without. Risk factor analysis for development of incisional hernia was performed. A total of 1564 kidney recipients were included. Fifty patients (3.2%) developed incisional hernia. On univariate analysis, female gender (54% vs. 35% p = 0.006), BMI>30 kg/m2 (38 % vs. 17%, p< 0.001), concurrent abdominal wall hernia (30% vs. 16%, p=0.007), multiple explorations of the ipsilateral iliac fossa (38% vs. 19%, p=0.001), left iliac fossa implantation (36% vs 24%, p=0.046), history of smoking (72% vs 57%, p=0.032) and duration of surgery (210 minutes vs. 188 minutes, p=0.020) were associated with the development of incisional hernia. In multivariate analyses, female gender (HR 2.6), history of smoking (HR 2.2), obesity (BMI >30) (HR 2.9), multiple explorations of the ipsilateral iliac fossa (HR 2.0), duration of surgery (HR 1.007), and concurrent abdominal wall hernia (HR 2.3) were independent risk factors. Twenty-six of 50 patients (52%) underwent surgical repair, of which nine (35%) required emergency repair. The incidence of incisional hernia following kidney transplantation is 3.2%. We found obesity (BMI>30), female gender, concurrent abdominal wall hernias, history of smoking, duration of surgery, and multiple explorations to be independent risk factors for the development of incisional hernia after kidney transplantation. These risk factors should be taken into account to prevent incisional hernia.

Introduction

Incisional hernia is one of the most frequent postoperative complications after abdominal surgery. The incidence varies between 11 and 20% in general population and may be even higher in risk subgroups (1-4). Incisional hernia has great impact on the health related quality of life and body image (4, 5). Known risk factors for development of incisional hernia are obesity, aneurysm of the abdominal aorta, immunosuppressive therapy, and postoperative wound infection (1, 4-7). Hence, transplant recipients may have an increased risk to develop incisional hernia due to the use of postoperative immunosuppressive therapy resulting in impaired wound healing (5, 7).

The incidence of incisional hernia after kidney transplantation in literature, however, is reported to be remarkably low and varies between 1% and 7% (6, 8-14).

The use of a mesh is the gold standard for the treatment of incisional hernia. However, also with mesh placement, recurrence rates are still very high, up to 32%, and the use of mesh facilitates possible mesh related complications such as seroma formation, hematoma, mesh infection, and enterocutaneous fistula (2). Additionally, mesh placement after kidney transplantations makes the iliac fossa less accessible for future transplant removal or kidney retransplantation in the ipsilateral iliac fossa. On the other hand, a conservative treatment of incisional hernia leads to secondarily high crossover rates to surgical hernia repair with increased postoperative morbidity and mortality, particularly in patients who need emergency surgery due to incarceration of the hernia contents (15).

We conducted this retrospective case control study to evaluate the incidence and treatment of incisional hernia following kidney transplantation, and to identify independent potential risk factors for the development of incisional hernia.

Methods

A retrospective cohort study was performed at the department of Transplant Surgery of the Erasmus University Medical Center, Rotterdam, the Netherlands. All patients who underwent kidney transplantation between January 2002 and December 2012 were identified from the electronic hospital data systems. Electronic hospital data systems and medical charts of all kidney transplantations were manually reviewed and patients diagnosed with incisional hernia were identified. Second transplantations in the contralateral fossa were considered to be new cases; on the other hand, a second transplantation in

the ipsilateral fossa was defined as a surgical re-intervention. Our cohort was divided in two groups, one group of kidney transplant recipients that developed incisional hernia and one who did not develop incisional hernia during follow up. The following patient characteristics and clinical data were registered in search for potential risk factors: patient demographics (i.e. gender, body mass index (BMI), age), preoperative comorbidities associated with impaired wound healing or incisional hernia (i.e. diabetes mellitus (DM), preoperative immunosuppressive therapy, smoking, pre-emptive transplantation, other concurrent hernia), perioperative data (i.e. deceased/living donor, implantation side, duration of surgery, surgery during after hours, and multiple explorations of ipsilateral fossa) and hernia characteristics (i.e. time to diagnose, treatment, emergency repair, use of mesh, recurrence). After hours were defined as surgery starting between 5 p.m. and 8 a.m. Exploration of the ipsilateral iliac fossa included re-transplantations, transplant removal, or complication surgery (i.e. urological complications, bleeding). All patients had a semilunaire supra inguinal incision to gain access to retroperitoneal space. Standard immunosuppressive therapy consisted of tacrolimus, mycophenolate mofetil, and prednisolone. Prednisone was gradually tapered and eventually stopped at 4 months. On indication, conversions to ciclosporin, azathioprine, sirolimus or prednisone have been performed in individual patients. Incisional hernias were diagnosed at the outpatient clinic or emergency department. The follow-up of kidney transplant recipients is done by the nephrologists in our center. In case the nephrologist assumed an incisional hernia, the patient was referred to the surgical outpatient clinic. Incisional hernias were generally diagnosed by physical examination by surgeons. When there was doubt after physical examination additional radiologic imaging was performed. In case of incisional hernia repair, defects were corrected either primary or with mesh in intraperitoneal, preperitoneal, sublay or onlay fashion. If possible a tension free, non-bridging technique was preferred over a bridging technique to close the defect.

Data analysis

SPSS 21.0 (IBM Corp. Released 2012. IBM SPSS Statistics for Windows, version 21.0. Armonk, NY: IBM Corp.) was used for all statistical analyses. Continuous variables were presented as means with Standard Deviations (SD) or as medians with Inter Quartile Range (IQR). Categorical variables were presented as numbers with percentages (%). Independent T-test, Mann-Whitney U and Chi-square tests were used to compare risk factors for incisional hernia after kidney transplantation. Univariate regression analyses were performed for development of incisional hernia with risk factors by analysing each potential risk factor separately. Potential risk factors that were significantly related to incisional hernia in the univariate regression analysis (i.e. BMI >30 kg/m2, gender, concurrent abdominal wall hernia, history of smoking, multiple explorations of the ipsilateral fossa, duration of surgery, and implantation side) were included in our multivariate

regression analyses. The multivariate regression analyses were performed using a Cox Proportional Hazards (CPH) model to control for effects of multiple potential risk factors. A p-value less than 0.05 was considered statistically significant.

Results

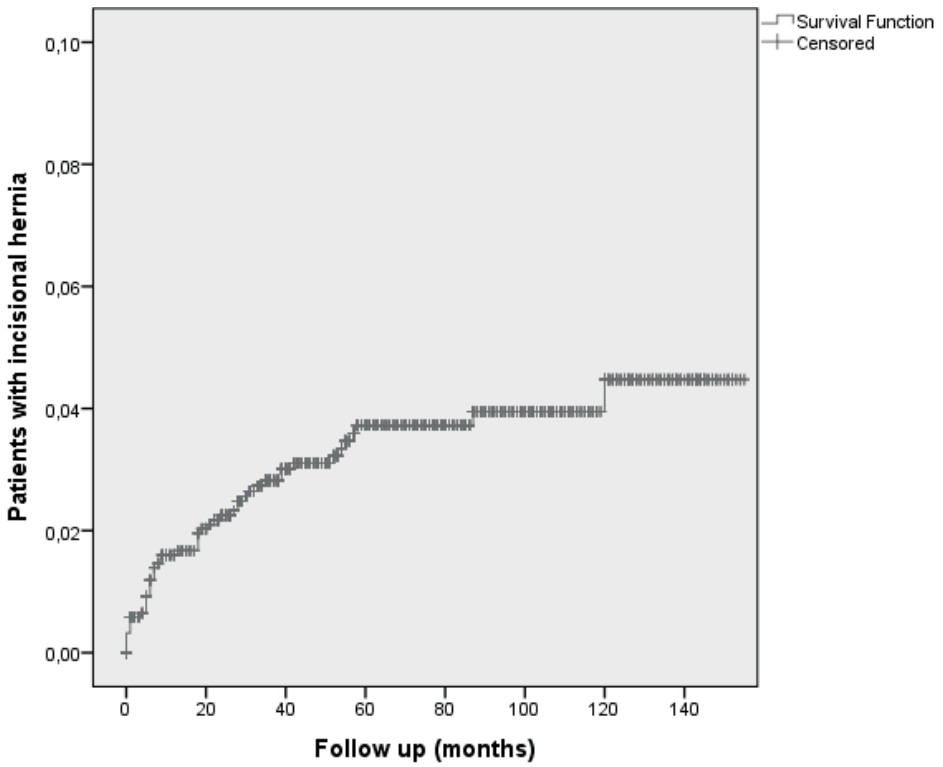
Baseline characteristics demography table

Between 2002 and 2012 1564 kidney transplantations were performed; 1004 (64%) were male recipients, mean age at transplantation was 51 years (SD 14.4 years). Mean BMI was 25.7 (SD 4.7). Median follow up was 59 months (IQR 34-95 months), 274 (17.5%) patients died during follow up. Preoperatively, 349 (23%) patients reported to be current smokers at time of transplantation, 532 (35%) had a smoked in the past and 659 (42%) never smoked. One thousand and twenty-two (65%) transplantations concerned kidneys of a living donor, 542 (35%) grafts were from deceased donors. Prior to transplantation 370 (24%) patients did not receive hemo- or peritoneal dialysis. Preoperatively, in total 222 (14%) patients already used immunosuppressive drugs of whom 3 patients (6%) developed incisional hernia and 219 patients (15%) did not, (p=0.089). 1187 (76%) kidneys were placed in the right and 377 (24%) in the left iliac fossa. Mean duration of surgery was 188 minutes (SD 44 minutes) and 294 (19%) transplantations took place during after-hours (between 5:00 p.m. and 7:59 a.m.). Three hundred and one (19%) patients needed surgery in the same fossa after initial transplantation due to bleeding, urological complications or transplant removal.

Incisional hernia

A total of 50 (3.2%) patients developed incisional hernia. Median time between transplantation and the development of incisional hernia was 68 weeks (IQR 24-149 weeks). The time to develop incisional hernia after kidney transplantation is presented in Figure 1. The cumulative incidence of development of incisional hernia was 1.6% at 12 months after transplantation, 3.7% at 60 months and 4.4% at 120 months postoperative. Potential risk factors for incisional hernia, after univariate analyses are presented in Table 1. Surgical repair of the incisional hernia was performed in 26 patients (52%), 24 (48 %) were treated conservatively. Surgical repair was performed with polypropylene mesh in 15 patients, 4 polyester meshes were placed, 1 Vicryl® mesh was placed because of a contaminated environment, and 6 patients underwent hernia repair without mesh (5 patients without mesh placement were operated during an emergency repair). The mesh was placed with bridging technique in 11 patients and in 7 patients non-bridging techniques was used, in 2 patients the details of the technique were not documented. Nine patients (35%) required emergency repair due to small bowel incarceration. In 6

Figure 1. Development of incisional hernia following kidney transplantation



of 26 (23%) patients recurrence of incisional hernia occurred. Two patients with a recurrence were initially corrected with polyester mesh, 2 with polypropylene mesh, 1 with Vicryl ® mesh, and 1 defect was closed primarily.

Risk factor analyses

Univariate regression analysis showed that concurrent abdominal wall hernia (HR 2.4; p=0. 005), female gender (HR 2.1; p=0.011), history of smoking (HR 1.9; p=0.035), obesity (HR 3.0; p<0.001), multiple explorations in the ipsilateral fossa (HR 2.7; p=0.001), duration of surgery (HR 1.009; p<0.001), left sided implantation (HR 1.8 p=0.046) were associated with the development of incisional hernia. When we corrected for possible confounding variables in the multivariate regression analysis, all aforementioned risk factors except for the implantation side remained independent risk factors for the development of incisional hernia after transplantation. Hazard ratios with 95% confidence intervals are presented in Table 2.

Table 1. Univariate analyses

	With IH (n=50)	Without IH (n=1514)	**P-value**
Female gender (%)	27 (54)	533 (35)	**0.006**
BMI, kg/m^2 (mean) (SD)	28.7 (5.6)	25.6 (4.6)	**<0.001**
BMI > 30 kg/m^2 (%)	19 (38)	260 (17)	**<0.001**
Age (mean) (SD)	51.4 (12.1)	51.4 (14.5)	0.968
Diabetes mellitus (%)	12 (24)	300 (20)	0.466
Pre-emptive transplantation (%)	16 (32)	354 (23)	0.158
Pre-operative immunosuppression	3 (6)	219 (15)	0.089
Current smoking (%)	11 (22)	338 (23)	0.909
History of smoking* (%)	36 (72)	845 (57)	**0.032**
Concurrent abdominal wall hernia (%)	15 (30)	238 (16)	**0.007**
Living donor (%)	31 (62)	991 (66)	0.613
Left side implantation (%)	18 (36)	359 (24)	**0.046**
Duration surgery, min (mean) (SD)	210 (64)	188 (43)	**0.020**
Surgery during after-hours (%)	12 (24)	282 (19)	0.340
Multiple explorations same fossa (%)	19 (38)	282 (19)	**0.001**

*History of smoking includes all current and past smokers
P-values are 2-sided. For dichotomous variables chi-square test and for continuous variables Mann-Whitney U or t-test was performed.
IH, Incisional hernia; BMI, body mass index;

Table 2. Multivariable risk factor analyses

	HR	95% CI	**P-value**
BMI >30 kg/m2	2.9	1.6-5.2	**<0.001**
Female gender	2.6	1.4-4.7	**0.002**
Concurrent abdominal wall hernia	2.3	1.2-4.3	**0.009**
History of smoking	2.2	1.1-4.1	**0.019**
Multiple explorations	2.0	1.1-3.7	**0.026**
Left sided implantation	1.6	0.9-2.8	0.132
Duration of surgery, min	1.007	1.001-1.012	**0.014**

2-sided chi-square tests were performed
HR, hazard ratio; CI, confidence interval; BMI, body mass index.

Discussion

In this retrospective analysis, we found an incidence of incisional hernia after kidney transplantation of 3.2%. Presumably this incidence is lower compared to other abdominal wall incisions due to the anatomical location of the iliac incision in kidney transplantation and the transfascial and muscular approach perpendicular to the tension lines of the abdomen. The outcome corresponds with the incidence described in literature

(6, 12-14). Beside the known risk factors smoking and obesity, we found female gender, duration of surgery, other abdominal wall hernia, and multiple exploration of the ipsilateral iliac fossa to be new independent risk factors for development of incisional hernia after kidney transplantation. Surgical repair of the incisional hernia was performed in 26 (52%) patients; nine (35%) required emergency repair.

This study describes new independent risk factors for the development of incisional hernia after transplantation and gives information about the treatment of incisional hernia in a well-defined surgical population. A recent publication provided an overview of incisional hernia formation following abdominal organ transplantation, including 2247 kidney transplantations. The authors reported an incidence of 7% after 10 years follow up. The only independent risk factors for development of incisional hernia in their cohort were the non-use of mycophenolate mofetil and surgical site infection (6). In this study, we identified predisposing independent risk factors, such as female gender, duration of surgery, obesity, other abdominal wall hernia, multiple explorations, and smoking. These preoperative and perioperative risk factors should be taken into account by surgeons when closing the fascia.

According to the guidelines of the European Hernia Society on abdominal wall closure, small bite sutures are suggested for fascia closure after midline incisions in order to prevent incisional hernia. In the small bite technique the laparotomy wound is closed with a single layer suturing technique taking bites of fascia of 5–8 mm and placing stitches every 5 mm (16, 17). Furthermore, a running suture length to wound length ratio of at least 4 to 1 is advised (16, 18). Although this technique in advised for midline incisions, it can also be considered during iliac fossa closure in high-risk transplant recipients. However, more research is necessary to prove the effect of small bite sutures in iliac fossa incisions. Prophylactic mesh placement in kidney transplant recipients with non-modifiable pre-operative risk factors is not preferrable, as this would make future explorations of the iliac fossa more difficult. Moreover, the use of immunosuppressive drugs postoperatively could make meshes more prone for mesh infection.

Preoperative weight reduction in obese patients should not only be advised to benefit graft survival, prevent diabetes and reduce hospital stay, but also to prevent postoperative complications such as wound infection and incisional hernia (19).

Another publication reported an incidence of 2.6% for incisional hernia after kidney transplantation of which 71% needed surgical repair. These authors reported a recurrence rate of 20%. This corresponds with our recurrence rate of 23% and recurrence rates after other abdominal incisional hernia (2, 13).

Synthetic polypropylene was the mesh most frequently used in our cohort, which is also being mentioned in literature for surgical repair of incisional hernia after kidney transplantation (10-14). Nevertheless, it is conceivable that biological prosthesis (i.e. porcine dermis collagen) could be useful in patients who are prone to develop wound infection. Biological meshes are already deemed feasible and safe, however, the number of patients treated with these meshes is still limited and the advantage over synthetic meshes is not yet properly investigated (20).

The prolonged duration of the transplantation procedure in the group that developed incisional hernia can be explained by the complexity of the procedure. Also, the relationship between obesity and prolonged duration of surgery has previously been described (19).

The present study has few limitations most of them attributable to the retrospective design. A few potential risk factors, for instance number of wound infections, which are known to be a potential risk factor for the development of incisional hernia, could not be analyzed thoroughly in our hospital data systems (6, 21). Because the diagnosis of incisional hernia is made clinically and radiography is not a standard procedure, the number of incisional hernias could be underestimated. However, patients had meticulous follow up with physical examination postoperatively in our outpatient clinic. Moreover, patients who developed incisional hernia who present in another hospital are always referred to the surgical department in our center.

In conclusion, we found that the incidence of incisional hernia following kidney transplantation is 3.2%. The emergency surgical repair rate of the incisional hernia was 35% and recurrences occurred in 23%. Beside the known risk factor obesity (BMI>30) and smoking, we found female gender, concurrent abdominal wall hernias, duration of surgery, and multiple explorations appear to be new independent risk factors for the development of incisional hernia after kidney transplantation. Surgeons should be aware of these risk factors when closing the fascia after transplantation or re-exploration in order to prevent incisional hernia.

References

1. Bevis PM, Windhaber RA, Lear PA, et al. Randomized clinical trial of mesh versus sutured wound closure after open abdominal aortic aneurysm surgery. Br J Surg. 2010 Oct;97:1497-502.
2. Burger JW, Luijendijk RW, Hop WC, et al. Long-term follow-up of a randomized controlled trial of suture versus mesh repair of incisional hernia. Ann Surg. 2004 Oct;240:578-83; discussion 83-5.
3. van 't Riet M, Steyerberg EW, Nellensteyn J, et al. Meta-analysis of techniques for closure of midline abdominal incisions. Br J Surg. 2002 Nov;89:1350-6.
4. van Ramshorst GH, Eker HH, Hop WC, et al. Impact of incisional hernia on health-related quality of life and body image: a prospective cohort study. Am J Surg. 2012 Aug;204:144-50.
5. de Goede B, Eker HH, Klitsie PJ, et al. Incisional hernia after liver transplantation: risk factors and health-related quality of life. Clin Transplant. 2014 Jul;28:829-36.
6. Smith CT, Katz MG, Foley D, et al. Incidence and risk factors of incisional hernia formation following abdominal organ transplantation. Surg Endosc. 2015 Feb;29:398-404.
7. Knight RJ, Villa M, Laskey R, et al. Risk factors for impaired wound healing in sirolimus-treated renal transplant recipients. Clin Transplant. 2007 Jul-Aug;21:460-5.
8. Massarweh NN, Clayton JL, Mangum CA, et al. High body mass index and short- and long-term renal allograft survival in adults. Transplantation. 2005 Nov 27;80:1430-4.
9. Singh D, Lawen J, Alkhudair W. Does pretransplant obesity affect the outcome in kidney transplant recipients? Transplant Proc. 2005 Mar;37:717-20.
10. Birolini C, Mazzucchi E, Utiyama EM, et al. Prosthetic repair of incisional hernia in kidney transplant patients. A technique with onlay polypropylene mesh. Hernia. 2001 Mar;5:31-5.
11. Li EN, Silverman RP, Goldberg NH. Incisional hernia repair in renal transplantation patients. Hernia. 2005 Oct;9:231-7.
12. Mahdavi R, Mehrabi M. Incisional hernia after renal transplantation and its repair with propylene mesh. Urol J. 2004 Fall;1:259-62.
13. Mazzucchi E, Nahas WC, Antonopoulos I, et al. Incisional hernia and its repair with polypropylene mesh in renal transplant recipients. J Urol. 2001 Sep;166:816-9.
14. Varga M, Matia I, Kucera M, et al. Polypropylene mesh repair of incisional hernia after kidney transplantation: single-center experience and review of the literature. Ann Transplant. 2011 Jul-Sep;16:121-5.
15. Verhelst J, Timmermans L, van de Velde M, et al. Watchful waiting in incisional hernia: is it safe? Surgery. 2015 Feb;157:297-303.
16. Millbourn D, Cengiz Y, Israelsson LA. Effect of stitch length on wound complications after closure of midline incisions: a randomized controlled trial. Arch Surg. 2009 Nov;144:1056-9.
17. Muysoms FE, Antoniou SA, Bury K, et al. European Hernia Society guidelines on the closure of abdominal wall incisions. Hernia. 2015 Feb;19:1-24.
18. Israelsson LA, Jonsson T, Knutsson A. Suture technique and wound healing in midline laparotomy incisions. Eur J Surg. 1996 Aug;162:605-9.
19. Lafranca JA, Hagen SM, Dols LF, et al. Systematic review and meta-analysis of the relation between body mass index and short-term donor outcome of laparoscopic donor nephrectomy. Kidney international. 2013 May;83:931-9.
20. M LS, Carlomagno N, Spiezia S, et al. Use of biological prostheses in transplant patients with incisional hernias. Preliminary experience. Ann Ital Chir. 2013 Jul-Aug;84:471-5.
21. Humar A, Ramcharan T, Denny R, et al. Are wound complications after a kidney transplant more common with modern immunosuppression? Transplantation. 2001 Dec 27;72:1920-3.

CHAPTER 9

Kidney retransplantation in the ipsilateral iliac fossa: a surgical challenge

L.S.S. Ooms[1], J.I. Roodnat[2], F.J.M.F. Dor[1], T.C.K. Tran[1], H.J.A.N. Kimenai[1], J.N.M. Ijzermans[1], T. Terkivatan[1]

1. Department of Surgery, Erasmus University Medical Center, Rotterdam, The Netherlands
2. Department of Nephrology, Erasmus University Medical Center, Rotterdam, The Netherlands

American Journal of Transplantation, 2015 Nov;15(11):2947-54

Abstract

The aim of this study is to review the surgical outcome of kidney retransplantation in the ipsilateral iliac fossa in comparison to first kidney transplants. The database was screened for retransplantations between 1995-2013. Each study patient was matched with 3 patients with a first kidney transplantation. Just for graft and patient survival analyses we added an extra control group including all patients receiving a second transplantation in the contralateral iliac fossa. We identified 99 patients that received a retransplantation in the ipsilateral iliac fossa. There was significantly more blood loss and longer operative time in the retransplantation group. The rate of vascular complications and graft nephrectomies within 1 year was significantly higher in the study group. The graft survival rates at 1 year and 3, 5 and 10 years were 76%, 67%, 61% and 47% in the study group vs. 94%, 88%, 77% and 67% ($P<0.001$) in the first control group vs. 91%, 86%, 78% and 57% ($P=0.008$) in the second control group. Patient survival did not differ significantly between the groups. Kidney retransplantation in ipsilateral iliac fossa is surgically challenging and associated with more vascular complications and graft loss within the first year after transplantation**.** Whenever feasible, the second renal transplant (first retransplant) should be performed contralateral to the prior failed one.

Introduction

Kidney transplantation is the treatment of choice for end stage renal disease (ESRD). It offers a better quality of life and longer survival compared to remaining on dialysis (1). In 2013, 25% of patients on the Dutch kidney transplant waiting list awaited a retransplant. The population enlisted for a retransplant differs from the population enlisted for the first time. Reasons for loss of the first kidney graft may also threaten following grafts. The most important factor probably is rejection. Both acute and chronic allograft rejection may result in immunization and increased chances for rejection of the following graft. Panel reactive antibody (PRA) best describes the degree of immunization and in multivariable analysis high levels are associated with graft failure censored for death. In multivariable analysis, the number of preceding renal transplants does not influence graft survival when PRA is present in the model (2).

Other reasons for first (and following) graft loss may be recurrence of original disease e.g. various types of glomerulonephritis (e.g FSGS, IgA nephropathy), systemic diseases and diabetes mellitus. Thrombosis of renal vein or artery after transplantation is an infrequent cause of graft loss and always leads to analysis of clotting disorders to prevent recurrence. Furthermore, retransplants also present a surgical challenge due to possible adhesions, difficulties reaching the iliac vasculature or earlier manipulation of the bladder to establish the ureterovescial anastomosis.

Several retransplantation techniques have been described including the transperitoneal, retroperitoneal and orthotopic approach (3-6). This raises the question which technique should be preferred. As in most centers, in first instance we implant the renal graft in the extraperitoneal iliac fossa. If a retransplantation must be performed, the use of the contralateral iliac fossa is advocated. However, in case of a third or even fourth retransplant, it is unavoidable to explore an iliac fossa that has already been dissected for the previous implantation and for removal of the non-functioning graft.

So far, only a limited number of studies have been published on the use of the ipsilateral iliac fossa for retransplantation and they included a low number of patients or patients undergoing simultaneous pancreas-kidney transplantation (7-9). This finding may be due to the exceptional indication for a third of fourth retransplant in the past. In this manuscript, we present a retrospective case-controlled study on the surgical challenges of kidney retransplantation in the ipsilateral iliac fossa including the largest number of patients reported to date.

Methods

Study population and data selection

The database of the Erasmus MC, University Medical Center, Rotterdam, includes a total of 2307 adult kidney transplants performed between January 1995 and December 2013. The database was screened for patients who received a retransplant in the ipsilateral iliac fossa. Pediatric patients were excluded.

We conducted a case-controlled study matching three control patients to each study patient. The criteria for the matching process were recipient gender and age, year of transplantation and type of donor (deceased vs. living). All control patients received a first kidney transplant. Patients with simultaneous liver and/or pancreas transplantation were excluded. Data on the surgical procedure, hospital stay as well as follow up data were analyzed. Baseline characteristics included recipient gender and age, implantation side, body mass index, number of transplants with a positive crossmatch, number of ABO-incompatible transplants, type of donor (deceased vs. living), left/right donor kidney, number of prior transplants, cold and warm ischemia time, number of arteries of the transplanted kidney, anti-thymocyte globulin (ATG) therapy and follow up in months. The immunologic risk was defined by current panel reactive antibodies (PRA), highest PRA and human leukocyte antigen (HLA) mismatches. Outcome parameters as operative time, estimated blood loss, urological complications (defined as percutaneous nephrostomy placement (PCN)), vascular complications and surgical re-interventions were analyzed. Surgical re-interventions were defined as all procedures performed within one year after kidney transplantation. Removal of a continuous ambulant peritoneal dialysis (CAPD) catheter was not included as re-intervention. Re-interventions were divided into 4 categories: 1) Surgical re-interventions due to post-operative bleeding; 2) Graft nephrectomy; 3) Surgery due to complications at the site of the ureterovesical anastomosis; 4) Other surgical re-interventions (abdominal, hemodialysis shunt, vascular, etc.). The glomerular filtration rate (GFR) was calculated at 3 and 12 months post transplantation using the Cockroft-Gault formula. Date of graft failure was defined as the first day that hemodialysis or peritoneal dialysis was resumed. Graft survival was defined as the number of months between date of kidney transplantation and date of graft failure or end of observation period. Graft survival was censored for death.

Just for graft and patient survival analyses, we added an extra control group including all patients receiving a second transplant in the contralateral iliac fossa between 1995-2013. Second transplants in the contralateral iliac fossa share a higher immunological risk, but lack the surgical difficulties of a fossa that has been explored earlier because

of a former transplantation with or without graft nephrectomy. Follow-up was until July 2014 for all cases and controls.

Surgical technique

All recipients were preoperatively screened by a nephrologist, a transplant surgeon and an anesthesiologist. Pre-operative screening by a cardiologist, urologist or other specialist was performed only when indicated by previous history or special findings at screening. The extraperitoneal approach of the iliac fossa was performed in all patients. Firstly, the renal vein was anastomosed to external iliac vein. In retransplant patients, the venous anastomosis could also be connected to the common iliac vein or the inferior vena cava. The renal artery was then anastomosed to the external iliac artery. If this artery was not suitable for a recurrent vascular anastomosis, the common iliac artery was used. All vascular anastomoses were performed in an end-to-side fashion. We did not use the epigastric vessels for the vascular anastomoses. Two types of anastomoses between donor ureter and recipient bladder have been performed in the period that we studied: an intravesical anastomosis according to a modified Politano-Leadbetter (10) or an extravesical anastomosis as described by Lich-Gregoir (11, 12). Until 2003, a ureterovesical stent was not part of our standard procedure. Between 2003 and 2010 all patients with residual urine production of the native kidneys or from a formerly transplanted kidney received a stent in the ureterovesicostomy. After 2010, the use of an 8-French stent was defined as standard care.

Immunosuppressive treatment

Standard immunosuppressive therapy consisted of tacrolimus, mycophenolate mofetil, and prednisolone. However, this changed over the years. In the first period immunosuppression consisted of ciclosporin and prednisone. Ciclosporin was dosed on 12-hour through levels, while prednisone was started on the day of transplantation and was gradually tapered until a maintenance dose of 10 mg per day was reached at 4 months after transplantation. In 1996, mycophenolate mofetyl was introduced in our center, and was combined with ciclosporin and prednisone. In 1999, tacrolimus was gradually introduced and eventually replaced ciclosporin as standard calcineurin inhibitor treatment. It was added to the combination of mycophenolate mofetyl and prednisone. Triple therapy was given until 4 months after transplantation: prednisone was gradually tapered and eventually stopped at 4 months. This protocol has been used as standard immunosuppressive medication since then. On indication, conversions to ciclosporin, azathioprine, sirolimus or prednisone have been performed in individual patients.

Statistical analysis

Categorical variables were presented as numbers (percentage). Continuous variables were presented as median (range) if not normally distributed; continuous variables with normal distribution were presented as means with standard deviation. Categorical variables were analysed using the Chi-square test. Continuous variables were analysed using the Mann-Whitney-U test or an independent T-test. All analyses were conducted using IBM SPSS Statistics for Windows (version 21.0. Armonk, NY: IBM Corp, USA). A p-value <0.05 (two-sided) was considered statistically significant. Graft and patient survival were presented using the Kaplan Meier method and compared with a Log rank test and Cox regression analyses.

Results

Baseline characteristics

From a total of 2307 kidney transplants conducted in our center between 1995 and 2013, we identified 99 (4%) patients that received a retransplant in the ipsilateral iliac fossa. Patients were counted multiple times if they had multiple transplants in non-virgin sites. Five patients received a second transplant in the ipsilateral iliac fossa due to an inaccessible contralateral iliac fossa. Seventy patients received a third kidney transplant, eighteen a fourth, five patients a fifth and one patient a sixth transplant. We selected 297 control patients matching on recipient gender and age, year of transplantation, and type of donor (deceased vs. living). In table 1 baseline characteristics of the study and control group are compared. As expected, recipient gender, age and type of donor were similar in both groups. There were no significant differences in the total number of arteries, HLA mismatches, warm and cold ischemia time, recipient BMI, left/right donor kidney, and median follow up between both groups. The study group had a significantly higher current and historic PRA (P<0.001). In the study group, there were 2 positive crossmatch transplants and 2 ABO-incompatible transplants. In the control group, 5 ABO-incompatible transplants were performed and no transplants across a positive crossmatch. ATG induction therapy was used in 11 (11%) recipients of the study group and in 25 (8%) of first transplants (P=0.419).

Surgical outcome

In 6 study patients graft nephrectomy of the failed kidney was performed during the same session as retransplantation. In 93 patients the failed transplants in the ipsilateral fossa were removed in an earlier session prior to retransplantation. For the venous anastomoses the external iliac vein was used in 87 patients and the common iliac vein in 7 patients of the study group. In 1 patient the renal vein was anastomosed to the

Table 1. Baseline characteristics

Characteristics	Cases (n= 99)	Control (n=297)	P-value
Recipient age in years mean ± SD	43 ± 13	45 ± 12	0.342
Recipient gender			
Male, n (%)	55 (56%)	165 (56%)	1.00
Female, n (%)	44 (44%)	132 (44%)	
Type of donor			
Deceased, n (%);	63 (64%)	189 (64%)	1.00
Living, n (%)	36 (36%)	108 (36%)	
Implantation side			
Left, n (%)	45 (46%)	73 (25%)	**<0.001**
Right, n (%)	53 (54%)	223 (75%)	
Donor kidney			
Left, n (%)	48 (53%)	130 (47%)	0.278
Right, n (%)	42 (47%)	148 (53%)	
ABO-incompatible, n (%)	2 (2%)	5 (1.7%)	0.826
Positive Crossmatch, n (%)	2 (2%)	0	**0.014**
HLA Mismatches median (range)	2.0 (0.0-6.0)	3.0 (0.0-6.0)	0.164
Current PRA in % mean ± SD	32 ± 33	7 ± 20	**<0.001**
Highest PRA in % mean ± SD	69 ± 31	15 ± 26	**<0.001**
Number of transplants median (range)	3 (2-6)	1	**<0.001**
ATG, n (%)	11 (11%)	25 (8%)	0.419
Recipients BMI median (range)	24 (17-38)	24 (15- 42)	0.065
Number arteries median (range)	1 (1-3)	1 (1-5)	0.712
Warm ischemia time in minutes median (range)	29 (11-72)	29 (13-323)	0.591
Cold ischemia time in minutes median (range)	960 (70-2040)	903 (90-2015)	0.096
Ureteroneocystostomy			
Intravesical, n (%)	47 (62%)	199 (73%)	0.055
Extravesical, n (%)	29 (38%)	73 (27%)	
Follow up in months median (range)	60 (0-229)	58 (0-229)	0.671

SD, standard deviation; HLA, human leukocyte antigen; PRA, panel reactive antibodies; ATG, anti-thymocyte globulin; BMI, body mass index

inferior vena cava and in 2 study patients the veins of the previously failed grafts were used (of whom one patient returned on dialysis again 35 months after transplantation and the other died with a functioning graft 71 months after transplantation). In the 88 patients of the study group, the renal artery was anastomosed to the external iliac artery and in 5 patients to the common iliac artery. In 2 patients the arterial anastomosis was made using a vascular prosthesis. One of these patients had primary non-function and the other had a partial renal venous thrombosis thus thrombectomy was performed 1 day after transplantation, hereafter graft function restored and the patient returned to

dialysis 28 months later due to chronic allograft nephropathy. In 2 patients the artery of the previously failed graft was used for arterial anastomosis. Both patients had a surgical re-intervention due to haemorrhage within 4 days, one graft is still functioning and the other failed after 35 months due chronic allograft nephropathy.

Forty-five (46%) retransplant grafts were implanted in the left iliac fossa and 53 (54%) in the right iliac fossa. In the control group 223 (75%) grafts were implanted in the right and 73 (25%) in the left iliac fossa. Significantly more grafts were implanted in the right iliac fossa in the control group (P<0.001). The intravesical technique for the ureteroneocystostomy was used in 47 (62%) study patients and in 199 first transplants (73%)(P=0.055).

Mean operative time was significantly higher in our study group (241 ± 69 minutes) compared to the control group (180 ± 38 minutes; P<0.001). The median estimated blood loss per-operatively was higher in the study group compared to the matched controls, 500ml (range, 0-2565) vs. 300ml (range, 0-3600) respectively (P<0.001). The number of hospitalization days was not significantly different between both groups (Table 2).

The incidence of urological complications, measured by placement of percutaneous nephrostomy catheters, did not differ significantly. However, the rate of vascular complications was higher in the study group: 8 patients (8%) vs. 6 patients in the control group (2%) (P=0.003). In the study group these were all due to thrombotic events whereas in the control group 4 were related to a thrombotic event and 2 to a venous laceration (Table 2).

Table 2. Surgical short- and long-term outcome

Characteristics	Cases (n=99)	Controls (n=297)	P-value
Operative time in minutes mean ± SD	241 ± 69	180 ± 38	**<0.001**
Blood loss in ml median (range)	500 (0-2565)	300 (0-3600)	**<0.001**
Hospital admitted days median (range)	15 (2-73)	14 (4-189)	0.118
PCN placement n (%)	14 (14%)	54 (18%)	0.376
Vascular complications n (%)	8 (8%)	6 (2%)	**0.003**
- Thrombotic event	8	4	
- Venous laceration	0	2	
GFR at 3 months median (range)	54 (9-116)	61 (8-144)	**0.003**
GFR at 12 months median (range)	54 (8-115)	62 (4-138)	**0.028**

SD, standard deviation; PCN, percutaneous nephrostomy

Surgical re-interventions within the first year after transplantation were indicated because of bleeding, urological complications, and other surgery, but did not differ between the study and the control group, as shown in Table 3. However, the rate of graft nephrectomies was significantly higher in our study group; 16 nephrectomies in the study group (16%) versus 14 nephrectomies (5%) in the matched control group (P<0.001). In the study group graft nephrectomy was due to cellular rejection in 5 cases (of whom 3 received ATG), circulatory problems in 7 cases (5 thrombotic events, 1 hypovolemic shock due to bleeding, and 1 case due to mechanic compression of the graft in the fossa). One graft nephrectomy in the study group was due to an infection, 1 due to calcium oxalate depositions in the kidney, 1 due to both humoral, and cellular rejection combined with thrombosis, and 1 due to recurrence of hemolytic uremic syndrome. In the control group graft nephrectomy was performed because of cellular rejection in 6 cases (of whom 2 received ATG), humoral rejection in 2, and circulatory problems in 5 (3 thrombotic events and 2 venous lacerations). One graft nephrectomy was indicated because of infarction of both the lower and upper pole of the kidney followed by necrosis, abscess formation, and cellular rejection due to cessation of immunosuppression (Table 3).

Table 3. Surgical re-intervention within 1 year

Cause	Cases (n=99)	Controls (n=297)	P-value
Bleeding n (%)	10 (10%)	14 (5%)	0.052
Graft nephrectomy n (%)	16 (16%)	14 (5%)	**<0.001**
- Cellular rejection	5	6	
- Humoral rejection	0	2	
- Circulation	7	5	
- Other	4	1	
Urological complications n (%)	6 (6%)	25 (8%)	0.450
Other surgical interventions n (%)	16 (16%)	33 (11%)	0.136
- Abdominal	4	15	
- Shunt related	4	8	
- Vascular	1	1	
- Rest	7	9	

One patient in the study group with a failed retransplant, who was scheduled to receive another retransplant in the ipsilateral fossa, was found not to be transplantable because of severe fibrosis of the iliac fossa per-operatively.

Long-term survival

The GFR was significantly lower in the study group compared to the control group at 3 and 12 months post transplantation (Table 2). The graft survival rates at 1 year and 3, 5 and 10 years were 76%, 67%, 61% and 47% in the study group vs. 94%, 88%, 77% and 67% in the control group. Table 4.

Just for survival analyses we added an extra control group of all 270 patients receiving a second kidney transplant in the contralateral iliac fossa between 1995-2013. This group had graft survival rates at 1 year and 3, 5 and 10 years of respectively 91%, 86%, 78% and 57%. Table 4. This group contained 164 males (61%) and 106 females (39%) of which 140 (52%) deceased donors and 130 (48%) living donors. Median number of HLA mismatches of the additional control group was 3.0 (0.0-6.0). This was significantly higher compared to the study group with a median of 2.0 (0.0-6.0; P=0.001) and control group of first transplants with a median of 3.0 (0.0-6.0; P=0.026). Mean current PRA of the additional control group was 16 ± 23%. This was significantly lower than the study group (32 ± 33%; P<0.001) and significantly higher than the control group of first transplants (7 ± 20%; P<0.001). The mean highest PRA of the additional control group was 40 ± 32%. This was significantly lower than the study group (69 ± 31%; P<0.001) and significantly higher than the control group of first transplants (15 ± 26%; P<0.001).

Table 4. One year and 3-, 5- and 10-years graft survival

	1-year survival	3-years survival	5-years survival	10-years survival	HR1*	*p*-value	HR2**	P-value
Control 1: First transplants (n=297)	94%	88%	77%	67%	1.00*	-	0.83**	0.257
Control 2: Second transplants contralateral (n= 270)	91%	86%	78%	57%	1.21*	0.257	1.00**	-
Study group overall (n= 99)	76%	67%	61%	47%	1.99*	**<0.001**	1.66**	**0.009**
- Second transplants ipsilateral (n=5)	60%	60%	60%	60%	2.98*	0.128	2.47**	0.207
- Third transplants (n= 70)	74%	63%	58%	45%	2.22*	**<0.001**	1.84**	**0.005**
- Fourth transplants (n=18)	89%	83%	76%	53%	1.25*	0.602	1.04**	0.934
- Fifth transplants (n=5)	80%	80%	60%	60%	1.38*	0.651	1.15**	0.848
- Sixth transplants (n=1)	0%	0%	0%	0%	16.12*	**0.006**	13.37**	**0.011**

HR, hazard ratio:

* hazard ratio with the first control group as indicator

** hazard ratio with the second control group as indicator

Table 4 shows the graft survival rates specified for each number of retransplants. The patient that received a sixth transplant had a thrombosis of the renal vessels the day after transplantation and graft nephrectomy was performed. Cox regression analyses were performed using both the first and second control group as indicator. Third and sixth transplants had a significantly higher risk for graft failure. Table 5 shows patient survival rates specified for each number of retransplants. There were no significant differences in patient survival between the groups.

Table 5. One year and 3-, 5-, 10- years patient survival

	1-year survival	3-years survival	5-years survival	10-years survival	HR1*	*p*-value	HR2**	P-value
Control 1: First transplants (n=297)	96%	91%	85%	71%	1.00*	-	1.17**	0.412
Control 2: Second transplants contralateral (n= 270)	95%	92%	87%	77%	0.85*	0.412	1.00**	-
Study group overall (n=99)	92%	86%	83%	64%	1.17*	0.513	1.37**	0.204
- Second transplants ipsilateral (n=5)	80%	80%	80%	40%	2.63*	0.181	3.07**	0.121
- Third transplants (n= 70)	90%	85%	79%	61%	1.31*	0.322	1.53**	0.123
- Fourth transplants (n=18)	94%	89%	89%	67%	0.89*	0.814	1.04**	0.945
- Fifth transplants (n=5)	100%	100%	100%	100%	0.00*	0.961	0.00**	0.962
- Sixth transplants (n=1)	100%	100%	100%	-	0.00*	0.986	0.00**	0.986

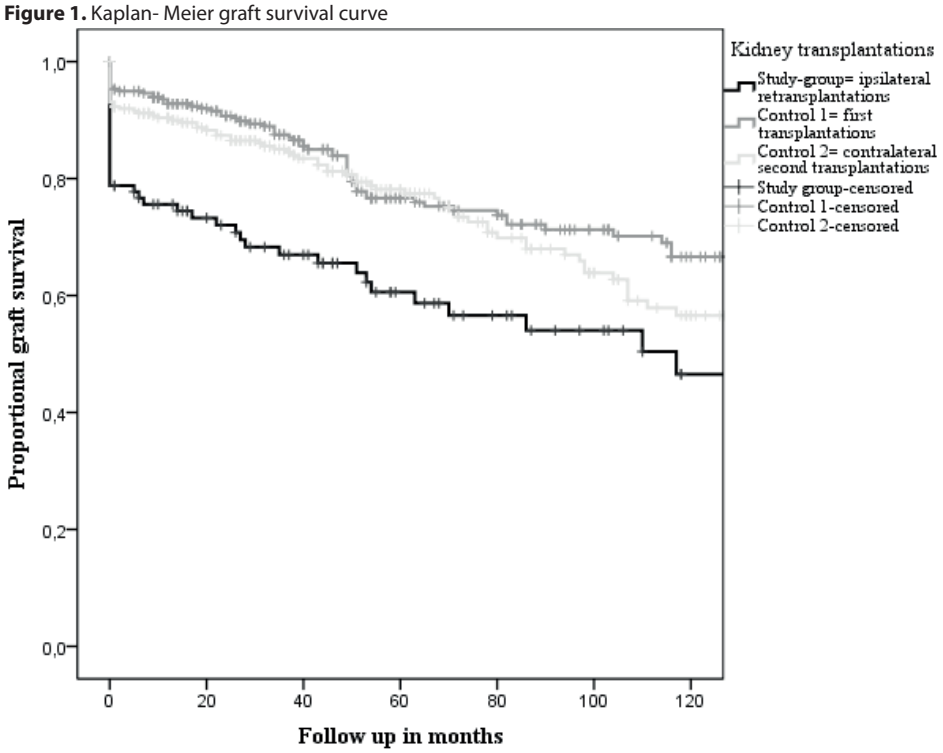
HR, hazard ratio:
* hazard ratio with the first control group as indicator
** hazard ratio with the second control group as indicator

Figure 1 shows the Kaplan-Meier graft survival curve of the study and both control groups. Most graft failures in the study group were within the first month after transplantation. After one year, graft survival curves were almost parallel. Log rank test of graft survival between the study and the first control group was P<0.001, between the study and the second control group it was P=0.008 and between the both control groups it was P=0.237. Figure 2 provides more insight in the patient survival of the study and both control groups. There were no significant differences in patient survival between the three groups.

Discussion

Renal retransplantation in the ipsilateral iliac fossa is surgically challenging. In this case-controlled study we showed that operative time and intra-operative estimated blood

Figure 1. Kaplan- Meier graft survival curve

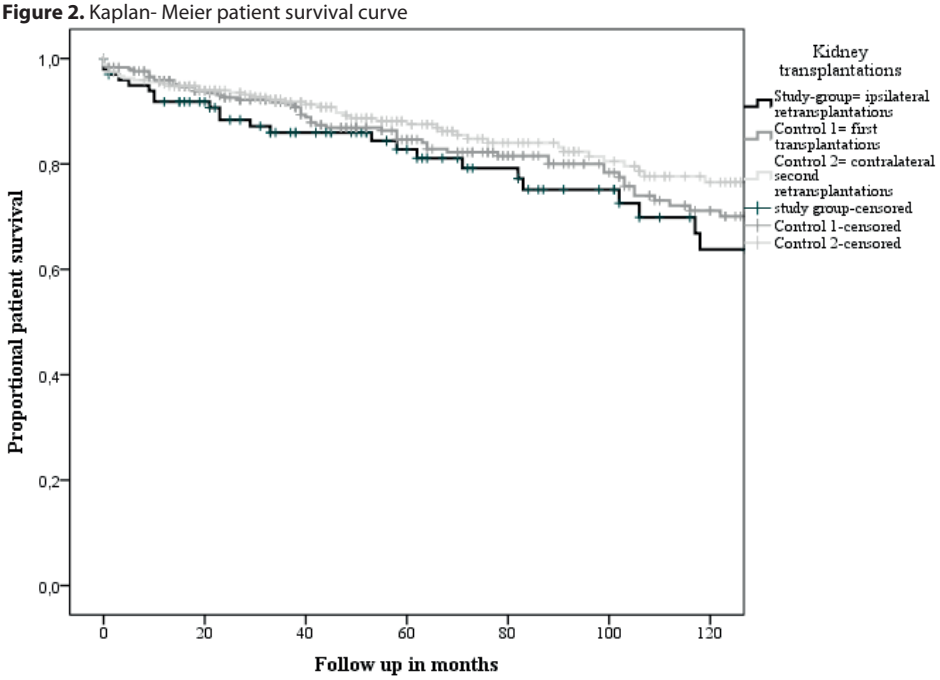


Annotation: Log rank test between the study and first control group (P<0.001). Log rank test between the study and the second control group (P=0.008). Log rank test between both control groups (P=0.237).

loss are significantly higher in patients that received a retransplant in the ipsilateral iliac fossa. Furthermore, patients with a retransplant have a significantly higher risk for thrombotic events of the renal vessels. The number of surgical re-interventions to solve urological complications, post-operative bleeding or other causes were comparable in both groups. However, the rate of graft nephrectomies performed in the first year after transplantation was significantly higher in the study group then in the first control group, with 16% vs 5%, respectively. The main reasons for graft nephrectomy within the study group were a thrombotic event in the renal vessels or cellular rejection. The overall graft survival was lower in the study group vs. both control groups, however patient survival was not affected by the number of transplantations.

There are a number of studies reporting on the use of the ipsilateral fossa in case of a retransplantation. Mazzucchi et al. included 21 third and following retransplants. Mean operative time was 327 minutes for retransplants and 212 minutes for first transplants. Surgical complications occurred in 4 patients, including two arterial thrombosis and two ureteral obstructions. One year graft survival was 57% for retransplants vs. 86%

Figure 2. Kaplan- Meier patient survival curve



Annotation: Log rank test between the study and the first control group (P=0.501). Log rank test between the study and the second control group (P=0.203). Log rank test between both control groups (P= 0.404).

for first transplants (7). Another study analyzed 30 patients who received their third transplant. Six out of 30 grafts were lost, 3 due to acute rejection, 2 due to chronic allograft nephropathy and 1 due to venous thrombosis. They reported 26.6% surgical complications. Graft survival at 1, 5 and 10 years were 87%, 76% and 57%, respectively (13). Kienzl- Wagner et al. analyzed 56 third and fourth kidney transplants. Third kidney graft survival rates at 1-5 year(s) were 73%- 54%. Surgical complications occurred in 21 patients including 4 patients with a wound dehiscence, 4 hydronephrosis, 4 hematomas, 2 lymfoceles, 2 perforations of the bowel, 1 rupture of the anastomosis, and 1 torsion of the kidney graft. Two grafts were lost due to the bowel perforation (14). LaMattina et al. have analyzed long-term graft survival for renal retranplants in prior simultaneous pancreas-kidney recipients. They found that most graft losses were not due to technical complications, but to immunological causes or patients who died with a functioning graft. However, they only included patients who received two transplants in the same iliac fossa compared to our study group where multiple explorations of the ipsilateral iliac fossa were performed including the transplantations and the removal of the previously failed grafts (8). Multiple explorations of the iliac fossa could result in more technical difficulties due to adhesions. Alternative surgical approaches for retransplants are described in literature. Chedid et al. have used renal vessel of the failed allograft

successfully in six retransplants with severe aortailiac atherosclerosis and fibrosis on the iliac vessels. There was one postoperative complication of diminished arterial inflow, that was corrected during a surgical re-intervention (9).

Although retransplantation is accompanied by more frequent complications and shorter graft survival, the results are superior to life time dialysis. The quality of life and patient survival are higher by avoiding lifelong dialysis and its societal cost-effectiveness is estimated to save $9,656 per quality- adjusted life-year (1, 15, 16).

There are some limitations to this study. First, the immunosuppressive regime between 1995 and 2013 has changed, which may have biased our results. We tried to resolve this point by matching the control group in the same year of transplantation. We tried to bypass the immunological challenges of retransplants by adding an additional control group of all 270 patients who received a second transplant in the contralateral iliac fossa between 1995-2013. This additional control group of only second transplants provides more insight in graft survival with a higher immunological risk however lacks the surgical difficulties of a fossa that has been explored earlier. The graft survival rates of the control group and the additional control group were respectively 94%, 88%, 77% and 67% vs. 91%, 86%, 78% and 57%, P=0.237. This emphasizes the surgical challenges of retransplants in an earlier explored iliac fossa with graft survival rates of 76%, 67%, 61%, and 47%, respectively. Due to the retrospective design, a few important variables, such as the number of urinary tract infections and surgical site infections, could not be analyzed thoroughly.

Renal retransplantation is a challenging surgical procedure with longer operative time, higher per-operative blood loss and a higher number of graft nephrectomies. In this series, retransplantation had no negative impact on patient survival as compared to a first transplant or to a second contralateral renal transplant. Regarding the patient survival benefits of having a functioning kidney allograft over being on dialysis, renal re-transplantation should be tried as much as possible whenever clinical condition allows for it. Ipsilateral retransplantation seems to be associated to more operative complications and should therefore be reserved to the case where the patient is undergoing a third (and following) renal retransplantation where both iliac fossae have been surgically explored. Graft survival in case of a retransplant is lower than in first transplants and second contralateral transplants, mainly due to the higher rate of graft failures in the first year after kidney retransplantation. Most of these graft nephrectomies were necessary because of thrombotic events of the renal vessels. However, after the first few months the Kaplan-Meier graft survival curves were parallel. Preventing thrombotic events of the renal vessels in patients that receive a kidney retransplant in the ipsilateral

fossa, should be one of the main priorities in the postoperative care. Despite the above-mentioned limitations, this case-controlled study provides an insight into the surgical challenges involving kidney retransplantation in the ipsilateral iliac fossa. This article provides transplant professionals a valid base to thoroughly inform patients who are considered for a kidney retransplant in the ipsilateral iliac fossa.

References

1. Hornberger JC, Best JH, Garrison LP, Jr. Cost-effectiveness of repeat medical procedures: kidney transplantation as an example. Med Decis Making. 1997 Oct-Dec;17(4):363-72.
2. Laging M, Kal-van Gestel JA, Haasnoot GW, Claas FH, van de Wetering J, Ijzermans JN, et al. Transplantation results of completely HLA-mismatched living and completely HLA-matched deceased-donor kidneys are comparable. Transplantation. 2014 Feb 15;97(3):330-6.
3. Nourbala MH, Ghaheri H, Kardavani B. Our experience with third renal transplantation: results, surgical techniques and complications. Int J Urol. 2007 Dec;14(12):1057-9; discussion 9.
4. Halawa A. The third and fourth renal transplant; technically challenging, but still a valid option. Ann Transplant. 2012 Dec 31;17(4):125-32.
5. Musquera M, Peri LL, Alvarez-Vijande R, Oppenheimer F, Gil-Vernet JM, Alcaraz A. Orthotopic kidney transplantation: an alternative surgical technique in selected patients. Eur Urol. 2010 Dec;58(6):927-33.
6. Park SC, Moon IS, Koh YB. Second and third kidney transplantations. Transplant Proc. 2006 Sep;38(7):1995-7.
7. Mazzucchi E, Danilovic A, Antonopoulos IM, Piovesan AC, Nahas WC, Lucon AM, et al. Surgical aspects of third and subsequent renal transplants performed by the extraperitoneal access. Transplantation. 2006 Mar 27;81(6):840-4.
8. Lamattina J, Sollinger H, Becker Y, Mezrich J, Pirsch J, Odorico J. Long-term pancreatic allograft survival after renal retransplantation in prior simultaneous pancreas-kidney recipients. Am J Transplant. 2012 Apr;12(4):937-46.
9. Chedid MF, Moreno Gonzales M, Raghavaiah S, Chauhan A, Taner T, Nedredal GI, et al. Renal retransplantation after kidney and pancreas transplantation using the renal vessels of the failed allograft: pitfalls and pearls. Clin Transplant. 2014 Jun;28(6):669-74.
10. Politano VA, Leadbetter WF. An operative technique for the correction of vesicoureteral reflux. J Urol. 1958 Jun;79(6):932-41.
11. Gregoir W. [the Surgical Treatment of Congenital Vesico-Ureteral Reflux] Le Traitement Chirurgical Du Reflux V'esico-Ur'et'eral Cong'enital. Acta Chir Belg. 1964 Apr;63:431-9.
12. Lich R, Jr., Howerton LW, Davis LA. Childhood urosepsis. J Ky Med Assoc. 1961 Dec;59:1177-9.
13. Blanco M, Medina J, Gonzalez E, Dominguez M, Rodriguez A, Pamplona M, et al. Third kidney transplantation: a permanent medical-surgical challenge. Transplant Proc. 2009 Jul-Aug;41(6):2366-9.
14. Kienzl-Wagner K, Mark W, Maglione M, Brandacher G, Ollinger R, Margreiter R, et al. Single-center experience with third and fourth kidney transplants. Transpl Int. 2011 Aug;24(8):780-6.
15. Marcen R, Teruel Briones JL. Patients with a failed renal transplant. Minerva Urol Nefrol. 2011 Mar;63(1):35-44.
16. Montgomery RA, Lonze BE, King KE, Kraus ES, Kucirka LM, Locke JE, et al. Desensitization in HLA-incompatible kidney recipients and survival. N Engl J Med. 2011 Jul 28;365(4):318-26.

CHAPTER 10

General discussion and future perspectives

Kidney transplantation is the best treatment for end stage renal disease and increases patient survival compared to dialysis. Due the continuing developments in the field of surgery and immunosuppressive therapy, kidney transplantation can be performed succesfully and nowadays may be offered to many patients with end stage renal disease. Since the 1950s, the surgical procedure includes placement of the transplant in the extraperitoneal iliac fossa, according to the so-called 'Küss procedure'. Complications after kidney transplantation may be related to immunological or surgical events and both may comprise graft outcome. Reduction of surgical complications is still one of the challenges in kidney transplantation. We focused on urological complications after kidney transplantation, including urinary leakage and ureteral strictures, both associated with significant morbidity, interventions, prolonged hospital stay and in a few cases, mortality. Most urological complications are related to the ureteroneocystostomy and optimizing the ureteral anastomosis is a main goal to improve the overall outcome of kidney transplantation.

In a previously conducted randomized controlled trial (INEX trial) we investigated the type of ureteral anastomosis (extravesical vs intravesical). No difference was observed in the number of urological complications between the intra- and extravesical anastomosis, however, the number of urinary tract infections was lower in the extravesical group. Therefore, the extravesical anastomosis was chosen as the standard procedure for our surgical protocol. As the type of ureterovesical anastomosis did not influence the number of urological complications, our next aim was to investigate the relevance of using ureteral stents. To date 5, randomized controlled trials on stent placement have been reported. These studies differ in study design and include living as well as deceased donation, intravesical and extravesical anastomosis and various types of stenting. Stenting seemed to be in favour, but it remained open for discussion whether this should be on routine basis or only on strictly defined criteria. A meta-analysis on this topic supports the use of ureteral stents in selected recipients, but a statement on routine stenting, type of stent and timing of stent removal is not available. Based on the preliminary results of a randomized controlled SPLINT trial (chapter 2) we tend to conclude that ureteral stent placement significantly reduces the number of PCN placements, urinary leakage and surgical re-interventions due to urological complications compared to no stent placement.

However, the type of stent remains a dispute. A Cochrane review debates which stent caliber and stent duration is best to avoid urological complications. Although the type of stent was mostly similar (double J stent was used in all but one study), the time until stent removal diverged from 7 days until 3 months and stent caliber varied from 5 to 7 French (Fr) between all studies. Furthermore, most included studies were of retrospec-

tive nature and included studies of an evidence level of 3. In our center, we prefer the use of external stents over double J stents, because of several advantages like the possibility of monitoring the grafts urine production and the simplicity of stent removal without a cystoscopy. In chapter 3, two different types of externalized ureteral stents are evaluated. Type A stenting refers to an 8 Fr 'Covidien' polyvinyl chloride tube and type B stenting refers to a 7 Fr polyurethane 'Teleflex' single J stent. We found a significantly higher incidence of urological complications in the group of patients receiving type A stenting and a higher incidence of rejection and urinary tract infections in the group receiving type B stenting.

Several risk factors are presumed to influence the number of urological complications after kidney transplantation, such as pre-emptive transplantations, male gender of recipient and donor and the presence of multiple renal arteries. The native vascularization of the ureter is supplied by segmental arteries derived from the renal, vesicle, gonadal, common iliac or internal iliac vessels or directly from the abdominal aorta. During donor nephrectomy these segmental branches are dissected, resulting in the renal artery as the main blood supply of the ureter. Therefore, it can be hypothesized that a shorter ureteral length is accommodated with better vascularization and may possibly cause less urological complications. However, in chapter 4, we conclude that ureteral length does not influence the number of urological complications after kidney transplantation. More insight should be established in the microcirculation and perfusion of the ureteral blood flow. To our knowledge, only one animal study has shown that a ureteral access sheath can cause a transient decrease in ureteral blood flow. This raises the question whether the use of a ureterovesical stent in kidney transplantation influences the ureter microcirculation.

Ureteral obstruction is initially treated with a percutaneous nephrostomy (PCN). In many cases the obstruction will resolve spontaneously, but in a few cases additional treatment is necessary. Treatment options for ureteral strictures include long term double J catheter insertion, balloon dilatation or surgical revision of the ureteroneocystostomy. In literature, only a few studies are available that report on the success-rate of these treatments. Balloon dilatation did prove its efficacy in the treatment of the ureterovesical junction for an obstructive mega-ureter and in uretero-ileal strictures of 1cm or less in patients after surgical urinary diversion. In chapter 5, a case series of fifty kidney transplant recipients who underwent antegrade balloon dilatation because of ureteral strictures is presented. In 7 patients, it was impossible to pass the strictured segment with the guidewire. In 20/43(47%) the procedure was clinically successful. Therefore, we believe that balloon dilatation should be advocated as the first treatment for ureter strictures, as it is less invasive than open surgical ureter reconstruction.

Infectious complications may affect the recovery of patients receiving high-dose immunosuppressive therapy. The most commonly reported infectious complications after kidney transplantation are urinary tract infections. In chapter 6, we report that 28% of patients developed a urinary tract infection within 3 months after transplantation. The most common causative agent was *Escherichia coli*, followed by *Enterococcus faecalis* and *Klebsiella pneumoniae*. The variables that were independently related to a urinary tract infection were female gender, recipients age above 60 years, percutaneous nephrostomy placement and surgical re-intervention. Mean glomerular filtration rate was significantly lower in the group of patients with a urinary tract infection at 3, 6, 9 and 12 months postoperatively compared to those patients who did not have a urinary tract infection. In literature, incidence rates of 38% have been described and a relation between UTI and diminished graft function has been well described.

A less known complication after KT is incisional hernia. Incisional hernia is one of the most frequent postoperative complications after regular abdominal surgery. The incidence varies between 11 and 20% in general population. Known risk factors for development of incisional hernia are obesity, aneurysm of the abdominal aorta, immunosuppressive therapy, and postoperative wound infection. Hence, transplant recipients may have an increased risk to develop incisional hernia due to the use of postoperative immunosuppressive therapy resulting in impaired wound healing. The incidence of incisional hernia after kidney transplantation in literature, however, is reported to be remarkably low and varies between 1% and 7%. In chapter 8, we report an incidence of incisional hernia following kidney transplantation of 3.2%. We found obesity (BMI>30), female gender, concurrent abdominal wall hernias, history of smoking, duration of surgery, and multiple explorations to be independent risk factors for the development of incisional hernia after kidney transplantation.

Currently, 26% of patients on the Dutch kidney transplant waiting list awaits a retransplant. Besides immunological difficulties, retransplantation may offer surgical challenges. Several techniques for retransplantation have been described, including the transperitoneal, retroperitoneal and orthotopic approach. As in most centers, we primarily implant the renal graft in the extraperitoneal iliac fossa. If a retransplantation must be performed, use of the contralateral iliac fossa is advocated. However, in case of a third or even fourth retransplant, it is unavoidable to explore an iliac fossa that has already been dissected for the previous implantation and for removal of the non-functioning graft. In chapter 9, ipsilateral retransplantations are compared to first transplants. Ipsilateral retransplantations had a longer operative time, higher per-operative blood loss and a higher number of graft nephrectomies. Graft survival in case of an ipsilateral retransplant is lower than in first transplants and second contralateral transplants, mainly due

to the higher rate of graft failures in the first year after kidney retransplantation. Most of these graft nephrectomies were necessary because of thrombotic events of the renal vessels. This should be noticed and emphasized during the informed consent in case of patients that are planned or listed to receive an ipsilateral retransplant.

Conclusions and future perspectives

In this thesis, we have evaluated surgical complications that may occur after kidney transplantation. We demonstrated that externalized ureteral stent placement significantly reduces urological complications, compared to not stenting the ureteral anastomosis. However, the type of stent is still under debate. Double J stenting seems to reduce the number of urological complications even more effectively, according current literature. Yet external stenting has several advantages like monitoring the grafts urine production and the simplicity of stent removal without cystoscopy. Therefore, we suggest a randomized controlled trial between externalized stenting and the use of a double J stent, as suggested in chapter 7. In case of an externalized stent, we recommend a 7 Fr polyurethane single J over an 8 Fr polyvinyl chloride straight tube, as it significantly reduced the number of urological complications in our retrospective cohort.

Furthermore, we have demonstrated that ureteral length does not influence the number of complications. It is of important for surgeons to realize that the vascularization of the ureter is fragile and gentle tissue handling is pivotal to prevent collateral damage to the microvessels in the ureter wall.

In case of a ureteral stricture, we recommend balloon dilatation as first treatment. Based on our data, this approach may be successful in 47% of the patients and it is less invasive than open surgical ureter reconstruction.

Urinary tract infections are a common problem after kidney transplantation. We have identified female gender, recipients age above 60 years, percutaneous nephrostomy placement and surgical re-intervention as risk factors. In our center, a urinary bladder catheter and an externalized stent are placed and removed on respectively day 7 and day 9 after transplantation, both without antibiotic prophylaxis. It may be advocated to remove the stent in patients with these risk factors protected by antibiotic prophylaxis, although there is no strong evidence for this approach. A well-designed prospective randomized controlled trial in KT recipients with an externalized stent could provide the answer to this issue.

The incidence of incisional hernia following kidney transplantation is 3.2%. We found obesity (BMI>30), female gender, concurrent abdominal wall hernias, history of smoking, duration of surgery, and multiple explorations to be independent risk factors for the development of incisional hernia after kidney transplantation. These risk factors should be considered when closing the fascia.

Ipsilateral retransplantation is associated with more operative complications and should therefore be reserved to the case where the patient is undergoing a third (and following) renal retransplantation where both iliac fossae have already been surgically explored. Regarding the patient survival benefits of having a functioning kidney allograft over being on dialysis, renal retransplantation is the best treatment option whenever the clinician condition of the recipients permits it. Graft survival in case of a retransplant is lower than in first transplants and second contralateral transplants. Most of these graft nephrectomies were necessary because of thrombotic events of the renal vessels. Preventing thrombotic events of the renal vessels in patients that receive a kidney retransplant in the ipsilateral fossa, should be one of the main priorities in the postoperative care. This should be noticed and emphasized during the informed consent in retransplant patients.

CHAPTER 11

Summary in English and Dutch

This thesis describes surgical techniques used in kidney transplantation. Modifications that may minimize surgical complications and optimize outcome after kidney transplantation are focus of the studies described.

In chapter 1 a historical overview of kidney failure and kidney transplantation is presented. Besides immunological challenges, surgical complications after kidney transplantation can cause significant mortality, morbidity and result in graft loss. Common complications are related to the urological reconstruction where the new anastomosis between the graft ureter and the bladder of the recipients may lead to urinary leakage or ureteral stenosis. In addition, urinary tract infections may occur frequently. Preventing these surgical complications that comprise graft outcome, remains one of the challenges in kidney transplantation.

Chapter 2 describes the preliminary data of a randomized controlled trial performed in our center. This (SPLINT) trial compares the use of a suprapubic externalized stent with no stent placement during living donor kidney transplantations. Two hundred consecutive recipients were included in this trial between April 2014 and March 2017. The number of percutaneous nephrostomy placements within 1 month was defined as the primary outcome of this study. In the no stent group, there were significantly more PCN placements, more urinary leakages and surgical re-interventions due to urological complications. In the stent group, there were more patients with haematuria, graft rejection, and prolonged hospital stay. Mean GFR at day 7, 14, 21 and 1 month after transplantation was equal in both groups. In a multivariate risk factor analyses, the variables that were independently related to PCN placement were no stent placement, a history of smoking and the first warm ischemia time. Therefore, we conclude that stenting the ureteral anastomosis should be advocated in living donor kidney transplant recipients.

In chapter 3, we describe results of a retrospective study in which we evaluated the influence of 2 different types of externalized ureteral stents (type A was an 8F polyvinyl chloride tube and type B was a 7F polyurethane single J stent) on the incidence of urological complications. We wondered whether one stent was superior to the other. We found a significantly higher incidence of PCN placements in patients who received the type A stent and a higher incidence of rejection and urinary tract infections in patients who received the type B stent. There were no significant differences in the reason for PCN placement or for patient or graft survival between both groups.

Several risk factors are presumed to influence the number of urological complications after kidney transplantation. During donor nephrectomy segmental branches of the native vascularization of the ureter are being dissected, leaving the renal artery as the

solitary blood supply of the ureter. Therefore, it can be hypothesized that a shorter ureteral length is accommodated with better vascularization and may cause less urological complications. This hypothesis was studied in chapter 4. Using data on the length of the ureter from the previously conducted randomized trial (INEX), we conclude that ureteral length does not influence the number of urological complications after kidney transplantation.

In chapter 5, we analyzed the outcome of balloon dilatation as treatment for ureter strictures after kidney transplantation in a case series of 50 patients treated in the Erasmus University Medical Center and the Academic Medical Center. The technical success-rate was 86% and the subsequent clinical success-rate of balloon dilatation treatment 47%. We could not identify any factors that may have contributed to a (non)successful outcome of a balloon dilatation. The length of the stenosis was not found to be predictive for the treatment outcome. We believe that balloon dilatation should be advocated as the first treatment for ureter strictures because it is less invasive than open surgical ureter reconstruction.

Chapter 6 includes the results of a retrospective study in which we analyzed the number of urinary tract infections that occur after kidney transplantation and its effect on graft function. We tried to identify risk factors for development of urinary tract infections. In this study, we identified 115 out of 417 patients (28%) who developed a urinary tract infection after kidney transplantation. In multivariate analysis, variables that were independently related to the development of a urinary tract infection were female gender, recipients' age>60y, PCN placement and surgical re-interventions within 3 months after transplantation. Mean GFR at 3, 6, 9 and 12 months after transplantation was significantly lower in patients who had a urinary tract infection.

In current literature, there is no evidence whether external stenting or internal double J stenting is superior. In chapter 7, a new study protocol is proposed to assess if double J stenting of the ureteroneocystostomy during kidney transplantation is superior in preventing urological complications compared to externalized single J stenting. This will be a single-centre randomized controlled trial with a superiority design. All adult kidney transplant recipients (>18yrs) are invited to participate and in total 300 recipients will be included. The primary study outcome will be the number of percutaneous nephrostomy placements.

A less known complication after kidney transplantation is incisional hernia. Incisional hernia is one of the most frequent postoperative complications after regular abdominal surgery. Immunosuppressive therapy is a known risk factor for the development of

incisional hernia. Hence, transplant recipients may have an increased risk to develop incisional hernia. In chapter 8, we report an incidence of incisional hernia following kidney transplantation of 3.2%. We found obesity (BMI>30), female gender, concurrent abdominal wall hernias, history of smoking, duration of surgery, and multiple explorations to be independent risk factors for the development of incisional hernia after kidney transplantation. These risk factors should be taken into account by surgeons, when closing the fascia.

As multiple explorations of a fossa is a risk factor for the development of incisional hernia, this may be an important issue as an increasing number of patients are listed to receive a retransplantation. In chapter 9, we present a retrospective case-controlled study on the surgical challenges of kidney retransplantation in the ipsilateral iliac fossa. Three control patients (first transplants) were matched to each study patient (ipsilateral retransplant). We showed that operative time and intra-operative estimated blood loss are significantly higher in patients that received a retransplant in the ipsilateral iliac fossa. Furthermore, patients with a retransplant have a significantly higher risk for thrombotic events of the renal vessels. The number of urological complications was not higher. The rate of graft nephrectomies performed in the first year after transplantation was significantly higher in the study group then in the control group, with 16% vs 5%, respectively. The overall graft survival was lower in the study group, however patient survival was not affected by the number of transplantations.

In chapter 10, the studies performed in chapter 2 until 9 are discussed and ideas for future studies that may address remaining questions are presented.

Samenvatting

Dit proefschrift beschrijft de chirurgische technieken die worden uitgevoerd tijdens niertransplantaties. Wij hebben onderzoek gedaan naar manieren om chirurgische complicaties te minimaliseren en het resultaat na niertransplantatie te optimaliseren.

In hoofdstuk 1 wordt een historisch overzicht gegeven van nierfalen en niertransplantatie. Naast immunologische uitdagingen die een rol spelen bij niertransplantaties, kunnen ook chirurgische complicaties voor significante mortaliteit en morbiditeit zorgen en zelfs tot transplantaat verlies leiden. De meest bekende chirurgische complicaties na niertransplantatie zijn de urologische complicaties. Dit zijn complicaties die zich afspelen rondom de nieuwe aansluiting tussen de donor urineleider en de blaas van de ontvanger, zoals urinelekkage of vernauwingen van de urineleider. Andere complicaties die rondom de transplantatie kunnen voorkomen zijn infecties, waarvan de urineweginfectie de meest voorkomende is. Het voorkomen van deze chirurgische complicaties die tot transplantaat verlies kunnen leiden, blijft een van de uitdagingen bij niertransplantaties.

Hoofdstuk 2 beschrijft de voorlopige resultaten van een gerandomiseerd en gecontroleerd onderzoek, dat in ons centrum werd uitgevoerd. Deze (SPLINT) trial vergelijkt het gebruik van een suprapubisch geëxternaliseerde stent met het niet plaatsen van een stent bij niertransplantaties van levende donoren. Tweehonderd opeenvolgende nier ontvangers namen deel aan dit onderzoek, tussen april 2014 en maart 2017. Percutane nefrostomie plaatsing binnen 1 maand was de primaire uitkomstmaat van deze studie. In de geen-stent-groep waren er aanzienlijk meer percutane nefrostomie plaatsingen, urine lekkages en chirurgische re-interventies als gevolg van urologische complicaties. In de stent-groep waren er meer patiënten met hematurie, afstoting van het transplantaat en deze groep was langer opgenomen in het ziekenhuis na de transplantatie. De gemiddelde GFR op dag 7, 14, 21 en 1 maand na transplantatie was gelijk in beide groepen. In een multivariate risicofactor analyse waren: geen stent plaatsing, roken (of vroeger roken) en de eerste warme ischemie tijd onafhankelijk verbonden met PCN-plaatsing. Daarom moet de nieuwe anastomose tussen urineleider en blaas gestent worden bij niertransplantaties van levende donoren.

In hoofdstuk 3 beschrijven we de resultaten van een retrospectieve studie. In dit onderzoek hebben we 2 verschillende types geëxternaliseerde stents met elkaar vergeleken. Type A was een 8 french polyvinylchloride stent en type B een 7 french polyurethaan stent met een krul aan de tip. We vonden een significant hogere incidentie van PCN-plaatsingen in patiënten met het type A-stent en meer afstotingen en urineweginfecties

bij patiënten die het type B-stent kregen. Er waren geen significante verschillen in de reden voor het plaatsen van een PCN. Ook vonden we geen verschillen in mortaliteit en transplantaat-overleving tussen beide groepen.

Er zijn verschillende factoren bekend die het risico op urologische complicaties na niertransplantatie vergroten. Gedurende de donor nefrectomie worden de segmentale takken van de oorspronkelijke vascularisatie van de urineleider doorgenomen. Dit zorgt ervoor dat de nier arterie als enige bloedtoevoer van de urineleider fungeert. Daarom kan worden verondersteld dat een kortere urineleider gepaard gaat met een betere vascularisatie en mogelijk met minder urologische complicaties. In hoofdstuk 4 concluderen we echter dat de lengte van de urineleider het aantal urologische complicaties na niertransplantatie niet beïnvloedt. Voor deze analyse hebben we de gegevens van een eerder uitgevoerde gerandomiseerde trial (INEX) gebruikt.

In hoofdstuk 5 analyseerden we het effect van ballondilataties (dotterprocedures) als behandeling voor vernauwingen in de urineleider na niertransplantaties. Deze serie bestaat uit 50 patiënten die behandeld zijn in het Erasmus Universitair Medisch Centrum en het Academisch Medisch Centrum. Het was technisch succesvol in 86% van de patiënten en het daaropvolgende klinische succes was 47%. We konden geen factoren identificeren die van te voren konden voorspellen of de dotterbehandeling zinvol zou zijn of niet. Wij zijn van mening dat de ballondilatatie de eerste behandelkeus moet zijn bij patiënten met vernauwingen in de urineleider, omdat het minder invasief is dan een chirurgische correctie.

Hoofdstuk 6 bevat de resultaten van een retrospectieve studie waarin we het aantal urineweginfecties na niertransplantatie analyseerden. Daarnaast hebben we geprobeerd risicofactoren voor het ontwikkelen van urineweginfecties te identificeren. Er bleken 115 van de 417 patiënten (28%) een urineweginfectie te ontwikkelden na niertransplantatie. In een multivariate analyse waren de variabelen die onafhankelijk verband hielden met het ontwikkelen van een urineweginfectie de volgende: vrouwelijk geslacht, leeftijd van de ontvangers> 60 jaar, PCN-plaatsing en chirurgische re-interventies binnen 3 maanden na transplantatie. De gemiddelde GFR op 3, 6, 9 en 12 maanden na transplantatie was significant lager bij patiënten die een urineweginfectie hadden doorgemaakt.

In de huidige literatuur is er geen sluitend bewijs dat de dubbel J stent beter is dan de externe stent. In hoofdstuk 7 stellen we een nieuw onderzoeksprotocol voor. In dit onderzoek willen we beoordelen of de dubbel J stent beter is dan de suprapubisch geëxternaliseerde stent in het voorkomen van urologische complicaties na niertransplantaties. Dit onderzoek zal worden uitgevoerd in het Erasmus MC en zal een zogehe-

ten 'superiority design' hebben. Alle niertransplantatie ontvangers (> 18 jaar) worden uitgenodigd om deel te nemen aan dit onderzoek. In totaal willen we 300 ontvangers in deze studie includeren. De primaire uitkomstmaat van dit onderzoek zal het aantal percutane nefrostomie plaatsingen zijn.

Een minder bekende complicatie na niertransplantatie is een littekenbreuk. Littekenbreuken zijn echter wel een van de meest voorkomende complicaties na reguliere buikoperaties. Immunosuppressieve medicatie is een bekende risicofactor voor het ontwikkelen van een littekenbreuk. Daarom kunnen transplantatiepatiënten een verhoogd risico hebben om een littekenbreuk te ontwikkelen. In hoofdstuk 8 rapporteren we een incidentie van 3.2% littekenbreuken na niertransplantaties. We hebben een aantal risicofactoren gevonden die de kans op een littekenbreuk doen toenemen. Dit zijn obesitas (BMI> 30), het vrouwelijk geslacht, gelijktijdige andere buikwand hernia's, roken (of in het verleden gerookt), duur van de operatie en meerdere operaties via dezelfde incisie. Deze risicofactoren moet door de operateur worden meegenomen als ze de fascie sluiten.

Het vaker opereren via dezelfde incisie geeft dus een verhoogd risico op een litteken breuk. Dit zal dus in de toekomst mogelijk een groter probleem worden omdat steeds meer patiënten op de wachtlijst staan om een re-transplantatie te ondergaan. In hoofdstuk 9 presenteren we een retrospectieve case-control studie over de chirurgische uitdagingen van niertransplantatie in een al eerder gebruikte fossa. Drie controle patiënten (eerste transplantaties) werden gematcht aan elke studie patiënt (ipsilaterale re-transplantatie). We laten in dit onderzoek zien dat de operatieduur langer en het bloedverlies significant hoger is bij patiënten die een re-transplantatie ondergaan. Bovendien hebben patiënten met een re-transplantaat een significant hoger risico op een trombotisch event van de vaten van het niertransplantaat. Het aantal urologische complicaties was niet groter. In het eerste jaar na transplantatie is het aantal verwijderde transplantaten in de studie groep aanzienlijk hoger dan in de controle groep, respectievelijk 16% versus 5%. De transplantaat-overleving was lager in de studie groep ten opzichte van de controle groep, maar de patiënt-overleving werd niet beïnvloed door het aantal transplantaties.

In hoofdstuk 10 worden de onderzoeken van hoofdstuk 2 tot en met 9 besproken en suggesties voor toekomstig onderzoek worden gegeven.

CHAPTER 12

Contributing authors
Dankwoord
List of publications
PhD Portfolio
Curriculum Vitae

Contributing authors

Dr. T. Terkivatan
Department of Surgery
Erasmus MC University Medical Center
Rotterdam

Dr. F.J.M.F. Dor
Department of Surgery
Hammersmith Hospital
London, United Kingdom

Drs. T.C.K. Tran
Department of Surgery
Erasmus MC University Medical Center
Rotterdam

Dr. R.C. Minnee
Department of Surgery
Erasmus MC University Medical Center
Rotterdam

Dr. J. van de Wetering
Department of Internal Medicine
Erasmus MC University Medical Center
Rotterdam

Dr. I.K.B. Slagt
Department of Surgery
Erasmus MC University Medical Center
Rotterdam

Prof. Dr. J. Jeekel
Department of Neuroscience
Erasmus MC University Medical Center
Rotterdam

L.G. Spaans
Department of Surgery
Erasmus MC University Medical Center
Rotterdam

Dr. M.M. Idu
Department of Surgery
Amsterdam Medical Center
Amsterdam

A.F. Voor in 't holt
Department of Microbiology
Erasmus MC University Medical Center
Rotterdam

Prof. Dr. J.N.M. Ijzermans
Department of Surgery
Erasmus MC University Medical Center
Rotterdam

Drs. H.J.A.N. Kimenai
Department of Surgery
Erasmus MC University Medical Center
Rotterdam

Dr. H. Hartog
Department of Surgery
Erasmus MC University Medical Center
Rotterdam

Dr. J.I. Roodnat
Department of Internal Medicine
Erasmus MC University Medical Center
Rotterdam

Dr. M.G.H. Betjes
Department of Internal Medicine
Erasmus MC University Medical Center
Rotterdam

Dr. J. Verhelst
Department of Surgery
Erasmus MC University Medical Center
Rotterdam

Prof. Dr. J.F. Lange
Department of Surgery
Erasmus MC University Medical Center
Rotterdam

Dr. A. Moelker
Department of Radiology
Erasmus MC University Medical Center
Rotterdam

Prof. Dr. M.C. Vos
Department of Microbiology
Erasmus MC University Medical Center
Rotterdam

Dankwoord

Na 3,5 jaar is het eindelijk zover, mijn proefschrift is af. Dit proefschrift is tot stand gekomen door de hulp van een groot team. Ik wil dus ook iedereen bedanken die mij hiermee heeft geholpen. Er zijn een aantal mensen die ik in het bijzonder wil benoemen.

Beste professor Ijzermans, mijn promotor. Bedankt voor het vertrouwen wat ik van u heb gekregen om de SPLINT trial te coördineren, en natuurlijk niet te vergeten de DINO, aka broccoli trial, waarbij ik wekelijks met broccoli-kiemen door het EMC mocht lopen. Ik ben erg benieuwd naar de uitkomsten. U heeft me de afgelopen jaren veel geleerd en u gaf me de ruimte om me zowel op wetenschappelijk als persoonlijk gebied verder te ontwikkelen. Alhoewel mijn schrijfstijl niet altijd de uwe was, ben ik ervan overtuigd dat we samen iets moois hebben neergezet.

Beste Turkan, mijn copromotor. Bedankt voor de vrijheid die je me gaf als ik weer eens met een nieuw idee kwam, wat ik vaak dan ook mocht uitvoeren. Ik ben er trots op dat we de SPLINT trial met veel succes hebben afgerond en het volgende onderzoeksvoorstel al klaar ligt. Je met de hand gecorrigeerde artikelen, ga ik nog missen. Bedankt voor je eeuwige kritische blik en inzet voor mijn promotie.

Beste professor Zietse, de secretaris van mij leescommissie. Hartelijk dank voor het beoordelen van mijn proefschrift. Ik kijk nog altijd met een lach terug naar mijn masteronderzoek, waarbij u me heeft begeleid in het onderzoek naar de invloed van cisplatine op de magnesium huishouding.

Beste overige leescommissie leden, professor Alwayn en professor Hilbrands, zeer veel dank voor het beoordelen van mijn proefschrift en uw waardevolle bijdragen. Tevens wil ik mijn overige opponenten bedanken voor hun bereidheid om zitting te nemen in mijn commissie.

Verder wil ik de 200 deelnemers van de SPLINT trial bedanken voor de genomen tijd en moeite om deel te nemen. Zonder uw waardevolle bijdragen aan dit onderzoek, zou dit proefschrift er niet zijn geweest.

Beste Diederik, Frank, Khe, Hermien, Robert, Kelly en Ellen bedankt voor jullie hulp tijd en vooral geduld tijdens de uitvoering van de SPLINT trial. Dagelijks kreeg ik van jullie een appje dat er ge-TOP-t was, waarop ik snel met het lootje jullie kant op kon. Beste Diederik, ik heb veel van je geleerd, waarbij ik met name altijd onder de indruk was van hoe jij met patiënten communiceert en veel hart voor de zaak hebt. Naast de vele uren

op de poli, hebben we er ook genoeg samen doorgebracht aan de bar op congressen en wintersport. Je bent altijd bereid geweest met me mee te denken op persoonlijk en wetenschappelijk aspect en dat stel ik ontzettend op prijs. Beste Frank, nu ondertussen al een tijd in Londen, maar ook zeker nauw betrokken geweest met het tot stand komen van dit proefschrift. Ons uitstapje naar de mircoRNAS in nierperfusaten is nog niet zo een succes als we hoopten, wellicht komt dat nog in een later stadium. Jij ook bedankt voor de leuke tijd op de OK, de zangsessies tijdens de LIDO en de late uurtjes op congressen. Beste Khe, geen splint of wel een splint, het was altijd wat jij nét niet wilde. Bedankt dat je me de mogelijkheid hebt gegeven om naast mijn promotie me ook te ontwikkelen op persoonlijk vlak met de organisatie van de chirurgencup. Hopelijk lukt het volgend jaar om wel die cup weer mee naar Rotterdam te nemen. Beste Hermien en Robert, beiden zijn jullie meer betrokken geraakt in een later stadium van mijn onderzoeksperiode, maar absoluut even waardevol. Ook jullie hebben mij geholpen en gesteund en wilden altijd meedenken over verbetering, waarvoor heel veel dank. Lieve Kelly en Ellen, bedankt voor onze leuke tijd samen.

Beste nefrologen, ook jullie hartelijk dank voor het meedenken en natuurlijk voor de nauwkeurige follow up van de niertransplantatie patiënten, waardoor dit onderzoek mogelijk is geworden.

Beste co-auteurs, bedankt voor jullie kritische blikken, tips en aanvullingen op mijn manuscripten.

Mijn paranimfen verdienen ook een bijzondere vermelding, kamertje 1 bravo. Beste Joost, alweer een jaar geleden mocht ik vol trots aan jouw zijde pronken als paranimf en ik waardeer het enorm dat je het nu ook andersom wilt doen. Onze tijd begon samen in traumacentrum IJsselland in 2012. Een half jaar na jou, kon ik ook in de Z-flat beginnen, waar jij al snel een plekje voor me had gereserveerd in kamertje 1. Ondertussen ben jij al een jaar in opleiding en spreken we elkaar niet meer dagelijks helaas, desalniettemin ben je voor mij een steun geweest tijdens alle lange uurtjes op de 8ste, bedankt hiervoor. Lieve Marcia, lekkere Eskimo, jij kwam in het mooiste kamertje in het najaar van 2014. Je moest aan het begin even wennen aan de danssessies op stoelen van mij en Joost, maar al snel bracht je Taylor Swift in en konden we gewoon lekker samen feesten. Ik mis onze app sessies als Shanaisha en Karishma, jammer dat je je telefoonnummer aan het einde moest veranderen. Ook ons concert met JB was natuurlijk the bomb, 'sorry'.

Lieve overige Z-buddies, lieve Gulia, bedankt voor de leuke tijd in onze kamer, ondanks dat jouw hart misschien bij de MDL lag, was je absoluut kamertje 1 waardig ;) Lieve Mus, fietsmaatje, bedankt voor de lange gesprekken en adviezen. Lieve Annie, mijn renmaatje,

helaas heb ik de marathon niet gered, maar ben ik wel heel blij dat je nog mijn liesbreuk hebt staan reponeren op de brug. Lieve Kiko, bedankt voor de gezellige gesprekken, je bent altijd betrokken en bereid om voor anderen klaar te staan en dat waardeer ik erg in je. Beste Coebergh, wij gaan al terug naar 2005 toen we samen aankwamen op de mooiste studentenverenging, ik heb van je genoten. Overige Z-flatters, traumajongens, Danielers en Lablui, hartelijk dank voor de leuke tijd en gezelligere borrels. Hou vol ook voor jullie komt dit moment.

Lieve IJsvogels, bedankt voor de ontzettend leuke tijd en steun tijdens mijn 'lange promotie onderzoek'. Jullie zijn allemaal van de categorie; 'been there, done that' en wisten precies wat ik meemaakte.

Beste Maasstad-ers, na al die jaren onderzoek was de overstap naar de kliniek weer even wennen. Bedankt voor jullie steun en gezelligheid in de afgelopen maanden.

Beste Carola, jij hebt geen idee hoeveel je voor de transplantatie sector betekend. Ik snap dat het even wennen was voor iedereen, toen jij overstapte naar het onderzoeksbureau. Bedankt voor al jouw hulp, ik zou niet weten wat ik zonder je had gemoeten.

Lieve vrienden en vriendinnen, medisch en niet medisch. Jullie gezelligheid heeft de afgelopen jaren makkelijker gemaakt voor mij. Ik kon altijd op jullie bouwen voor steun in de vorm van een drankje en een lekker hapje. Ik ben blij dat ik al mijn ontwikkelingen met jullie heb kunnen delen en ik kijk ernaar uit om weer meer tijd te hebben voor een borrel, feestje of uitstapje.

Lieve familie, we zijn er altijd voor elkaar en ik kan altijd op jullie rekenen. Bedankt voor jullie luisterende oor als het weer eens tegenzat en jullie betrokkenheid bij mijn promotieonderzoek! Ik verheug me erop dat ik straks weer meer tijd heb voor kaasplanken, Franse wijn en Elbmeister! Ik hou van jullie.

Lieve Guid, onwijze pitbull van me, wat ben ik blij dat jij een doorzetter bent. We hebben elkaar ontmoet tijdens mijn promotie en wonen nu alweer een half jaar samen. Bedankt voor je steun, interesse en het meedenken. Dankzij jou maak ik eindelijk wat stappen de juiste kant op. Ik zal jou ook helpen bij de laatste loodjes als jouw proefschrift aan het einde komt. Ik ben stapelgek op je.

List of publications

Kidney retransplantation in the ipsilateral iliac fossa: a surgical challenge**. L.S.S. Ooms**, J.I. Roodnat, F.J.M.F. Dor, T.C.K. Tran, H.J.A.N. Kimenai, J.N.M. Ijzermans, T. Terkivatan. American Journal of Transplantation 2015

Ureteral length in living donor kidney transplantation: does size matter? **L.S.S. Ooms**, I. Slagt, F.J.M.F. Dor, T.C.K. Tran, H.J.A.N. Kimenai, J.N.M. Ijzermans, M.G.H. Betjes, T. Terkivatan. Transplant International 2015

Incidence, risk factors and treatment of incisional hernia after kidney transplantation: an analysis of 1564 consecutive patients. **L.S.S. Ooms**[*], J. Verhelst[*], J. Jeekel, J.N.M. IJzermans, J.F. Lange, T. Terkivatan. Surgery 2016

Minimizing the number of urological complications after kidney transplant: a comparative study of two types of external ureteral stents. **L.S.S. Ooms,** L.G. Spaans, M.G.H. Betjes, J.N.M. IJzermans, T. Terkivatan. Experimental and Clinical Transplantation 2016

Antegrade balloon dilatation for post-transplantation ureteral strictures: case series. **L.S.S. Ooms**, A. Moelker, J.I. Roodnat , M.M. Idu, J.N.M. Ijzermans, T.Terkivatan. Accepted for publication in Experimental and Clinical Transplantation

Urinary tract infections after kidney transplantation: a risk factor analysis of 417 patients. **L.S.S. Ooms,** A.F. Voor in 't holt, M.C. Vos, M.G.H. Betjes, J.N.M. Ijzermans, T. Terkivatan. Annals of Transplantation 2017

Proteins secreted into donor kidney preservation fluid predict delayed graft function of kidneys from donors after circulatory death. B.W.M. van Balkom, **L.S.S. Ooms**, H. Gremmels, R.J. Toorop, F.J.M.F. Dor, O.G. de Jong, L.A. Michielsen, G. de Borst, W. de Jager, A. D. van Zuilen, M.C. Verhaar. Clinical Journal of American Society of Nephrology 2017

Reconstruction of the lower eyelid using Hughes' tarsoconjunctival flap: long term follow up of 28 cases. **L.S.S. Ooms**, M.R. Beets, E.C. Grosfeld, E. Beems, G.A. Krekels, J.M. Smit, M.M. Hoogbergen. Journal of Plastic Reconstructive & Aesthetic Surgery 2014

PhD Portfolio

Name PhD student: Liselotte Ooms
PhD period: 2014 -2017
Erasmus MC Department: Surgery
Promotor: Prof. Dr. J.N.M. IJzermans
Research School: Molecular Medicine
Supervisor: Dr. T. Terkivatan

PHD training	Year	Workload (ECTS)
General courses		
- Survival Analyses Course	2016	0.5
- Cursus Photoshop & illustrator	2014	0.3
- Basic Introduction Course SPSS	2014	1.0
- Cursus Wetenschappelijke integriteit	2014	0.3
- BROK (Basiscursus Regelgeving Klinisch Onderzoek)	2014	1.8
Specific courses		
- Life Donor Nephrectomy Course	2015-2016	2.0
Oral and poster presentations		
- European Society of Organ Transplantation Congress	2015	3.0
- American Transplant Congress	2015-2016	4.0
- European Society for Surgical Research Congress	2016	3.0
- Nederlandse Transplantatie Vereniging Congres	2015-2016	3.0
- Symposium Experimenteel onderzoek Heelkundige Specialisme	2014	1.0
- Wetenschapsdag Heelkunde Erasmus MC	2015	2.0
- Molecular Medicine Day	2015	1.0
Attendance at (inter)national Conferences and Seminars		
- Chirurgendagen	2014-2016	3.0
- Wetenschapsdag Heelkunde Erasmus MC	2014	1.0
Teaching		
- Examination of Basic Life Support of medical students	2014-2016	1.0
- Teaching Minor 'Orgaantransplantatie'	2015-2016	2.0
- Supervising Master Thesis Laura Spaans	2015	2.0
- Supervising medical student Tim Knuppe	2016	1.0
Total	**32.9**	

Curriculum Vitae

Liselotte Susanne Sophie Ooms werd op 28 januari 1987 geboren in Wageningen. Hier groeide zij op en behaalde in 2005 haar VWO diploma aan het Marnix College in Ede. Haar opleiding geneeskunde vond plaats aan de Erasmus Universiteit te Rotterdam. In de laatste fase van haar opleiding heeft zij 2 maanden doorgebracht in Suriname voor een keuze coschap chirurgie in het Academisch Ziekenhuis Paramaribo. Haar oudste coschap plastische chirurgie volgde zij in het Catharina Ziekenhuis te Eindhoven.

Na het behalen van haar artsexamen in november 2012 werkte zij met veel plezier als arts-assistent bij de afdeling heelkunde in het IJsselland Ziekenhuis te Capelle a/d IJssel (Dr. I. Dawson). In januari 2014 startte ze als arts-onderzoeker op de afdeling transplantatiechirurgie in het Erasmus MC Universitair Medisch Centrum te Rotterdam (promotor: Prof. dr. J.N.M. IJzermans en copromotor: Dr. T. Terkivatan). De resultaten van haar onderzoek naar chirurgische complicaties na niertransplantaties zijn gebundeld in dit proefschrift. Na afronding van haar promotietraject is zij in november 2016 weer terug gekeerd naar klinische werkzaamheden in het Maasstad Ziekenhuis (Dr. R.A. Klaassen).

Liselotte woont samen in Rotterdam met haar vriend Guido die ze tijdens haar promotieonderzoek in het Erasmus MC heeft ontmoet.