UROLOGICAL COMPLICATIONS IN KIDNEY TRANSPLANTATION

Inez K.B.Slagt

The studies described in this thesis were performed at the Department of Surgery, Erasmus MC, Rotterdam, the Netherlands.

This research was financially supported by Erasmus MC Cost-Effectiveness Research (Doelmatigheid- en Zorgonderzoek).

Printing of this thesis has been financially supported by: Erasmus MC - afdeling Heelkunde Nederlandse Transplantatie Vereniging Nierstichting Takeda

ISBN: 978-94-6169-592-5

Cover design by Wouter Droog
Layout and printing: Optima Grafische Communicatie, Rotterdam, The Netherlands.

UROLOGICAL COMPLICATIONS IN KIDNEY TRANSPLANTATION

Urologische complicaties 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 besluit van het College voor Promoties.

De openbare verdediging zal plaatsvinden op
vrijdag 30 januari 2015 om 11.30 uur

Inez Kirsten Beatrice Slagt

geboren te Rotterdam

PROMOTIECOMMISSIE

Promotor	Prof.dr. J.N.M. IJzermans
Overige leden	Prof.dr. H.W. Tilanus Prof.dr. W. Weimar Prof.dr. C.H. Bangma
Copromotor	Dr. T. Terkivatan

CONTENT

Chapter 1
General introduction and outline of the thesis

Inez K.B. Slagt, Jan N.M. IJzermans, Türkan Terkivatan

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

KIDNEY TRANSPLANTATION

The kidney is an essential organ that plays an crucial role in acid-base balance, sodium and potassium balance, calcium metabolism, regulation of blood pressure, red blood cell synthesis and excretion of metabolites. Kidney diseases may result in kidney failure with the requirement of kidney replacement therapy like dialysis. Hemodialysis and peritoneal dialysis may extend patient survival but does not cure the kidney failure. Kidney transplantation is considered the optimal kidney replacement therapy for patients with end stage kidney failure, resulting in decreased morbidity, improved quality of life and higher costs effectiveness when compared to dialysis.

History of kidney transplantation

In the early years of experimental kidney transplantation, donor kidneys were placed in the thigh with cutaneous ureterostomy drainage or in the iliac fossa with drainage by ureteroureterostomy to the recipient native ureter. In January 1951, Rene Kuss placed a donor kidney into the iliopelvic region of the recipient with cutaneous ureterostomy.[1, 2] Soon thereafter another French surgical team established the concept that a kidney placed in the iliac fossa provides a short ureter with possibilities for drainage to the bladder. Although these early attempts of kidney transplantation resulted in failure, Joseph Murray and John Hartwell Harrison completed the first successful kidney transplantation on identical twins in Boston on December 23, 1954.[3] The recipient was prepared with hemodialysis, and monozygosity was confirmed by the successful exchange of full thickness skin grafts between the twins. The left donor kidney was transplanted in the right recipient's iliac fossa, and a intravesical ureteroneocystostomy with a submucosal tunnel was established. A small polyethylene catheter was placed up the transplant ureter and was suprapubicly externalized. After renal vascularization by doctor Murray, doctor Harrison assisted with the urinary tract reconstruction. The kidney functioned directly after transplantation and the patient was discharged on day 37 postoperative. The kidney function maintained good and was functioning until cardiac death 8 years later occur.[4] This successful transplantation between identical twins enhanced the opinion that the pelvic location with possibilities of bladder drainage was the most physiological and natural position for the kidney graft.[1] Nevertheless, the intervention of adequate immunosuppressive therapy in the 1960s enabled kidney transplantation on a larger scale.

Ureteroneocystostomy

Although the position and the vascular anastomoses of the transplanted kidney have remained unchanged over time, multiple techniques have been described for managing the urinary continuity. Techniques like ureteroneocystostomy, ureteropyelostyomy and uretero-ureterostomy have been used.

Two types of ureteroneocystostomy are common, the intravescial or transvesical anastomosis (Figure 1) and the extravesical anastomosis (Figure 2). The intravesical anastomosis, first described by Politano-Leadbetter, was frequently used during the early days of transplantation.[5, 6] However, this method is associated with intrusive bladder dissection and therefore an extravesical approach was designed.[7] This extravesical anastomosis, first described by Lich-Gregoir, was presented at the German Congress of Surgery in April 1961.[7] Many modifications of the extravesical anastomosis have been developed, like Shanfield, Taguchi and Barry techniques.[1]

Other techniques to obtain urinary continuity, ureteropyelostomy and uretero-ureterostomy, have good outcomes, but these techniques are reserved for reconstruction situations. Ureteroneocystostomy is widely accepted for establishing urinary continuity, and is associated with the lowest number of complications. However, no consensus exists regarding superiority of either the intravesical anastomosis or the extravesical anastomosis.

Urological complications

One of the main concerns after kidney transplantation is a major urological complication, such as leakage and stenosis of the ureter. These complications are often related to the junction site of the ureteroneocystostomy with a reported incidence up to 10% and require additional radiological or even surgical intervention. If signs of leakage or obstruction appear, a percutaneous nephrostomy (PCN) is placed to insure a consistent urinary drainage.

Risk factors contributing to urological complications have been described rarely in the literature, but include donor and recipient characteristics. Donor related factors like deceased or living, problems during graft retrieval, multiple renal arteries, age or diabetes mellitus could influence the graft quality. Recipient factors like anatomy, vascular status, need of dialysis, type of ureteroneocystostomy or stent placement may also contribute to development of urological complications.

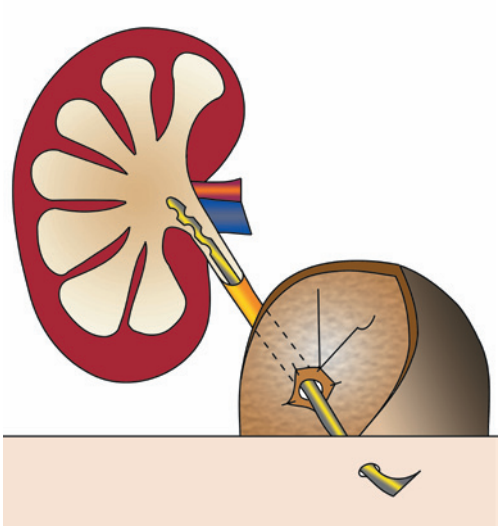

Figure 1 Intravesical anastomosis with a stent placed in the pelvis of the kidney and externalized as a suprapubic catheter.

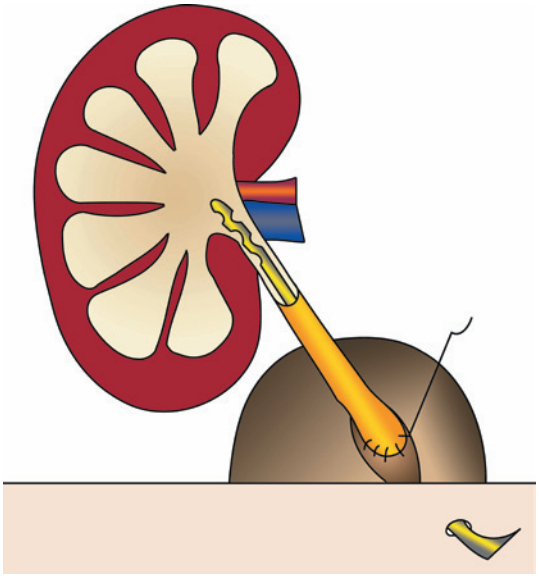

Figure 2 Extravesical anastomosis with a stent placed in the pelvis of the kidney and externalized as a suprapubic catheter.

AIM AND OUTLINE OF THE THESIS

This thesis includes studies that address various aspects related to urological complications after kidney transplantation. Surgical techniques are compared, risk factors are determined, costs are calculated, and experience in scare cases of kidney transplantation are described.

Ureteroneocystostomy technique

No consensus exists on the preferred operative technique of the ureteroneocystostomy. Two most common techniques are the intravesical anastomosis and the extravesical anastomosis. In **chapter two** a systematic review and meta-analysis is performed on existing literature comparing these two anastomoses.

To reach the best level of evidence on the topic of type ureteroneocystostomy we performed a Randomized Controlled Trial (RCT) on the intravesical anastomosis versus the extravesical anastomosis. This study is presented in **chapter three**.

Identification and costs of urological complications

Risk factors contributing to the prevalence of urological complications need to be determined. Factors associated with urological complications are donor and recipient characteristics. Regarding the differences in organ retrieval between deceased and living donor kidney transplantation and the extended donor criteria, we wanted to determine risk factors for urological complications in deceased donor kidney transplantation. **Chapter four** describes an analysis to identify independent risk factors for urological complications.

Kidney transplantation has a great advantage on patient's quality of life in comparison to dialysis. Also, kidney transplantation results in decreased medical costs compared to dialysis. However, urological complications following transplantation incur additional costs, especially in case of major urological complications. In these cases additional radiological interventions or even surgical interventions are often inevitable. **Chapter five** represents the long-term clinical outcome of patients requiring a radiological or surgical ureter reconstruction with an additional cost analysis.

Kidney transplantation in a reconstructed urinary tract

Formerly, patients that underwent a urinary reconstructive procedure have been excluded from kidney transplantation, because it was thought that the bladder contributed to the destruction of the native kidneys and would destruct the transplant graft. Literature describes only 0.2-2.3% of adult patients with a reconstructed urinary tract receiving a kidney transplantation. In **chapter six** we describe our long-term outcome of these patients with a reconstructed urinary tract receiving a kidney transplant.

General discussion and future perspective, summary and conclusions

In **chapter seven** the results of the studies performed in this thesis are discussed. Finally, **chapter eight** contains summaries in English and Dutch.

REFERENCES

1 Veale JL, Yew J, Gjertson DW, et al. Long-term comparative outcomes between 2 common ureteroneocystostomy techniques for renal transplantation. J Urol (2007);177:632-636.

2 Kuss R Human renal transplantation memories 1951 to 1981 History of Transplantation: Thirty-Five Recollections. Regents of the University of California 1991; 3-4 and 39-40.

3 Harrison JH, Merrill JP, Murray JE Renal homotransplantation in identical twins. Surg Forum. (1956);6:432.

4 Barry JM, Murray JE The first human renal transplants. J Urol (2006);176:888-890.

5 Politano VA, Leadbetter WF An operative technique for the correction of vesicoureteral reflux. J Urol (1958);79:932-941.

6 Secin FP, Rovegno AR, Marrugat RE, Virasoro R, Lautersztein GA, Fernandez H Comparing Taguchi and Lich-Gregoir ureterovesical reimplantation techniques for kidney transplants. J Urol (2002);168:926-30.

7 Gregoir W the Surgical Treatment of Congenital Vesico-Ureteral Reflux Le Traitement Chirurgical Du Reflux Vesico-Ureteral Congenital. Acta Chir Belg (1964);63:431-439.

Chapter 2

Intravesical versus extravesical ureteroneocystostomy in kidney transplantation: A systematic review and meta-analysis

Inez K.B. Slagt, Karel W.J. Klop , Jan N.M. IJzermans , Türkan Terkivatan

Department of Surgery, Erasmus MC,
University Medical Center, Rotterdam, the Netherlands

Transplantation. 2012 Dec 27;94(12):1179-84.

ABSTRACT

Introduction

Urological complications are still a major problem postoperatively with a reported incidence of up to 30%, associated with significant morbidity, mortality, prolonged hospital stay and high medical costs. To date, there is no evidence favouring either an extravesical or an intravesical approach. The purpose of this systematic review and meta-analysis is to determine if an intravesical or extravesical anastomosis in kidney transplantation is to be preferred.

Patients and Methods

Comprehensive searches were conducted in PubMed, Embase and the Cochrane Library. Reference lists were searched manually. The methodology was in accordance with the PRISMA statement. Two randomized controlled trials and seventeen cohort studies were identified.

Results

Based on the meta-analysis, outcome was in favour of the extravesical anastomosis. A relative risk (RR) for stenosis of 0.67 (confidence interval (CI), 0.48-0.93; p=0.02), for leakage 0.55 (CI 0.39-0.80; p=0.001) for the total number of urological complications 0.56 (CI 0.41-0.76; p<0.001) and for haematuria of 0.41 (CI 0.22-0.76; p=0.005) was demonstrated.

Conclusion

Based on our results, we conclude that there is evidence in favour of the extravesical ureteroneocystostomy for having a smaller amount of urological complications in kidney transplantation.

INTRODUCTION

Kidney transplantation is considered the gold standard in treatment of patients with end stage renal disease (ESRD), resulting in a decrease in morbidity, better quality of life and higher cost effectiveness when compared with hemo- or peritoneal dialysis.[1] During the 1950s, the surgical technique for kidney transplantation was developed, engrafting the kidney extraperitoneally in the iliac fossa with vascular anastomosis to the iliac vessels.[2-4] Several variations for achieving urinary continuity of the transplanted kidney include ureteroneocystostomy, ureteropyelostomy, uretero-ureterostomy and cutaneous ureterostomy. Of these various techniques, the ureteroneocystostomy appears to be most widely accepted and is associated with the lowest number of complications.[5] Nevertheless, urological complications including urinary tract infections are still a major problem postoperatively with a reported incidence of up to 30%, associated with significant morbidity, mortality and prolonged hospital stay.[6] Major urological complications, mostly existing of stenosis or leakage with a reported incidence beneath 10%, are frequently related to the junction site of the ureteroneocystostomy and often require percutaneous or surgical intervention.[7]

In literature, there is no consensus on the preferred operative technique for the ureteroneocystostomy. The most common techniques for ureteroneocystostomy are the intra- or transvesical approach, first described by Politano-Leadbetter (PL)[8], and the extravesical approach as described by Lich-Gregoir (LG).[9] Most studies focus on a single technique and are retrospectively performed. Furthermore, a lot of the literature on the surgical techniques and outcome of ureteroneocystostomy has been published in the early years of kidney transplantation.[5, 7-9] The aim of the present study was to assess the superiority of either the intra- or extravesical anastomosis in kidney transplantation, after a systematic review and when systematically analyzing and reviewing the literature.

METHODS

All aspects of the Preferred Reporting Items for Systematic Reviews and Meta-Analysis (PRISMA)[10] statement were followed.

Literature search strategy

A systematic search of PubMed, Embase and the Cochrane library was performed. Articles relevant to kidney transplantation and ureteroneocystostomy with in the limits "human related" and "English language" were selected. The MeSH term 'kidney transplantation' was used in Pubmed. Other key words used were 'ureteroneocystostomy', 'Politano-

Leadbetter', 'Lich-Gregoir', 'intravesical', 'extravesical', 'surgery' and 'anastomosis'. Manual reference checks of accepted papers in recent reviews and included papers were performed to supplement the electronic searches.

Literature screening

Studies were evaluated on relevance by two independent researchers (IKBS, KWJK) before inclusion. A random cross-check was performed by a senior researcher (TT). Study selection was accomplished by three levels of screening (Figure 1). At level 1, studies were excluded by title and abstract for the following reasons: case series, case reports, letters, editorials, comments, reporting on children, uretero-ureterostomy, two ureters or kidney transplantation combined with pancreas transplantation. At level 2, the full text of studies accepted at level 1 was reviewed for relevance according to the same criteria. Specific attention was paid to a comparison between intravesical and extravesical anastomoses or double published data. Stent placement, primary or re-transplantation and living versus deceased donor did not interfere with our selection.

Data extraction and critical appraisal

Data, design and population were extracted from all included studies. Raw data on the amount of patients undergoing the different techniques had to be available for inclusion. Studies that included two different types of intra- or extravesical anastomosis were excluded. The level of evidence of each study was scored using the Oxford Centre for Evidence-based Medicine Level of Evidence scale.[11] The quality of each study was calculated using the Jadad-score[12] for the randomized controlled trials and by the Newcastle-Ottawa Scale[13] for all cohort studies.

Statistical analysis

Risk ratios (RR) and their 95% confidence interval (CI) were calculated from raw data with the intravesical anastomoses group as reference. A meta-analysis was performed with urological complications as outcome using Review Manager (RevMan) software (version 5.1.4; The Nordic Cochrane Center Copenhagen, Denmark). Each study was weighted by sample size, not by quality. Statistical heterogeneity was explored by inspecting the forest plot, testing the Q (heterogeneity χ^2) and the I^2 statistics. Summary estimators of treatment effects were calculated using a random effects model with RR and its 95% CI. Overall effects were determined using the Z-test. End points were set on 'stenosis', 'leakage', 'total number of urological complications', 'haematuria' and 'urinary tract infection'. A subdivision was made for stenosis into ureterovesicaljunction (UVJ) stenosis and pyelo-ureterojunction (PUJ) stenosis. Leakage was divided into UVJ leakage and vesical leakage. To asses publication bias funnel plots were made.

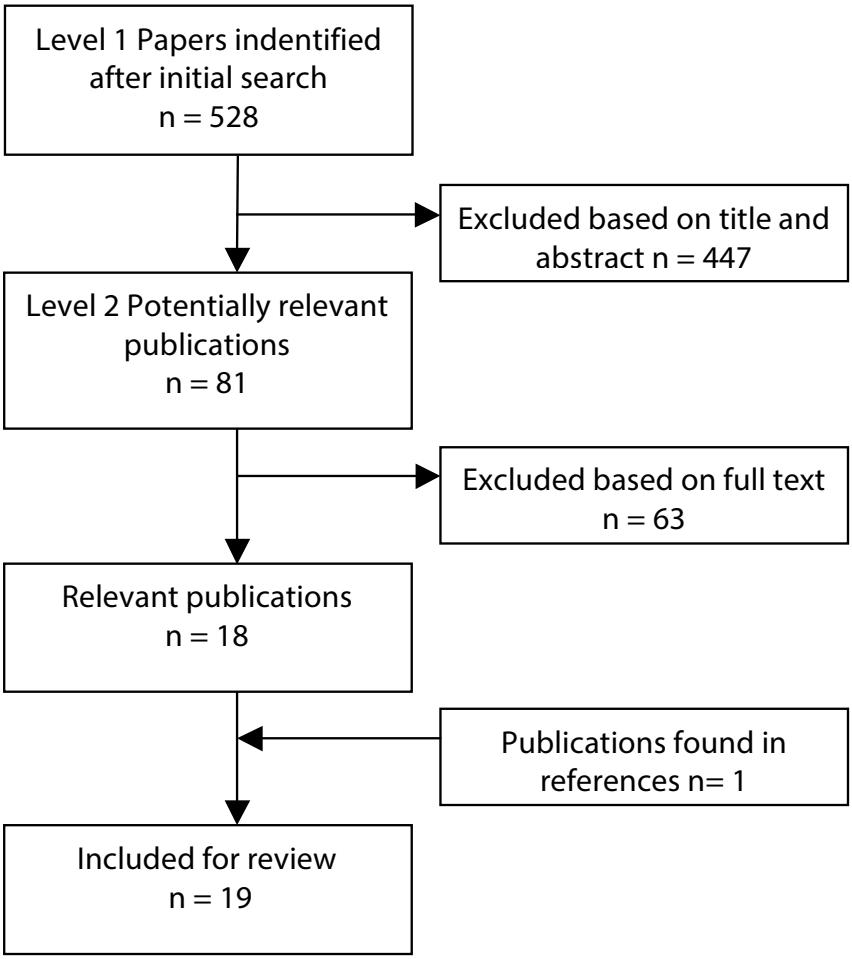

Figure 1 PRISMA flowchart of the systematic literature search

Outline of surgical techniques

The PL anastomosis is created by performing a cystotomy on the anterior side to visualize the interior of the bladder and expose the trigone. A second cystotomy is performed to create a new ureteric orifice. The transplanted ureter is tunnelled submucosally for approximately 2 centimetres. The distal site is trimmed and spatulated anteriorly at an optimal length to ensure a tension free anastomosis. The distal ureter is sutured to the bladder mucosa with interrupted absorbable stitches. The cystotomy is closed in two layers to ensure a watertight anastomosis.

The LG anastomosis is created by performing a cystotomy for 2 to 3 centimetres on the anterolateral surface of the bladder dome to expose mucosa of the bladder wall. A small incision is made in the mucosa. The transplanted ureter is trimmed and spatulated posteriorly. The mucosa of the bladder is sutured to the ureteral end with interrupted absorbable sutures. The detrusor muscle is closed over the anastomosis to create a sub mucosal tunnel with an antireflux mechanism.

RESULTS

Of the 528 studies that were found after the initial search, eighteen were selected based on relevancy. One was added after a manual reference check of the included articles. These 19 manuscripts[14-32] fell within the scope of the study (Figure 1) after full screening (PRISMA flowchart). All had a case distribution for intravesical versus extravesical ureteroneocystostomy after kidney transplantation, but outcome measures were diverse. The provided level of evidence on the Oxford Level of Evidence scale was level 4. Because of the low level of evidence and quality in the overall literature, no manuscript was excluded by the Jadad or Newcastle-Ottawa Scale. The meta-analysis was performed using studies with comparable outcome measures as described in the methods; study characteristics are presented in Table 1.

Stenosis

Seventeen studies[14-23, 25, 26, 28-32] reported on incidence of stenosis after ureteroneocystostomy with a total of 7681 patients, these studies were included for meta-analysis. The incidence of ureteral stenosis was significantly lower in the group of patients that received an extravesical anastomosis; RR 0.67 (95% CI 0.48-0.93; p=0.02) and I^2 of 18% (Figure 2). The percentage of stenosis was 3.13% and 3.51% for respectively the group with an extravesical an intravesical anastomosis. Some of these studies also reported on the location of the stenosis; at the UVJ[18, 23, 29, 30], the PUJ[16, 18, 29, 30, 32] or (mid) ureteral.[21, 29, 30] In these groups there was no statistical difference. The RR for a stenosis

Table 1 References: 19 included studies

Reference	Year	Country	Study type	Group N	Stent	Outcome
Belli (10)	1985	Italy	R cohort	E: 115 I: 185	NM	1, 5, 8
Butterworth (11)	1997	UK	P cohort	E: 108 I: 140	E: stent I: no stent	1, 5, 8, 9, 10
Dohi (12)	1984	Japan	U cohort	E: 49 I: 21	NM	1, 3, 5, 8, 9
Georgiev (13)	2007	Swiss	R cohort	E: 348 I: 149	E: 162 stent on demand, 186 stent I: stent on demand	1, 5, 8
Hakim (14)	1994	USA	U cohort	E: 773 I: 410	NM	1, 2, 3, 6, 8, 9
Hooghe (15)	1977	Belgium	U cohort	E: 133 I: 108	NM	1, 5
Jindal (16)	1994	USA	U cohort	E: 69 I: 116	NM	1, 5, 10
Leungwattanakij (17)	2000	Thailand	U cohort	E: 245 I: 93	NM	1, 4, 6, 8, 9
Li Marzi (18)	2005	Italy	U cohort	E: 260 I: 199	All double J stent	1, 5
Masahiko (19)	2000	Japan	U cohort	E: 225 I: 962	NM	1, 2, 5, 8
Mehta (20)	1978	UK	U cohort	E: 32 I: 87	E: NM I: no stent	8
Pleass (21)	1995	UK	RCT	E: 150 I: 150	E: 75 (no) stent I: 75 (no) stent	1, 5
Rizvi (22)	1996	Pakistan	U cohort	E: 148 I: 202	NM	1, 5, 8
Shah (23)	1987	India	U cohort	E: 125 I: 125	NM	5, 6, 7
Taghavi (24)	2003	Iran	U cohort	E: 68 I: 50	E: no stent I: no stent	1, 5, 6, 7
Thrasher (25)	1990	USA	U cohort	E: 160 I: 160	NM	1, 2, 3, 4, 5, 8, 9
Tillou (26)	2009	France	R cohort	E: 412 I: 265	95,5% stent	1, 2, 3, 4, 5, 6, 8
Waltke (27)	1982	USA	Randomization on date	E: 72 I: 59	E: stent I: no stent	1, 5, 10
Whang (28)	2003	USA	R cohort	E: 1010 I: 67	E: stent I: no stent	1, 3, 5, 8

Randomization on date: randomization according to which surgeon was scheduled that date
E: extravesical; I: intravesical; NM: not mentioned; N: number; R: retrospective;
P: prospective; U: unclear; RCT: randomized control trial
1 stenosis; 2 UVJ stenosis; 3 PUJ stenosis; 4 ureter stenosis; 5 leakage; 6 UVJ leakage; 7 vesical leakage; 8 total number of urological complications; 9 haematuria; 10 urinary tract infection

at the UVJ was 0.63 (95% CI 0.29-1.37; p=0.25) with I^2 of 33%, at the PUJ 0.55 (95% CI 0.15-2.08; p=0.38) I^2 43% and for a (mid) ureteral stenosis 0.56 (95% CI 0.20-1.58; p=0.27) I^2 0% when comparing intravesical with extravesical ureteroneocystostomy.

Leakage

Urinary leakage was meta-analyzed in a total of 6410 patients from sixteen studies.[14-17, 19, 20, 22, 23, 25-32] The incidence of urinary leakage was significantly lower in the group of patients that underwent an extravesical anastomosis with a RR of 0.55 (95% CI 0.39-0.80; p=0.001) and an I^2 of 0% (Figure 3). The percentage of leakage was 1.65% for the extravesical and 3.25% for the intravesical anastomosis. A few studies pooled their data into UVJ leakage[18, 21, 27, 28, 30] and vesical leakage.[27, 28] The difference in number

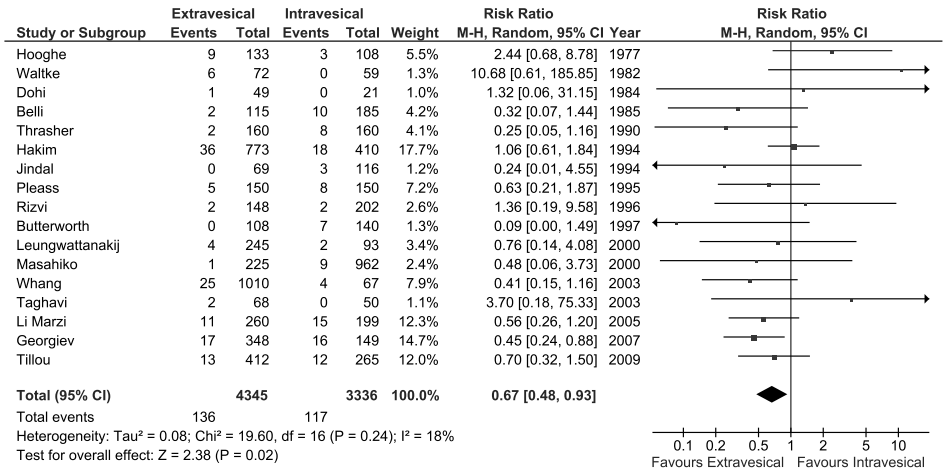

Figure 2 Forest plot of stenosis rate in patients with an extravesical anastomosis *versus* those with an intravesical anastomosis. Risk ratio estimates, shown with 95% confidence intervals, were calculated using the random-effects model. The tilted square represents the overall treatment effect from the 17 pooled studies spanning the 95% confidence interval.

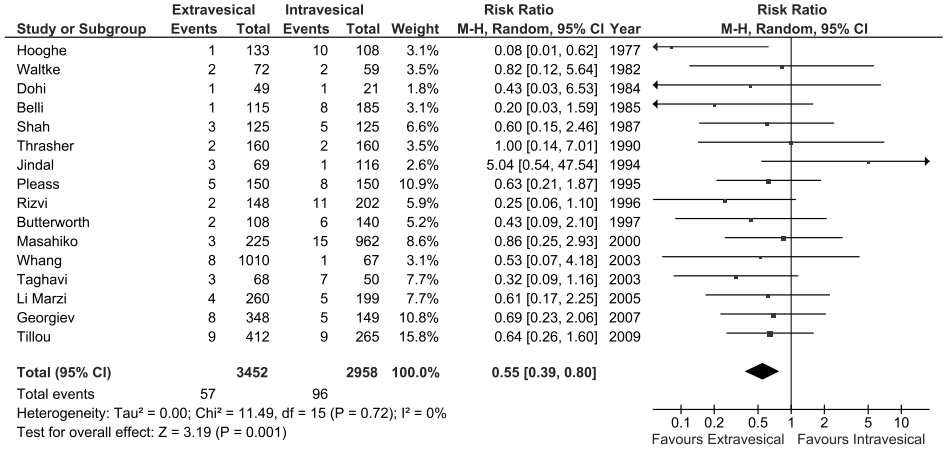

Figure 3 Forest plot of leakage rate in patients with an extravesical anastomosis *versus* those with an intravesical anastomosis. Risk ratio estimates, shown with 95% confidence intervals, were calculated using the random-effects model. The tilted square represents the overall treatment effect from the 16 pooled studies spanning the 95% confidence interval.

of UVJ leakage was statistically significant with a RR of 0.47 (95% CI 0.25-0.89; p=0.02) and an I^2 of 0% in favour of the extravesical group while vesical leakage did not show a statistically significant difference, RR 0.13 (95% CI 0.02-1.04; p=0.05) with I^2 0%.

Total number of urinary complications

Twelve studies[14-18, 21, 23, 24, 26, 29, 30, 32] reported on the total number of urological complications in a total of 6366 patients, and were included in our meta-analysis. The overall complication rate was significantly lower in the extravesical group with a RR of 0.56 (95% CI 0.41-0.76, p<0.001) and an I^2 of 44% (Figure 4). In percentages, 5.41% of these complications were seen in the extravesical group and 8.61% in the intravesical group.

Haematuria

The incidence of haematuria post transplantation was described in five studies[15, 16, 18, 21, 29] with a total of 2159 patients. The meta-analysis showed significantly less frequent haematuria in the extravesical group with a RR of 0.41 (95% CI 0.22-0.76; p=0.005) and an I^2 of 0%. Haematuria occurred in 1,20% and 4% in respectively the group of patients with an extravesical and intravesical anastomosis.

Urinary tract infections

Three studies (564 patients) [15, 20, 31] reported on urinary tract infections. These data were used for meta-analysis and no statistical difference was found between the intra- and extravesical group; RR 1.00 (95% CI 0.77-1.28 with p=0.97) and I^2 of 0%. Urinary tract infections were seen in 26,9% of the extravesical group and in 28,25% of the intravesical group.

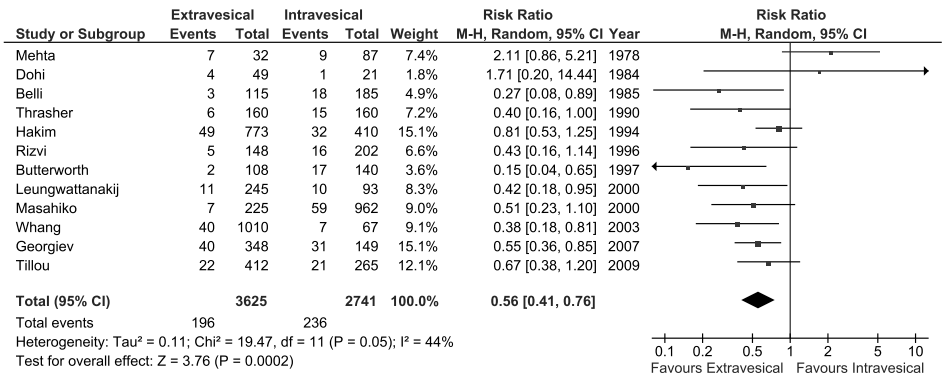

Figure 4 Forest plot of the total number of urological complication rate in patients with an extravesical anastomosis *versus* those with an intravesical anastomosis. Risk ratio estimates, shown with 95% confidence intervals, were calculated using the random-effects model. The tilted square represents the overall treatment effect from the 12 pooled studies spanning the 95% confidence interval.

DISCUSSION

Despite a variety of urinary tract reconstruction techniques, postoperative urological complications are the most frequent technical adverse event in kidney transplantation. These complications are frequently associated with substantial morbidity and generate excess costs caused by re-admissions to the hospital, percutaneous (re-) interventions, imaging and surgical revisions of the ureteroneocystostomy.[6]

The present systematic review and meta-analysis reveals an advantage of the extravesical anastomosis in kidney transplantation compared to the intravesical anastomosis. A statistically significant difference was found in stenosis, leakage, total number of urological complications and haematuria (Figure 2, 3, 4), all in favour of the extravesical anastomosis. Regarding urinary tract infections, no significant difference was found between both types of anastomosis.

The majority of kidney transplant centers are performing an extravesical ureteroneocystostomy. However, no consensus exists in literature on the preferred technique. In 2010 a review of the literature on ureteroneocystostomy techniques in case of kidney transplantation was published by Kayler et al.[3] A historical and technical description of four surgical techniques was provided and analyzed, focusing on 4 specific urological complications; urinary leakage, ureteric obstruction, haematuria and symptomatic vesicoureteral reflux. Only two randomized controlled trials were performed and both showed a preference for the extravesical technique and the use of a prophylactic ureteric stent.[25, 31]

Appointed benefits of the extravesical ureteral anastomosis are shorter operation time due to simplicity of the technique, a shorter ureteral length and an additional reduced risk of ischemic injury to the distal ureter. Furthermore, the avoidance of a separate cystotomy with the additional risk of postoperative urinary leakage or ganglion injury (causing persistent neurogenic bladder dysfunction) is another advantage of an extravesical ureteroneocystostomy.[3]

Although this systematic review and meta-analysis provides important evidence for the technique of the ureteroneocystostomy in kidney transplantation, we must note some limitations of our study. The ureteroneocystostomy should provide a watertight, tension free and non-refluxing anastomosis with good passage of urine production and without obstruction.[7, 20] Many modifications of the extravesical technique have been described, such as the use of running instead of interrupted sutures to create the ureteral mucosal anastomosis and tunnelling by sub mucosal blunt dissection instead of muscular

imbrications.[3] All of these so-called modified techniques include extravesical access and an urothelial anastomosis. The use of these modified techniques may have biased the results of our meta-analysis. In addition, only Waltke et al.[31] describe a radiographic contrast injection before stent removal. None of the included studies describe whether a pyelography has been performed routinely or only on indication after clinical suspicion for early urological complications. Inevitably, this must have influenced the rate of leakage or stenosis.

Likewise, the strong diversity in the use or no use of the different stent types, e.g. double-J or tube stenting, might have been an important confounder in our meta-analysis. Since stenting may influence the healing of the anastomosis and thereby the total amount of urological complications. Proponents of stent placement advocate relief of the anastomosis because of the post-operative presence of oedema that may cause obstruction or leakage. The incidence of urinary tract infection was not increased in patients that receives a stent during kidney transplantation.[25]

The studies included in our meta-analysis were performed in different eras of immunosuppressive medication; this might be another confounding factor. Other nontechnical risk factors for the development of urological complications such as recipient age, number of renal arteries, and the occurrence of acute rejection episodes (not scored prospectively or independently) may have interfered with our analysis. Furthermore, the limited availability of prospective trials, selection bias may have occurred. For example, most of the described series included living and deceased donor grafts without having performed a multivariate analysis.

This systematic review and meta-analysis is the first step in providing a definite answer on superiority of either the extra- or intravesical techniques, accounting for urological complications and long-term outcome. To provide a superior level of evidence for either technique of ureteroneocystostomy, a sufficiently powered randomized controlled trial is recommended. Due to our systematic search, processing raw data and computed RR we managed to produce the best possible evidence. The results of our meta-analysis demonstrate superior results after extravesical anastomosis in kidney transplantation.

REFERENCES

1 Zomorrodi A, Buhluli A New technique for allograft ureteroneocystomy for better transvesical endoscopic handling of allograft urological complications. Saudi J Kidney Dis Transpl (2007);18:365-369.

2 Barry JM, Murray JE The first human renal transplants. J Urol (2006);176:888-890.

3 Kayler L, Kang D, Molmenti E, Howard R Kidney transplant ureteroneocystostomy techniques and complications: review of the literature. Transplant Proc (2010);42:1413-1420.

4 Veale JL, Yew J, Gjertson DW, et al. Long-term comparative outcomes between 2 common ureteroneocystostomy techniques for renal transplantation. J Urol (2007);177:632-636.

5 Woodruff MW, Bachrach P, Corica A, Marden HE, Jr. Ureteroneocystostomy in renal transplantation. Urology (1973);1:414-416.

6 Dols LF, Terkivatan T, Kok NF, et al. Use of stenting in living donor kidney transplantation: does it reduce vesicoureteral complications? Transplant Proc (2011);43:1623-1626.

7 Tan EC, Lim SM, Rauff A Techniques of ureteric reimplantation in kidney transplantation and its related urological complications. Ann Acad Med Singapore (1991);20:524-528.

8 Politano VA, Leadbetter WF An operative technique for the correction of vesicoureteral reflux. J Urol (1958);79:932-941.

9 Gregoir W the Surgical Treatment of Congenital Vesico-Ureteral Reflux Le Traitement Chirurgical Du Reflux Vesico-Ureteral Congenital. Acta Chir Belg (1964);63:431-439.

10 Moher D, Liberati A, Tetzlaff J, Altman DG, Group P Reprint--preferred reporting items for systematic reviews and meta-analyses: the PRISMA statement. Phys Ther (2009);89:873-880.

11 Oxford Centre Evidence-Based Medicine Levels of Evidence Working Group = Jeremy Howick ICJLL, Paul Glasziou, Trish Greenhalgh, Carl Heneghan, Alessandro Liberati, Ivan Moschetti, Bob Phillips, Hazel Thornton, Olive Goddard and Mary Hodgkinson. OCEBM Levels of Evidence Working Group. "The Oxford 2011 Levels of Evidence". Oxford Centre for Evidence-Based Medicine.; Available from: http://www.cebm.net/index.aspx?o=5653.

12 Jadad AR, Moore RA, Carroll D, et al. Assessing the quality of reports of randomized clinical trials: is blinding necessary? Control Clin Trials (1996);17:1-12.

13 GA Wells BS, D O'Connell, J Peterson, V Welch, M Losos, P Tugwell. The Newcastle-Ottawa Scale (NOS) for assessing the quality if nonrandomized studies in meta-analyses.

14 Belli L, Minetti L, Civati G, et al. Influence of technical factors and different immunosuppressive regimens on kidney graft survival. Retrospective analysis on 300 kidney transplants. Ital J Surg Sci (1985);15:323-328.

15 Butterworth PC, Horsburgh T, Veitch PS, Bell PR, Nicholson ML Urological complications in renal transplantation: impact of a change of technique. Br J Urol (1997);79:499-502.

16 Dohi K, Fukuda Y, Asahara T, et al. Urological complications of ureteroneocystostomy in renal transplantation; a comparison between intravesical ureteroneocystostomy and extravesical ureteroneocystostomy. Hiroshima J Med Sci (1984);33:721-725.

17 Georgiev P, Boni C, Dahm F, et al. Routine stenting reduces urologic complications as compared with stenting "on demand" in adult kidney transplantation. Urology (2007);70:893-897.

18 Hakim NS, Benedetti E, Pirenne J, et al. Complications of ureterovesical anastomosis in kidney transplant patients: the Minnesota experience. Clin Transplant (1994);8:504-507.

19 Hooghe L, Kinnaert P, Schulman CC, Toussaint C, Van Geertruyden J, Vereerstraeten P Ureterocystostomy in renal transplantation: comparison of endo- and extravesical anastomoses. World J Surg (1977);2:231-255.

20 Jindal RM, Carpinito G, Bernard D, et al. Trial of intravesical versus extravesical ureteroneocystostomy in renal transplant recipients. Clin Transplant (1994);8:396-398.
21 Leungwattanakij S, Eamtanaporn P, Kochakarn W, et al. The urological complications of renal transplantation: an 11-year-experience at Ramathibodi Hospital. J Med Assoc Thai (2000);83:28-36.
22 Li Marzi V, Filocamo MT, Dattolo E, et al. The treatment of fistulae and ureteral stenosis after kidney transplantation. Transplant Proc (2005);37:2516-2517.
23 Masahiko H, Kazunari T, Tokumoto T, Ishikawa N, Yagisawa T, Toma H Comparative study of urosurgical complications in renal transplantation: intravesical versus extravesical ureterocystoneostomy. Transplant Proc (2000);32:1844-1846.
24 Mehta SN, Kennedy JA, Loughridge WG, Douglas JF, Donaldson RA, McGeown MG Urological complications in 119 consecutive renal transplants. Br J Urol (1979);51:184-187.
25 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);27:1091-1092.
26 Rizvi A, Askari H, Hussain M, et al. Comparison of extravesical versus internal ureteroneocystostomy in renal transplants. Transplant Proc (1996);28:1553-1554.
27 Shah S, Nath V, Gopalkrishnan G, Pandey AP, Shastri JC Evaluation of extravesical and Leadbetter-Politano ureteroneocystostomy in renal transplantation. Br J Urol (1988);62:412-413.
28 Taghavi R, Zafarghandi RM, Darabi MR Renal transplantation and ureteroneocystostomy (living and cadaveric donor). Transplant Proc (2003);35:2660-2661.
29 Thrasher JB, Temple DR, Spees EK Extravesical versus Leadbetter-Politano ureteroneocystostomy: a comparison of urological complications in 320 renal transplants. J Urol (1990);144:1105-1109.
30 Tillou X, Raynal G, Demailly M, Hakami F, Saint F, Petit J Endoscopic management of urologic complications following renal transplantation: impact of ureteral anastomosis. Transplant Proc (2009);41:3317-3319.
31 Waltke EA, Adams MB, Kauffman HM, Jr., Sampson D, Hodgson NB, Lawson RK Prospective randomized comparison of urologic complications in end-to-side versus Politano-Leadbetter ureteroneocystostomy in 131 human cadaver renal transplants. J Urol (1982);128:1170-1172.
32 Whang M, Geffner S, Baimeedi S, Bonomini L, Mulgaonkar S Urologic complications in over 1000 kidney transplants performed at the Saint Barnabas healthcare system. Transplant Proc (2003);35:1375-1377.

Chapter 3

Intravesical or extravesical ureteroneocystostomy in living donor kidney transplantation recipients: A randomized controlled trial

Inez K.B. Slagt[1], Frank J.M.F. Dor[1], T.C. Khe Tran[1], Hendrikus J.A.N. Kimenai[1], Willem Weimar[2], Jan N.M. IJzermans[1], Türkan Terkivatan[1]

1 Department of Surgery, Erasmus MC, University Medical Center, Rotterdam, the Netherlands
2 Department of Nephrology, Erasmus MC, University Medical Center, Rotterdam, the Netherlands

Kidney International. 2014 Feb;85(2):471-7.

ABSTRACT

Introduction

Urological complications after kidney transplantation are mostly related to the ureteroneocystostomy leading to significant morbidity, mortality, and high costs. The most commonly used techniques for the ureteroneocystostomy are the intravesical and the extravesical anastomosis No evidence in favor of one of these two anastomoses exists. Our aim was to determine the technique with the best outcome regarding urological complications in a randomized controlled trial (registered in the Netherlands Trial Register NTR2320).

Patients and Methods

From October 2010 to December 2012, 200 consecutive recipients of a living donor kidney were randomized for either an intravesical or an extravesical anastomosis. The primary outcome was defined as placement of a percutaneous nephrostomy.

Results

No significant differences were found in the number of percutaneous nephrostomy placements or ureter re-interventions between both groups. Nevertheless, significantly fewer urinary tract infections ($p=0.04$) occurred in the group with an extravesical anastomosis. Additionally, this anastomosis was performed significantly faster ($p<0.001$) compared to the intravesical anastomosis.

Conclusion

There were no significant differences in the number of percutaneous nephrostomy placements after kidney transplantation comparing the two ureteroneocystostomy anastomoses. However, the extravesical approach was associated with significantly fewer urinary tract infections and might be preferable because of its surgical simplicity.

INTRODUCTION

Kidney transplantation is considered to be the gold standard in treatment of patients with end stage renal disease (ESRD); it reduces mortality, morbidity, brings better quality of life and is more cost-effective than hemodialysis or peritoneal dialysis.[1, 2] The surgical technique has evolved since the first kidney transplantation. Nowadays, the kidney graft is often positioned in the iliac fossa with vascular anastomoses to the external iliac vessels.[3-5] The most widely accepted technique for urinary continuity is the ureteroneocystostomy, which is associated with the lowest number of complications.[6-8] Although the overall complication rate is low, urological complications are still common after kidney transplantation, and may lead to increased morbidity, mortality, and prolonged hospital stay.[9-11] Major urological complications, such as leakage and stenosis, are reported up to 10.5% and are often related to the ureteroneocystostomy.[6, 12-17] These complications usually require an external urinary drainage by a percutaneous nephrostomy catheter. Sometimes, even a surgical ureter reconstruction (neo-ureteroneocystostomy) is required, increasing additional morbidity and costs.[11, 14, 16, 18]

The two most common techniques for ureteroneocystostomy are the intravesical approach, first described by Politano-Leadbetter[19], and the extravesical approach as described by Lich-Gregoir.[20] According to the literature, a preference for the extravesical anastomosis is reported for reasons such as the necessity for a shorter donor ureteral length, a shorter operation time (due to the simplicity of the technique) and avoidance of a separate cystotomy, which might cause an additional risk of post-operative urinary leakage, haematuria or ganglion injury.[4, 5,13, 21, 22] However, most of the literature was published in the early years of kidney transplantation with a focus on a single technique and most of them were performed retrospectively.[7, 19-21, 23] To determine which ureteroneocystostomy (intravesical or extravesical) is superior, we performed a randomized controlled clinical trial in living donor kidney transplantations.

PATIENT AND METHODS

A previous retrospective study in our center showed an incidence of 22% percutaneous nephrostomy placements in case of live donor kidney transplantation, using the intravesical ureteroneocystostomy.[11] For the purpose of power calculation we hypothesized that an extravesical ureteroneocystostomy would reduce the total number of percutaneous nephrostomy placements to 7%.[24] With an alpha of 0.05 and beta of 0.20 we calculated the need of 100 recipients in each study-arm, with a two-sided test.

Study design

After endotracheal intubation, we randomized two hundred consecutive recipients of a living donor kidney for either an intravesical (Politano-Leadbetter) or an extravesical ureteroneocystostomy (Lich-Gregoir). An independent statistician provided numbered sealed opaque envelopes, generated by a computer randomization list. To achieve a single blinded study, no participants or other care providers were informed about which anastomosis was performed. Exclusion criteria were age (<18 years), double ureter system of the donor kidney, robot assisted donor nephrectomy using the DaVinci Surgical System (because of an unknown surgical trauma to the ureter related to the technique itself), absent native bladder of the recipient, and recipients that were included into another clinical trial of our department (general agreement that patients will not be included in two clinical trials at the same department). The Medical Ethical Committee at Erasmus MC University Medical Center approved the trial protocol (MEC-2009-385), and the study was registered in the Netherlands Trial Register (NTR2320) with a follow-up of 1 year after transplantation, mainly because of one of the secondary end points, i.e. renal function at one year. In this manuscript, after post-hoc analysis, we report our 3 and 6 months data to focus on the urological complications after kidney transplantation. The study was conducted in accordance with the Declaration of Helsinki. All patients gave informed consent and were included by the 'intention to treat' principle.

Kidney transplantation

In our center, annually, over 150 kidney transplantations from living donors and more than 50 kidney transplantations from deceased donors are performed. Six certified transplant surgeons, all significantly experienced in both ureteroneocystostomy techniques, perform these procedures. After graft retrieval by either a laparoscopic donor nephrectomy or a hand assisted retroperitoneal donor nephrectomy, the kidney was transplanted extraperitoneally in the iliac fossa. Continuity of the urinary tract was established according to the randomized anastomosis. All recipients received a transurethral urinary catheter (14 French) at the time of the transplantation, which was left in situ for 7 days. During the ureterovesical anastomosis, a stent (8 French) was inserted through the anastomosis with the tip positioned in the kidney pelvis and externalized suprapubically. The stent was removed after 10 days. Postoperative care was standardized. All patients underwent an ultrasonography and a MAG-3 scan one day after kidney transplantation. Immunosuppression consisted of 20 mg basiliximab intravenously on the day of surgery and day four after transplantation. Post-operative immunosuppression consisted of prednisolone (starting with 50 mg), tacrolimus (dose was titrated based on serum value) and mycofenolate mofetil (1000 mg twice a day). Prednisolone was tapered off and discontinued at four months after transplantation. A prophylactic daily dose of 480 mg cotrimoxazole was given to prevent urinary tract

infections during 7 days. Cefazoline was given perioperative. A daily standard dose of 12.000U heparin was given intravenously during the first 5 postoperative days. Valganciclovir treatment was given to patients at risk for CMV infection or reactivation. Initial episodes of acute rejection were treated with methylprednisolone; 1000mg a day for 3 days, ATG was given on indication. Kidney function was monitored daily by measuring serum creatinine and urine production during the post-transplant period. If anastomotic disruption or obstruction of the ureter was suspected, the graft was evaluated with an additional ultrasound to exclude fluid collections or hydronephrosis.

Ureteroneocystostomy techniques

Intravesical anastomoses were created by performing a cystotomy on the anterior side to visualize the interior of the bladder and expose the trigone. A second (smaller) cystotomy was performed to create a new ureteric orifice. The ureter of the transplanted kidney was tunneled submucosally for approximately 2 centimeters. The distal end was trimmed and spatulated anteriorly at an optimal length to ensure a tension-free anastomosis. The distal ureter was sutured to the bladder mucosa with 5-6 interrupted absorbable stitches (PDS 5-0). The cystotomy was then closed with a running PDS 5-0 suture to ensure a watertight anastomosis (Figure 1).

Extravesical anastomoses were created by performing a 1-2 centimeter cystotomy on the anterolateral surface of the bladder dome to expose the mucosa of the bladder wall. A small incision was made in the mucosa. The transplant ureter was trimmed and spatulated posteriorly. The mucosa of the bladder was sutured to the ureteral end with a running absorbable suture (PDS 5-0). The detrusor muscle was closed over the anastomosis using one or two interrupted absorbable sutures (PDS 4-0) to create a submucosal tunnel with an anti-reflux mechanism (Figure 2). Time to establish the ureteroneocystostomy was measured by the bladder incision as starting point and the last suture to complete the anastomosis as endpoint.

Primary outcome

The primary outcome of our study was the incidence of percutaneous nephrostomy placement within 3 months after transplantation. A rise in serum creatinine level combined with a slight hydronephrosis or fluid collection on ultrasonography, leakage detected by the MAG-3 scan or proven by chemistry samples in case of extensive fluid production by the surgical site, drain or the wound, indicated and justified a percutaneous nephrostomy placement. Monitoring of the percutaneous nephrostomy position and imaging of the ureter was performed by an antegrade pyelography. If leakage of the ureteroneocystostomy was diagnosed with an antegrade pyelography, both a percutaneous nephrostomy and a urinary bladder catheter were placed until the

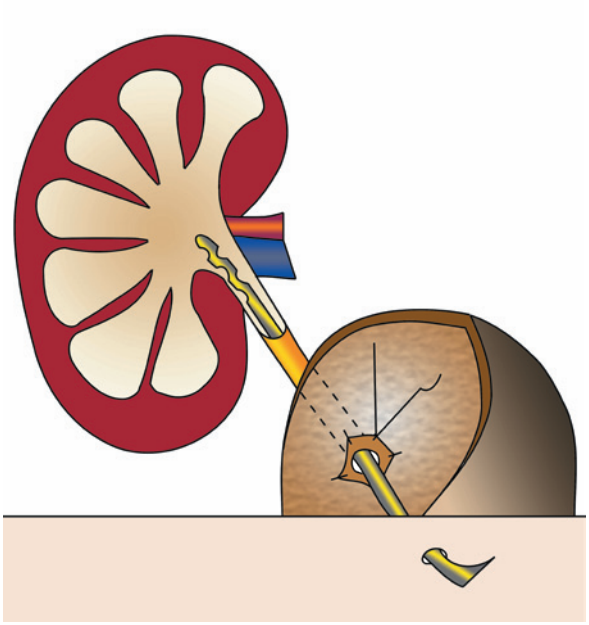

Figure 1 Intravesical anastomosis with a stent placed in the pelvis of the kidney and externalized as a suprapubic catheter.

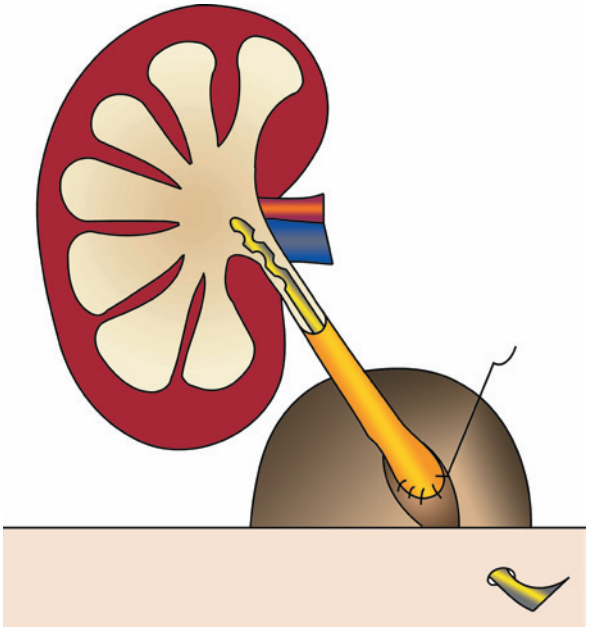

Figure 2 Extravesical anastomosis with a stent placed in the pelvis of the kidney and externalized as a suprapubic catheter.

leakage stopped. In case the leakage was diagnosed shortly after transplantation (within 24 hours), immediate surgical reconstruction was performed. If a total obstruction of the kidney graft ureter was diagnosed with an antegrade pyelography, surgical intervention was deemed inevitable. If the antegrade pyelography demonstrated a stenosed ureter but contrast reached the bladder, an endoscopic dilatation of the ureter was performed. Afterwards a percutaneous nephrocystostomy catheter is placed for 2 weeks. If the stenosis persisted on the long term, a surgical ureter reconstruction was indicated and performed by a transplant surgeon, together with an urologist. The method of ureter reconstruction depended on perioperative findings, including the degree of fibrosis, ureteral stricture length, aspect of the ureter and options for bladder mobilization.

Secondary outcome

Operation time of the kidney transplantation, graft ureteral length at time of ureteral implantation, time to establish the ureteroneocystostomy, type ureteroneocystostomy and possible procedure details (such as obesity, mechanical problems or bleedings) were listed during transplantation. All complications within 6 months after transplantation were prospectively scored: urinary tract infections (urine sample positive for bacteria), stent related complications, such as dysfunction and dislocation, tacrolimus toxicity (>15µg/l), rejection therapy (methylprednisolone), lymphoceles, urosepsis and surgical site infections. Surgical re-interventions and surgical ureteral reconstructions were registered during complete follow-up. Patients were tested for BK-viral infection in case of urological complications and 3 months after transplantation.

Statistical analysis

Statistical analysis was performed using IBM SPSS version 20.0 (IBM Corp., Armonk, NY, USA). Categorical variables were presented as number with percentage (%) and were tested using the Chi-square test. Continuous variables are presented as median with inter quartile range (IQR) and were tested with the Mann- Whitney U test. A p-value <0.05 was considered as statistically significant.

RESULTS

Baseline characteristics

Between October 2010 and December 2012, a total number of 305 patients were transplanted. A total of 55 patients did not meet our inclusion criteria. Another 50 patients were excluded based on no informed consent, impossibility of intravesical anastomoses or continued anti-coagulant use. Two hundred consecutive kidney transplantations were randomized to either an intravesical or extravesical ureteroneocystostomy

(Figure 3). Two equal groups were created without significant differences in baseline characteristics (Table 1) regarding donors and recipients.

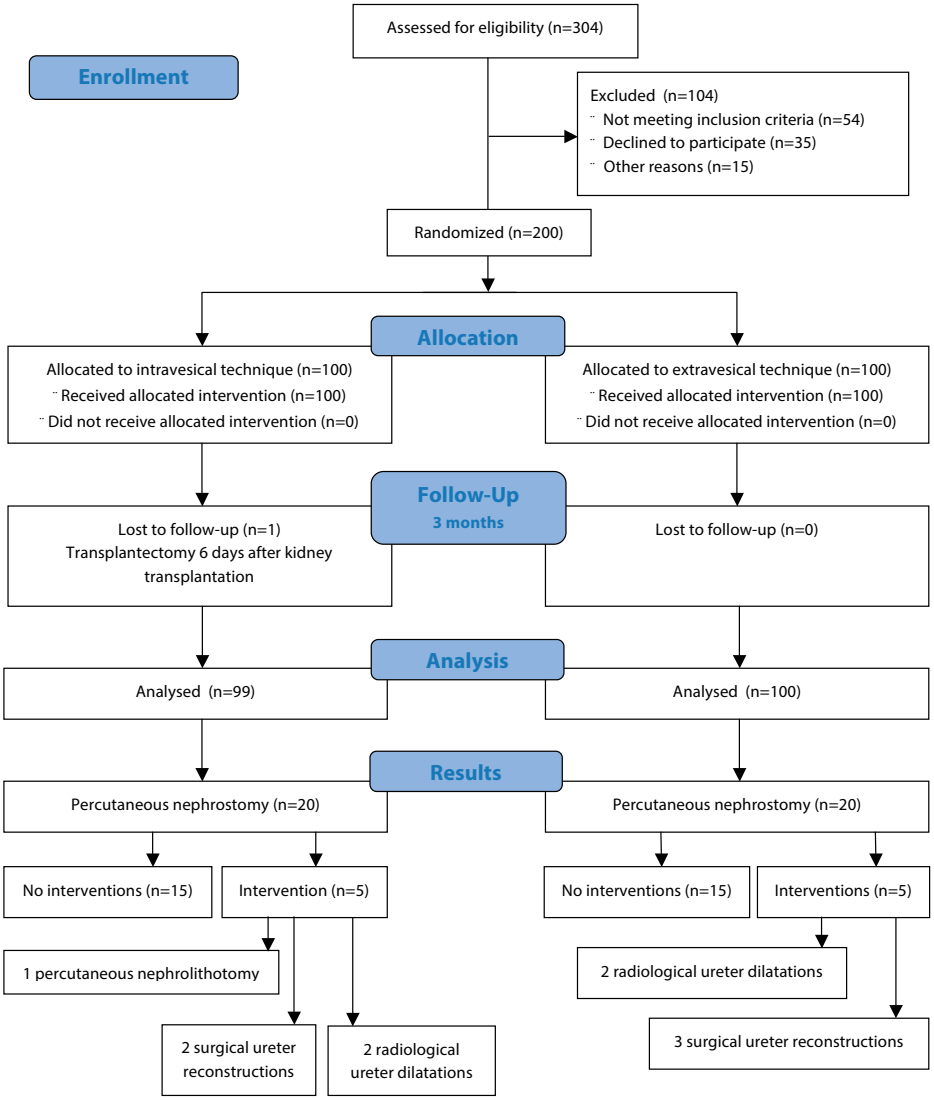

Figure 3 Flow-chart INEX study

Table 1 Baseline characteristics of the recipients and donors

	Intravesical (n=100)	Extravesical (n=100)	p-value
Recipients			
Male gender	63	68	0.46
Age (median) (IQR)	57.75 (46.35-63.90)	57.58 (47.29-64.40)	0.59
ASA (median) (IQR)	3.0 (3.0-3.0)	3.0 (3.0-3.0)	0.38
Pre-emptive transplantation	43	45	0.78
Total warm ischemia time (median in minutes) (IQR)	25 (21-29)	25 (22-29)	0.78
Cold ischemia time (median in minutes) (IQR)	143 (128-167)	145 (129-162)	0.70
Arterial reconstruction	14	19	0.34
Multiple transplantations (>1)	13	11	0.66
Donors			
Male gender	41	40	0.89
Age (median) (IQR)	53.54 (41.68-65.0)	53.42 (42.98-62.63)	0.50
ASA (median) (IQR)	1.0 (1.0-2.0)	1.0 (1.0-2.0)	0.66
Laparoscopic donor nephrectomy	66	67	0.94

IQR: inter quartile range, ASA: American Society of Anesthesiologists

Perioperative and postoperative outcome

Perioperative and postoperative measurements are presented in Table 2. The time to perform the ureteroneocystostomy was significantly shorter in the group of recipients with an extravesical anastomosis (median; 21 minutes intravesical versus 15 minutes extravesical) ($p<0.001$). There were no significant differences in ureteral length (median; 9.5 cm intravesical versus 10 cm extravesical), total operation time (median; 132 minutes intravesical versus 128 minutes extravesical), blood loss during transplantation (median; 250 ml intravesical versus 250 ml extravesical), and hospital admission time (median; 12 days intravesical versus 12 days extravesical) between the two groups.

Primary outcome

A total number of 40 (20%) percutaneous nephrostomy placements were performed after kidney transplantation, 7 because of leakage and 33 because of hydronephrosis (Table 3). The number of percutaneous nephrostomy placements was equally divided between both groups. The median time to the first percutaneous nephrostomy placement was 10 days, with a range from 2 to 182 days after transplantation. One patient did not reach the primary endpoint of six months due to transplantectomy on day 6 postoperatively, because of acute vascular rejection.

Table 2 Peroperative and postoperative outcomes

	Intravesical (n=100)	Extravesical (n=100)	p-value
Ureteroneocystostomy time (median in minutes) (IQR)	21 (18-25)	15 (12-17)	<0.001
Total time kidney transplantation (median in minutes) (IQR)	132 (117-151)	128 (109-147)	0.15
Blood loss during transplantation (median in ml) (IQR)	250 (150-500)	250 (100-395)	0.39
Ureteral length (median in cm) (IQR)	9.5 (8.63-10.73)	10.0 (8.63-11.0)	0.43
Hospital admission days (median) (IQR)	12 (10-15)	12 (10-17)	0.90
Urinary tract infections	29	17	0.04
Ureteral stent dysfunction	19	23	0.49
Urosepsis	5	2	0.25
Surgical site infection	1	3	0.31
Tacrolimus toxicity	45	42	0.67
Rejection therapy	22	14	0.14
Lymphocele	0	1	0.32
Surgical re-intervention	7	4	0.35
Median creatinine (µmol/L) 3 months after kidney transplantation (IQR)	134 (108-154)	125 (105-152)	0.41
Median creatinine (µmol/L) 6 months after kidney transplantation (IQR)	125 (111-152)	128 (102-156)	0.98
Follow-up (median in months) (IQR) (corrected for death and graft failure)	17.97 (12.31-27.33)	18.10 (12.80-27.79)	0.99
Graft failure	4	4	1.00
Death not related to kidney failure	1	5	0.10

IQR: inter quartile range, cm: centimeter, ml: milliliter

Secondary outcomes

Forty-six recipients (23%) developed a urinary tract infection (Escherichia coli or Enterococcus faecalis in the majority of cases, 76%), 29 in the group of patients with an intravesical and 17 with an extravesical ureteroneocystostomy (p=0.044). In 42 patients, stent dysfunction was suspected in the early postoperative phase: 19 patients with an intravesical and 23 patients with an extravesical ureteroneocystostomy (p=0.487). No significant differences between both groups were found with regard to urosepsis (p=0.248), surgical site infections (p=0.312), tacrolimus toxicity (p=0.669), rejection therapy (p=0.141) and lymphoceles (p=0.316) (Table 2).

Ten of the 200 recipients (5%) (5 intravesical/ 5 extravesical) required radiological ureter dilatation of the ureter or an additional surgical intervention (Table 3). In one case, a radiological ureter dilatation was performed without success, and an additional surgical reconstruction of the anastomosis was performed. Of the 10 patients requiring an additional intervention, only one patient was tested positive for BK-virus.

Surgical re-interventions during the same hospital stay of the transplantation were necessary in 12 recipients (7 intravesical/ 5 extravesical); 2 of these re-interventions were related to the ureteroneocystostomy (urine leakage from the wound). In 3 cases, a re-exploration was needed because of hemorrhage, 2 patients required a revision of their dialysis shunt because of shunt thrombosis, in 1 patient a transplantectomy was necessary because of therapy-resistant acute vascular rejection 6 days after transplantation, and 1 patient had a ruptured cyst in the transplanted kidney. In 1 patient the ureteral stent had to be removed surgically since it was impossible to extract it according to protocol after releasing the fixation suture on day 10 postoperatively. One of the recipients with a primary non-function and a need for temporary hemodialysis had to be operated because of a bleeding from the puncture site of the dialysis shunt in the superficial femoral artery. One recipient developed an incisional hernia, requiring mesh repair, three months after transplantation.

Table 3 Characteristics of the recipients with a percutaneous nephrostomy placement

	Intravesical (n=99)	**Extravesical (n=100)**	**p-value**
Percutaneous nephrostomy placement	20	20	-
Median time percutaneous nephrostomy placement (days post transplantation) (IQR)	9.5 (5.0-14.75)	13.0 (5.75-26.75)	0.53
Reason placement			
Leakage	4	3	0.70
Hydronephrosis	16	17	0.85
Treatment of 40 recipients with a percutaneous nephrostomy			
No re-intervention	15	15	-
Re-intervention	5	5	-
Type of re-intervention:			
Surgical ureter reconstruction	2	3	0.65
Radiological ureter dilatation	2	2	-
Percutaneous nephrolithotomy	1	0	0.32

IQR: Inter Quartile Range

Follow-up

Median graft follow-up was 18.1 months with a minimum of 6 days and a maximum of 33.1months. A total of 8 grafts failed after transplantation after a median time of 11.6 months, ranging from 6 to 908 days. One patient had an acute vascular rejection, three had an ongoing cellular rejection, two had recurrence of the primary disease (FSGS), one patient had a thrombotic microangiopathy eight months after transplantation, and one patient developed a graft failure at 10 months due to non-compliance.

Six patients died after a median of 7.9 months after transplantation. One patient died because of an out-of-hospital cardiac arrest. Two patients died of metastasized cancer, diagnosed 22 and 26 months after transplantation. One patient died because of cardiac complications after a surgical reconstruction of the ureteroneocystostomy that had been performed 169 days after transplantation. One patient died because of a pre-existing liver failure, and one due to an ongoing urosepsis with bleeding in the gastrointestinal tract and pulmonary embolism leading to an unsuccessful resuscitation. There were no significant differences in graft and patient survival between patients with an intravesical or extravesical ureteroneocystostomy (Table 2).

DISCUSSION

In our randomized controlled clinical trial, we found no significant difference between the number of percutaneous nephrostomy placements in the group of recipients with an intravesical anastomosis or an extravesical anastomosis. The extravesical anastomosis, however, was associated with fewer urinary tract infections, and was performed significantly faster than the intravesical anastomosis.

Previously, only two randomized controlled trials[9, 25] have been performed to compare the two most common techniques for ureteroneocystostomy in kidney transplantation; being the intravesical approach and the extravesical approach. Besides the fact that these studies included mixed cases of living and deceased donor kidney grafts, one is in favor of the intravesical anastomosis because of an unacceptable high rate of obstructions in the extravesical group and the other is in favor of the extravesical anastomosis since there were less urological complications in this group.

Furthermore, there are some other publications in the literature in favor of the extravesical anastomosis, such as a review by Kayler et al.[4] and our own systematic review with additional meta-analysis.[13] However, most of the studies that are included in these publications have several disadvantages such as retrospective design, small

cohort, and variation in surgical techniques. In addition they lack an overview of all urological complications, particularly the need for a percutaneous nephrostomy, which is often the first sign of a major urological complication.[11, 21]

Factors that may provoke urological complications, such as leakage and stenosis have not been identified in the literature. One possible factor is an insufficient blood supply to the ureter.[10, 26, 27] Since the 'golden triangle' (the site confined by ureter, kidney and renal artery) is believed to be responsible for the blood supply of the ureter, excessive dissection during organ retrieval should be avoided.[15] As failure of the blood supply might lead to necrosis of the distal ureter, a shorter ureter would be favorable during transplantation. Although it has been suggested that the length of the ureter is shorter in case of an extravesical anastomosis[28] which might reduce the risk for urological complications, our study does not support this; ureteral length was the same in both types of anastomosis (Table 2).

An important finding in our study is the higher rate of urinary tract infections after an intravesical anastomosis. One might argue that there is more surgical manipulation and dissection of the bladder when performing an intravesical ureteroneocystostomy, given the larger cystotomy, which causes bladder mucosa injury[5] with a potentially higher risk for infections. Furthermore, the knots of the interrupted sutures are situated at the internal mucosal surface of the bladder in case of the intravesical ureteroneocystostomy; this might be an explanation for the higher incidence of urinary tract infections in this group.

In our randomized controlled trial, twenty percent of all recipients of a kidney graft from a living donor had a urological complication, as defined by percutaneous nephrostomy placement. We realize that we do have a high percentage of percutaneous nephrostomy placements, especially compared to the literature. This might be explained by the postoperative protocol for kidney transplant recipients in our clinic. We notice a low threshold to place a percutaneous nephrostomy, as this is considered a minimally invasive event. Even a slight hydronephrosis on ultrasonography leads to a percutaneous nephrostomy placement, either for therapeutically benefit, or as diagnostic tool before performing a biopsy. In addition, it is a fact that collecting data prospectively results in accurate and complete databases. Inevitably, this is the reason that in randomized controlled trials complication rates might be higher than percentages that are documented in other kind of publications. Despite the number of percutaneous nephrostomy placements, only 10 recipients (5%) underwent radiological ureter dilatation or surgical ureter reconstruction, which is comparable to in the

literature.[14] Graft and patient survival were comparable between both groups, and also in consistency with the literature.

Although the total operation time was not significantly different between the two groups, the time needed to establish an extravesical ureteroneocystostomy (median; 15 minutes, IQR (12-17) was significantly shorter than for an intravesical approach (median; 21 minutes, IQR 18-25) ($p<0.001$) (Table 2), which is also supported by literature.[5] The surgical simplicity of this approach is a benefit in both performing and teaching. A shorter learning curve to perform the ureteroneocystostomy is an advantage in case of surgical transplant trainees.

Based on our results, we conclude that there is no significant difference in the number of urological complications as defined by percutaneous nephrostomy placement when comparing the two most commonly used intravesical and extravesical ureteroneocystostomy techniques. However, as the extravesical approach is associated with fewer urinary tract infections and with a time-sparing simplicity of the surgical technique, it may be advocated as first choice.

REFERENCES

1 Zomorrodi A, Buhluli A New technique for allograft ureteroneocystomy for better transvesical endoscopic handling of allograft urological complications. Saudi J Kidney Dis Transpl (2007);18:365-369.

2 Kocak T, Nane I, Ander H, Ziylan O, Oktar T, Ozsoy C Urological and surgical complications in 362 consecutive living related donor kidney transplantations. Urol Int (2004);72:252-256.

3 Barry JM, Murray JE The first human renal transplants. J Urol (2006);176:888-890.

4 Kayler L, Kang D, Molmenti E, Howard R Kidney transplant ureteroneocystostomy techniques and complications: review of the literature. Transplant Proc (2010);42:1413-1420.

5 Veale JL, Yew J, Gjertson DW, et al. Long-term comparative outcomes between 2 common ureteroneocystostomy techniques for renal transplantation. J Urol (2007);177:632-636.

6 Butterworth PC, Horsburgh T, Veitch PS, Bell PR, Nicholson ML Urological complications in renal transplantation: impact of a change of technique. Br J Urol (1997);79:499-502.

7 Woodruff MW, Bachrach P, Corica A, Marden HE, Jr. Ureteroneocystostomy in renal transplantation. Urology (1973);1:414-416.

8 Gurkan A, Yakupoglu YK, Dinckan A, et al. Comparing two ureter reimplantation techniques in kidney transplant recipients. Transpl Int (2006);19:802-806.

9 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);27:1091-1092.

10 Neri F, Tsivian M, Coccolini F, et al. Urological complications after kidney transplantation: experience of more than 1,000 transplantations. Transplant Proc (2009);41:1224-1226.

11 Dols LF, Terkivatan T, Kok NF, et al. Use of stenting in living donor kidney transplantation: does it reduce vesicoureteral complications? Transplant Proc (2011);43:1623-1626.

12 Masahiko H, Kazunari T, Tokumoto T, Ishikawa N, Yagisawa T, Toma H Comparative study of urosurgical complications in renal transplantation: intravesical versus extravesical ureterocystoneostomy. Transplant Proc (2000);32:1844-1846.

13 Slagt IK, Klop KW, IJzermans JN, Terkivatan T Intravesical versus extravesical ureteroneocystostomy in kidney transplantation: a systematic review and meta-analysis. Transplantation (2012);94:1179-1184.

14 Alberts VP, Minnee RC, Bemelman FJ, van Donselaar-van der Pant KA, Laguna Pes P, Idu MM Ureteral reconstruction after renal transplantation: clinical outcome and risk factors. Urol Int (2012);88:333-337.

15 Dinckan A, Tekin A, Turkyilmaz S, et al. Early and late urological complications corrected surgically following renal transplantation. Transpl Int (2007);20:702-707.

16 Helfand BT, Newman JP, Mongiu AK, Modi P, Meeks JJ, Gonzalez CM Reconstruction of late-onset transplant ureteral stricture disease. BJU Int (2011);107:982-987.

17 Streeter EH, Little DM, Cranston DW, Morris PJ The urological complications of renal transplantation: a series of 1535 patients. BJU Int (2002);90:627-634.

18 van Roijen JH, Kirkels WJ, Zietse R, Roodnat JI, Weimar W, IJzermans JN Long-term graft survival after urological complications of 695 kidney transplantations. J Urol (2001);165:1884-1887.

19 Politano VA, Leadbetter WF An operative technique for the correction of vesicoureteral reflux. J Urol (1958);79:932-941.

20 Gregoir W the Surgical Treatment of Congenital Vesico-Ureteral Reflux Le Traitement Chirurgical Du Reflux Vesico-Ureteral Congenital. Acta Chir Belg (1964);63:431-439.

21 Tan EC, Lim SM, Rauff A Techniques of ureteric reimplantation in kidney transplantation and its related urological complications. Ann Acad Med Singapore (1991);20:524-528.
22 Tillou X, Raynal G, Demailly M, Hakami F, Saint F, Petit J Endoscopic management of urologic complications following renal transplantation: impact of ureteral anastomosis. Transplant Proc (2009);41:3317-3319.
23 Thrasher JB, Temple DR, Spees EK Extravesical versus Leadbetter-Politano ureteroneocystostomy: a comparison of urological complications in 320 renal transplants. J Urol (1990);144:1105-1109.
24 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);38:2919-2920.
25 Waltke EA, Adams MB, Kauffman HM, Jr., Sampson D, Hodgson NB, Lawson RK Prospective randomized comparison of urologic complications in end-to-side versus Politano-Leadbetter ureteroneocystostomy in 131 human cadaver renal transplants. J Urol (1982);128:1170-1172.
26 Khauli RB, Ayvazian PJ Modified extravesical ureteroneocystostomy and routine ureteral stenting in renal transplantation: experience in 300 consecutive cases. Transplant Proc (2001);33:2665-2666.
27 Krol R, Ziaja J, Chudek J, et al. Surgical treatment of urological complications after kidney transplantation. Transplant Proc (2006);38:127-130.
28 Secin FP, Rovegno AR, Marrugat RE, Virasoro R, Lautersztein GA, Fernandez H Comparing Taguchi and Lich-Gregoir ureterovesical reimplantation techniques for kidney transplants. J Urol (2002);168:926-930.

Chapter 4

Independent risk factors for urological complications after deceased donor kidney transplantation

Inez K.B. Slagt[1], Jan N.M. IJzermans[1], Laurents J. Visser[1], Willem Weimar[2], Joke I. Roodnat[2], Türkan Terkivatan[1]

1 Department of Surgery, Erasmus MC, University Medical Center, Rotterdam, the Netherlands
2 Department of Nephrology, Erasmus MC, University Medical Center, Rotterdam, the Netherlands

PLoS One. 2014 Mar 7;9(3):e91211.

ABSTRACT

Introduction

Urological complications after kidney transplantation are mostly related to the ureteroneocystostomy, often requiring interventions with additional costs, morbidity and mortality. Our aim was to assess risk factors for urological complications in deceased donor kidney transplantation.

Patients and Methods

Between January 2000 and December 2011, 566 kidney transplantations were performed with deceased donor kidneys. Recipients were divided in a group with, and a group without urological complications, defined as the need for a percutaneous nephrostomy catheter or surgical revision of the ureteroneocystostomy. Univariate and multivariate analyses were performed.

Results

Univariate analysis showed increased number of male donors ($p=0.041$), male recipients ($p=0.002$), pre-emptively transplanted recipients ($p=0.007$), and arterial reconstructions ($p=0.004$) in the group with urological complications. Less urological complications occurred in recipients on hemodialysis ($p=0.005$). More overall surgical interventions ($p<0.001$), surgical site infections ($p=0.042$), urinary tract infections ($p<0.001$) and lymphoceles ($p<0.001$) occurred in the group with urological complications. Multivariate analysis showed that male recipients ($p=0.010$) and arterial reconstructions ($p=0.019$) were independent risk factors. No difference was found between both groups in patient or graft survival.

Conclusion

Recipient male gender and arterial reconstruction are independent risk factors for urological complications after deceased donor kidney transplantation. Nevertheless, graft and recipient survival is not different between both groups.

INTRODUCTION

Urological complications after kidney transplantation are reported to occur between 2.5% and 30% of all recipients.[1-5] Major urological complications, for example leakage and stenosis, are often related to the ureteroneocystostomy.[6-10] In most cases these complications require placement of a percutaneous nephrostomy (PCN). Sometimes, even a surgical revision is required, leading to additional morbidity and costs.[3, 8, 11]

Risk factors that contribute to the prevalence of urological complications need to be determined. So far, many factors have been described in literature, including several donor and recipient characteristics.[1, 12] Furthermore, problems encountered during graft recovery, prolonged ischemia times, type of ureteroneocystostomy, presence of accessory arteries or stent placement might be of influence on the incidence of urological complications.[1, 9, 11, 13]

Due to the increasing number of patients with end-stage kidney disease and a continuing shortage of donors, the demand for kidney grafts led to extension of donor criteria by the Dutch Transplant Foundation. Alongside the Donation after Brain Death (DBD) donors, Donation after Circulatory Death (DCD) (category III) donors have been deemed eligible for transplantation.[6, 14-16] A higher percentage of urological complications after deceased kidney donation has been reported, when compared to live donor kidney transplantation.[8, 11] We aimed to assess the incidence of urological complications after kidney transplantation with grafts from DBD and DCD donors and identify independent factors associated with the development of these complications, in a multivariate analysis.

PATIENTS AND METHODS

The Erasmus MC, University Medical Center internal review board issued a formal written waiver for the need of ethics approval and the need for written informed consent.

Between January 2000 and December 2011, all kidney transplantations performed with grafts from DBD and DCD (category III) donors at the Erasmus University Medical Center Rotterdam, were reviewed retrospectively. A total of 566 recipients were identified. The surgical reports and electronic patient system were screened for donor and recipient characteristics, and urological complications. Recipients were divided in two groups, one group with and one group without urological complications within 3 months' time after transplantation. A urological complication was defined as any event leading to

the placement of a PCN or surgical revision of the ureteroneocystostomy during follow-up. We argued that a PCN placement is the best possible parameter to identify those patients who had an adverse urological outcome. An increasing serum creatinine level combined with hydronephrosis on ultrasonography was reason for a PCN placement. Monitoring of the PCN position and imaging of the ureter is performed by an antegrade pyelography (APG). If leakage of the ureteroneocystostomy is diagnosed with an APG, both PCN and urinary bladder catheter are placed until the leakage stops. In case the leakage is diagnosed shortly after transplantation immediate surgical reconstruction is performed. If a total obstruction of the ureter is diagnosed with an APG, surgical intervention is inevitable. If the APG shows a stenosed ureter but contrast reaches the bladder radiological dilation of the ureter is performed. Afterwards a percutaneous nephrocystostomy catheter (PCNC) is placed for 2 weeks. If the stenosis persists a surgical ureter reconstruction is indicated and will be performed by a transplant surgeon, together with an urologist.

Overall complications

Tacrolimus toxicity (>15µg/l), suspected acute tubulus necrosis (ATN), treatment for rejection (methylprednisolone and/or ATG), lymphoceles, surgical site infections and urinary tract infections were scored during the first 3 months after transplantation. Besides ureteral revisions, all other re-interventions were documented: re-interventions because of re-bleeding, lymphocele drainage, transplantectomy and re-exploration because of vascular complications. Graft failure was defined as primary non-function or loss of function requiring dialysis. All recipients had a follow-up of at least one year in our center.

Surgical technique

All transplantations were performed by a transplant surgeon or vascular surgeon and transplants were engrafted extraperitoneally in the iliac fossa. In presence of multiple renal arteries (in majority of cases two arteries) a reconstruction was performed on the bench. Dependent on the length of the artery an end-to-side or an side-to-side anastomosis was created. Urinary continuity was established by either an intravesical[17] (Politano-Leadbetter) or extravesical[18] (Lich-Gregoir) ureteroneocystostomy. Intravesical anastomoses were created by performing a cystotomy on the anterior side to visualize the interior of the bladder and expose the trigone. A second (smaller) cystostomy was performed to create a new ureteric orifice. The ureter of the transplanted kidney as tunneled submucosally for approximately 2 centimeters. The distal end was trimmed, spatulated anteriorly at an optimal length to ensure a tension-free anastomosis and sutured to the bladder mucosa with 5-6 interrupted absorbable stitches. The cystotomy was then closed with a running suture. Extravesical anastomoses were created by

performing a 1-2 centimeter cystotomy on the anterolateral surface of the bladder dome to expose the mucosa of the bladder wall. A small incision was made in the mucosa. The transplant ureter was trimmed and spatulated posteriorly. The mucosa of the bladder was sutured to the ureteral end with a running absorbable suture. The detrusor muscle was closed over the anastomosis using one or two interrupted absorbable sutures to create a submucosal tunnel with an anti-reflux mechanism. Placement of a stent depended on pre-transplant urinary production, so that urinary production of the transplanted kidney can be determined. Stents were externalized suprapubicly with the tip positioned in the pelvis of the graft and removed after 10 days.

Postoperative medical care

Postoperatively, immunosuppressive therapy consisted of prednisolone (50mg a day), tacrolimus (dose was titrated based on serum value) and mycophenolate mofetil (1000mg twice a day). Basiliximab was used as induction therapy. Prednisolone was tapered and discontinued 4 months after transplantation. A prophylactic dose of 480mg cotrimoxazole per day was given to prevent urinary tract infections. Cefazoline was given perioperatively. Standard dose of 12.000U heparin daily was given during the first 5 post-operative day. Valganciclovir treatment was given to patients at risk for CMV infection or reactivation. Initial episodes of acute rejection were treated with methylprednisolone, 1000mg a day for 3 days, ATG was given on indication.

Statistical analyses

Statistical analysis was performed using IBM SPSS version 20.0 (IBM Corp., Armonk, NY, USA). Variables studied are presented in Table 1 and Table 2. Categorical variables are presented as number (percentage) and were compared using the Chi-square test. Continuous variables are presented as mean with standard deviation (SD) and were compared using an independent sample T-test. We calculated odds ratios (OR) with 95% confidence intervals (CI), using a univariate and multivariate generalized linear model to identify independent risk factors for urological complications. All variables with a p-value <0.10 in the univariate analysis were included in the multivariate analysis. A p-value of <0.05 in our multivariate model was considered statistically significant. Graft and patient survival were analyzed using a Kaplan-Meier curve for survival distribution and compared using a log-rank test.

Ethics

The manuscript is conducted in accordance to the principles expressed in the Declaration of Helsinki. Approval of our local ethics committee was not required for this study.

RESULTS

Baseline characteristics

Between January 2000 and December 2011, 566 kidney transplantations were performed with grafts from both DBD and DCD donors. An overview of the baseline characteristics is shown in Table 1. Urological complications were significantly more frequent in male donors, male recipients, pre-emptive transplantations and arterial reconstructions. Significantly less recipients on hemodialysis developed a urological complication. The number of kidney grafts from DBD and DCD donors was equally distributed in the group with and without urological complications.

Table 1 Baseline characteristics of the donors, recipients and grafts (n=566)

	Total group (n = 566)	**No urological complication (n = 448)**	**With urological complication (n = 118)**	**p-value***
Donors				
Male gender (%)	293 (51.8)	222 (49.6)	71 (60.2)	0.041
Age (mean) (SD)	50.48 (14.45)	50.35 (14.28)	51.01 (15.12)	0.661
DBD (%)	352 (62.0)	279 (62.3)	73 (61.9)	0.934
Recipients				
Male gender (%)	351 (62.0)	263 (58.7)	88 (74.6)	0.002
Age (mean) (SD)	52.96 (13.95)	52.70 (13.77)	53.98 (14.65)	0.376
Multiple transplantations (%)	137 (24.2)	108 (24.1)	29 (24.6)	0.916
Diabetes Mellitus (%)	130 (23.0)	105 (23.4)	25 (21.2)	0.651
Pre-emptive transplantation (%)	20 (3.5)	11 (2.5)	9 (7.6)	0.007
Hemodialysis (%)	383 (67.7)	316 (70.5)	67 (56.8)	0.005
BMI (SD)	25.75 (5.03) (n=516)	25.87 (5.11) (n=405)	25.33 (4.75) (n=111)	0.322
Grafts				
Warm ischemic time (mean in minutes) (SD)	38.67 (18.72)	38.76 (19.42)	38.36 (15.89)	0.837
Cold ischemic time (mean in minutes) (SD)	1083.42 (350.59)	1083.57 (349.37)	1082.84 (356.73)	0.984
Arterial reconstruction (%)	70 (12.4)	46 (10.3)	24 (20.3)	0.004
Extravesical ureteroneocystostomy (%)	124 (21.9)	98 (22.1)	26 (22.4)	0.946
Stent placement (%)	273 (48.2)	213 (47.7)	60 (51.3)	0.484

*: p-value is provided between the group without urological complications and the group with urological complications

SD: Standard Deviation; DBD: Donation after Brain Death; BMI: Body Mass Index

Urological complications

Of the total 566 recipients, 117 received a PCN. In 15 recipients a PCN was placed because of leakage and in 102 because of hydronephrosis on ultrasonography. An endoscopic dilatation of the ureter was performed in 4 recipients, in 3 patients successfully and in 1 recipient an additional surgical revision was required afterwards. A surgical ureteral revision was required in 31 recipients who previously received a PCN and in one recipient a surgical ureteral revision was required without a prior PCN placement based on leakage of the ureter shortly after transplantation. Choice of re-implantation was in 30 cases a new ureterovesicostomy, in one patient a pyelovesicostmy and in one a ureter-ureterostomy. Mean graft survival of the group with a surgical ureter reconstruction was 5.57 years (inter quartile range of 2.14-9.27). In 83 recipients, the PCN could be removed without additional intervention.

Overall complications

Comparisons of the overall complications according to absence or presence of urological complications are presented in Table 2. There were significantly more overall surgical interventions, surgical site infections, urinary tract infections and lymphoceles in the group of recipients with urological complications. Primary non-function prevailed significantly less frequently in recipients with urological complications.

Table 2 Overall complications

	Total Group (n = 566)	**No urological complication (n = 448)**	**With urological complication (n = 118)**	**p-value***
Overall surgical intervention (%)	132 (23.3)	85 (19.0)	47 (39.8)	<0.001
ATN (%)	240 (42.4)	187 (41.7)	53 (44.9)	0.535
Tacrolimus toxicity (>15µg/l) (%)	63 (11.1)	47 (10.5)	16 (13.6)	0.346
Surgical site infection (%)	50 (8.8)	34 (7.6)	16 (13.6)	0.042
Urinary tract infection (%)	130 (23.0)	84 (18.8)	46 (39.0)	<0.001
Lymphocele (%)	17 (3.0)	3 (0.7)	14 (11.9)	<0.001
Rejection treatment (%)	71 (12.5)	54 (12.0)	17 (14.4)	0.492
Primary non-function (%)	51 (9.0)	46 (10.3)	5 (4.2)	0.042

*: p-value is provided between the group without urological complications and the group with urological complications

PCN: Percutaneous Nephrostomy; ATN: Acute Tubulus Necrosis

Multivariate analysis

All odds ratios regarding urological complications using univariate and multivariate analysis were presented in Table 3. Five factors (donor gender, recipient gender, pre-emptive transplantation, hemodialysis, arterial reconstruction) implemented in our univariate analysis showed a significant influence on the presence of urological complications and were therefore analyzed in a multivariate model. Recipient gender and arterial reconstruction were identified as independent risk factors in our multivariate analysis.

Table 3 Results of the multivariate analysis regarding urological complications

	Univariate OR (95% CI)	**p-value***	**Multivariate OR (95% CI)**	**p-value***
Donors				
Male gender	1.57 (1.02-2.33)	0.041	1.46 (0.96-2.24)	0.080
Recipients				
Male gender	2.06 (1.32-3.29)	0.002	1.84 (1.15-2.93)	0.010
Pre-emptive transplantation	3.28 (1.29-8.12)	0.007	2.20 (0.82-5.81)	0.111
Hemodialysis	0.55 (0.36-0.83)	0.005	0.66 (0.42-1.04)	0.073
Grafts				
Arterial reconstruction	2.23 (1.28-3.81)	0.004	1.96 (1.10-3.40)	0.019

*: p-value is provided between the group without urological complications and the group with urological complications
OR: Odds Ratio; CI: Confidence Interval

Donor type and urological complications

In total 118 (20.8%) recipients developed a urological complication and 5.7% of all recipients (32 out of 566) underwent a surgical ureteral revision. Of all recipients who developed a urological complication, 73 had a DBD donor graft and 45 a DCD. Table 4 shows that DBD and DCD transplantations were not different regarding prevalence of urological complications. However, there were significantly more surgical site infections in the DCD group.

Follow-up

Mean graft survival time was 4.02 years with a standard deviation of 3.47. Minimum graft survival was 0 day due to primary non function and maximum was 12.1 years. Mean patient survival was 5.13 years. Death censored graft survival regarding urological complications was presented by a Kaplan-Meier curve (Figure 1). No significant difference occurred in graft survival between the group with or without urological complications (p=0.707).

Table 4 Characteristics and complications of the recipients with urological complications

	Total (n=118)	DBD (n=73)	DCD (n=45)	p-value*
Ureteral reconstruction (%)	32 (27.1)	24 (32.9)	8 (17.8)	0.130
Male gender recipient (%)	88 (74.6)	54 (74.0)	34 (75.6)	0.848
Male gender donor (%)	71 (60.2)	41 (56.2)	30 (66.7)	0.258
Arterial reconstruction (%)	24 (20.3)	16 (21.9)	8 (17.8)	0.587
Urinary tract infection (%)	46 (39.0)	28 (38.4)	18 (40.0)	0.859
Surgical site infection (%)	16 (13.6)	6 (8.2)	10 (22.2)	0.031
Lymphocele (%)	14 (11.9)	9 (12.3)	5 (11.1)	0.843

*: p-value is provided between the DBD and DCD group
DBD: Donation after Brain Death; DCD: Donation after Circulatory Death;
PCN: Percutaneous Nephrostomy

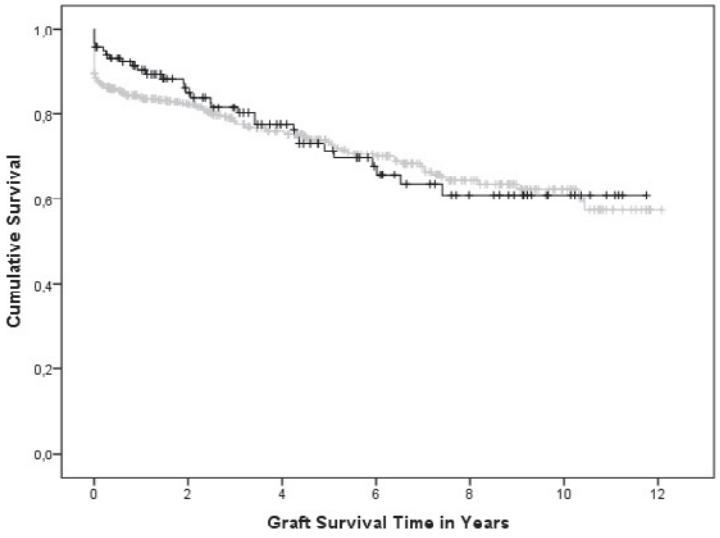

Figure 1 Kaplan-Meier survival, the black line corresponds to the group with urological complications and the grey line corresponds to the group without urological complications. This curve is censored for death. No significant difference occurred between both groups (p=0.707).

DISCUSSION

In our study, 20.8% of all recipients of a kidney graft from a deceased donor had a urological complication as defined by PCN placement or surgical ureteral revision. As PCN placement is considered as a minimally invasive event in our center, the threshold to use a PCN is low, either for therapy, or for diagnosis. Eventually, only 32 recipients (5.7%) underwent a surgical ureteral revision for leakage or stenosis and graft survival was not worse in the population with urological complications.

It has been suggested that urological complications are caused by an insufficient blood supply to the ureter. Excessive dissection of the site known as 'golden triangle' (the site confined by ureter, kidney and renal artery) should therefore be avoided during graft recovery. Damage of this triangle might lead to necrosis of the distal ureter in 70% of the cases.[4, 10, 11]

Potential risk factors for urological complications including age, prolonged cold ischemia and recipient Diabetes Mellitus were reported not to play an important role in the occurrence of urological complications.[1, 11] These findings are supported by our data (Table 1). In our study more urological complications occurred in male donors, male recipients and pre-emptive transplantations. The reason why male recipients may develop more urological complications is not exactly clear. An anatomical cause due to the presence of the funiculus that crosses the ureter might be an explanation, considering the ligamentum rotundum is ligated in females during the implantation. Furthermore, arterial reconstruction of the donor graft was highly associated with the prevalence of urological complications (Table 1), which is confirmed in the literature.[19-21] Relative ischemia of the ureter by an insufficient arterial blood supply is suggested to be the cause for leakage and stenosis. Malperfusion of accessory arteries may result from a small anastomosis with flow-limitation, greater turbulence or more vulnerability for traction injury.

There is growing evidence on the superiority of the extravesical ureteroneocystostomy when compared with the intravesical technique, with or without additional routine stent placement.[2, 9, 13, 22-24] In our population, the type of ureteroneocystostomy was depended on surgeons' preference and stent placement on residual urinary production. Both, type of ureteroneocystostomy and the presence of a stent could not be defined as a risk factor in our analysis (Table 1). However, there were significantly more surgical site infections, urinary tract infections, lymphoceles and surgical re-explorations because of hemorrhage, transplantectomies or vascular complications (Table 2), in the group with urological complications.

Although the mean graft survival of DCD donors is suspected to be shorter than that of DBD donors, there are no studies on the occurrence of urological complications in those groups. Therefore, the finding that grafts from a DBD donor were not superior to DCD donor grafts with respect to urological complications (Table 4) is an important finding. In addition, our Kaplan Meier survival analysis (Figure 1) demonstrates no difference in long term graft survival between the populations with and without urological complications which is supported by other studies.[2, 8, 11] It should however be kept in mind that the population with urological complications is a selection with a functioning graft.

Another important finding in our study was the fact that primary non-function of the graft or graft loss within 3 months was significantly lower in the group without urological complications (Table 2). This probably is a bias since urological complications like leakage and hydronephrosis by a stenosis at the ureteroneocystostomy junction site cannot be detected in a non-functioning graft. Furthermore, recipients transplanted pre-emptively, had a significantly higher risk to develop urological complications. There is no clear explanation for this finding. However, this subgroup consists of only 20 recipients, which might have biased the statistical outcome. One other limitation of our study is the fact that some potential risk factors, such as donor BMI, ureteral vascularization or length of the ureter could not be documented prospectively. Despite the retrospective character of our study and its disadvantages, we describe the most detailed group regarding urological complications of kidney graft recipients from a deceased donor so far as known from the literature.

Based on our study of kidney transplantations from a deceased donor, we conclude that recipient's gender and arterial reconstruction are independent risk factors to develop a urological complication. However, donor type (DBD and DCD), primary non-function, type of anastomosis, and the presence of multiple transplantations could not be defined as risk factor in our univariate and multivariate analyses. This means that donor type and surgical anastomosis technique are less important factors for the urological outcome, which is in contrast to what one might argue.

REFERENCES

1 Streeter EH, Little DM, Cranston DW, Morris PJ The urological complications of renal transplantation: a series of 1535 patients. BJU Int (2002);90:627-634.

2 Alberts VP, Minnee RC, Bemelman FJ, van Donselaar-van der Pant KA, Laguna Pes P, Idu MM Ureteral reconstruction after renal transplantation: clinical outcome and risk factors. Urol Int (2012);88:333-337.

3 Dols LF, Terkivatan T, Kok NF, et al. Use of stenting in living donor kidney transplantation: does it reduce vesicoureteral complications? Transplant Proc (2011);43:1623-1626.

4 Neri F, Tsivian M, Coccolini F, et al. Urological complications after kidney transplantation: experience of more than 1,000 transplantations. Transplant Proc (2009);41:1224-1226.

5 Zavos G, Pappas P, Karatzas T, et al. Urological complications: analysis and management of 1525 consecutive renal transplantations. Transplant Proc (2008);40:1386-1390.

6 Khairoun M, Baranski AG, van der Boog PJ, Haasnoot A, Mallat MJ, Marang-van de Mheen PJ Urological complications and their impact on survival after kidney transplantation from deceased cardiac death donors. Transpl Int (2009);22:192-197.

7 Praz V, Leisinger HJ, Pascual M, Jichlinski P Urological complications in renal transplantation from cadaveric donor grafts: a retrospective analysis of 20 years. Urol Int (2005);75:144-149.

8 van Roijen JH, Kirkels WJ, Zietse R, Roodnat JI, Weimar W, IJzermans JN Long-term graft survival after urological complications of 695 kidney transplantations. J Urol (2001);165:1884-1887.

9 Butterworth PC, Horsburgh T, Veitch PS, Bell PR, Nicholson ML Urological complications in renal transplantation: impact of a change of technique. Br J Urol (1997);79:499-502.

10 Krol R, Ziaja J, Chudek J, et al. Surgical treatment of urological complications after kidney transplantation. Transplant Proc (2006);38:127-130.

11 Dinckan A, Tekin A, Turkyilmaz S, et al. Early and late urological complications corrected surgically following renal transplantation. Transpl Int (2007);20:702-707.

12 Laging M, Kal-van Gestel JA, van de Wetering J, Ijzermans JN, Weimar W, Roodnat JI The relative importance of donor age in deceased and living donor kidney transplantation. Transpl Int (2012).

13 Slagt IK, Klop KW, Ijzermans JN, Terkivatan T Intravesical versus extravesical ureteroneocystostomy in kidney transplantation: a systematic review and meta-analysis. Transplantation (2012);94:1179-1184.

14 Keizer KM, de Fijter JW, Haase-Kromwijk BJ, Weimar W Non-heart-beating donor kidneys in the Netherlands: allocation and outcome of transplantation. Transplantation (2005);79:1195-1199.

15 Kootstra G, Daemen JH, Oomen AP Categories of non-heart-beating donors. Transplant Proc (1995);27:2893-2894.

16 Koffman G, Gambaro G Renal transplantation from non-heart- beating donors: a review of the European experience. J Nephrol (2003);16:334-341.

17 Politano VA, Leadbetter WF An operative technique for the correction of vesicoureteral reflux. J Urol (1958);79:932-941.

18 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.

19 Carter JT, Freise CE, McTaggart RA, et al. Laparoscopic procurement of kidneys with multiple renal arteries is associated with increased ureteral complications in the recipient. Am J Transplant (2005);5:1312-1318.

20 Dunkin BJ, Johnson LB, Kuo PC A technical modification eliminates early ureteral complications after laparoscopic donor nephrectomy. J Am Coll Surg (2000);190:96-97.

21 Kuo PC, Cho ES, Flowers JL, Jacobs S, Bartlett ST, Johnson LB Laparoscopic living donor nephrectomy and multiple renal arteries. Am J Surg (1998);176:559-563.
22 Mangus RS, Haag BW Stented versus nonstented extravesical ureteroneocystostomy in renal transplantation: a metaanalysis. Am J Transplant (2004);4:1889-1896.
23 Wilson CH, Bhatti AA, Rix DA, Manas DM Routine intraoperative stenting for renal transplant recipients. Transplantation (2005);80:877-882.
24 Kayler L, Kang D, Molmenti E, Howard R Kidney transplant ureteroneocystostomy techniques and complications: review of the literature. Transplant Proc (2010);42:1413-1420.

Chapter 5
Urological complications after kidney transplantation clinical outcome and cost analysis

Inez K.B. Slagt[1], Jan N.M. IJzermans[1], Paul C.M.S. Verhagen[2], Joke I. Roodnat[3], T.C. Khe Tran[1], Willem Weimar[3], Frank J.M.F. Dor[1], Türkan Terkivatan[1]

1 Department of Surgery, Erasmus MC, University Medical Center, Rotterdam, The Netherlands
2 Department of Urology, Erasmus MC, University Medical Center, Rotterdam, The Netherlands
3 Department of Nephrology, Erasmus MC, University Medical Center, Rotterdam, The Netherlands

Submitted

ABSTRACT

Introduction

Major urological complications after kidney transplantation include leakage and stenosis of the ureter. Treatment by PCN placement, radiological dilatation or surgical reconstruction is associated with morbidity, risks and costs. We present clinical outcome and a cost analysis of patients with urological complications after kidney transplantation.

Patients and Methods

In a retrospective single center study, kidney transplantations that were performed between January 2007 and January 2012 from both deceased donors and living donors were analyzed. The hospital electronic patient system and surgical charts were reviewed for urological complications. Based on real prices, direct medical costs of urological complications were determined until one year after kidney transplantation.

Results

Out of 809 patients that underwent kidney transplantation, 188 recipients (23.4%) required PCN placement, 146 due to hydronephrosis and 42 due to leakage. In 47 recipients (5.8%) additional radiological and/ or surgical intervention was required. There was no graft loss caused by the radiological or surgical ureter re-intervention and graft survival between patients with or without urological complications was comparable. The total direct medical costs made for urological complications after kidney transplantation were on average € 2.322 per patient.

Conclusion

Urological complications after kidney transplantation may lead to an increase of costs up to € 2.322; however, these costs can be legitimized as the occurrence of urological complications does not influence graft survival.

INTRODUCTION

Kidney transplantation is the gold standard for patients with end stage kidney disease. Compared to dialysis, transplantation is advantageous for patient life expectancy, quality of life and it decreases medical costs.[1-3] While the total number of deceased donor kidney transplants remains stable, the incidence of live donor kidney transplantation increases considerably worldwide with superior graft survival.[4] However, during the initial years of live donor kidney transplantation, a higher rate of urological complications was found compared to deceased donor kidney transplantations. Nowadays, no difference in urological complications is reported between those two groups.[5-8]

Urological complications account for a significant cause of morbidity after kidney transplantation. The incidence is between 0.5% and 30%, depending on patient selection, definition of urological complications and follow-up.[6, 9-11] Deterioration of renal function is often the first sign of a major urological complication, for example, ureteral leakage or obstruction, and requires placement of a percutaneous nephrostomy (PCN).[12] In case of leakage or obstruction, radiological or surgical ureter reconstruction is required in up to 10% of these patients.[6, 13-16] The most important factors that might influence the urological outcome are the type of donor nephrectomy, type of organ preservation, vascular reconstruction of the renal artery[17-19] and ureteral implantation technique.[7, 10, 20, 21] Urological complications cause significant morbidity in recipients of a kidney transplant. Besides the inconvenience related to radiological and surgical re-interventions for urological complications are associated with increased medical costs. Our aim was to illustrate the clinical outcome of patients with urological complications and to perform a cost analysis of urological complications after kidney transplantation.

PATIENTS AND METHODS

Data from our electronic patient system were analyzed to identify all patients with a kidney transplant performed between January 2007 and January 2012. Using a prospective database, donor and recipient characteristics, as well as data on radiological and surgical re-interventions related to urological complications, were collected. Patients were divided into two groups, discriminating those without urological complications from those with urological complications. A urological complication was defined as the need for a PCN placement or surgical ureter revision following transplantation within 3 months after transplantation. We argued that a PCN is the best parameter to identify patients with an adverse urological outcome. In a sub-analysis we studied the incidence of urological complications in deceased and living donor kidney transplantation.

Kidney transplantation

Well-trained transplant surgeons performed all kidney transplantations. After extraperitoneal graft placement in the iliac fossa, continuity of the urinary tract was established by an ureteroneocystostomy (either a Politano-Leadbetter[22] or a Lich-Gregoir[23]). In those cases where the surgeon preferred stenting of the ureteral anastomosis, an 8 French stent was introduced into the donor ureter via the bladder and the stent was externalized suprapubically. Post-operative immunosuppression consisted of prednisolone (starting with 50mg a day), tacrolimus (dose was titrated based on serum value) and mycofenolate mofetil (2 times a day 1000mg). Baxiliximab was used as induction therapy. Prednisolone was tapered and discontinued within 4 months after transplantation. Until 4 months after transplantation, a prophylactic dose of cotrimoxazole (480mg a day) was given to prevent PCP infections and urinary tract infections. Valganciclovir treatment was given to patients at risk for CMV infection or reactivation. Episodes of acute rejection were treated with methylprednisolone, 1000mg a day for 3 days, ATG was given on indication.

Assessment of urological complications

During the early post-transplant period, daily monitoring of serum creatinine and urinary production was performed. When urine leakage occurred within 2 days after transplantation, immediate surgical ureter reconstruction was performed. Anastomotic ureter disruption was suspected when the patient complained of pain in the fossa, urinary production decreased, serum creatinine increased or in case of urine leakage via the wound. Obstruction of the ureter was suspected when serum creatinine increased. A routine ultrasonography of the graft was performed on day 1, and was repeated in the post transplantation period when obstruction or fluid collections were expected (Figure 1). In case of hydronephrosis, a PCN was inserted and an antegrade pyelography was performed. In case of leakage both a PCN and a urinary catheter were inserted. In case of hydronephrosis, the effect of the PCN was monitored by serum creatinine, when the serum creatinine did not show a decrease or even demonstrated an increase, hydronephrosis unlikely to be the cause for the deteriorated of kidney function. In that case, the PCN was removed and a kidney biopsy was performed. When the antegrade pyelography showed a complete stenosis of the anastomosis between the ureter and bladder, a surgical reconstruction was planned. When the antegrade pyelography showed a subtotal ureter stenosis with contrast passage into the bladder, the PCN was temporarily closed to await the effect on serum creatinine. When serum creatinine did not rise, the PCN was removed. When serum creatinine increased after closing the PCN it was reopened and further therapy was initiated. For a ureter stenosis with a maximum length of 1 centimeter, a radiological dilation of the ureter was performed. After dilatation, the PCN was placed through the ureter into the bladder. After two weeks, an antegrade pyelography was

repeated and when the relative stenosis persisted and serum creatinine increased after closing the PCN the radiological dilatation was repeated. When repetitive radiological dilatations remained unsuccessful, a surgical reconstruction of the anastomosis was performed. The technique of ureter reconstruction depended on findings during the operation, including degree of fibrosis, length of the ureteral stricture, aspect of the ureter and mobility of the bladder. All interventions were discussed in a multidisciplinary team meeting with the transplant surgeons, nephrologists, radiologists and urologists.

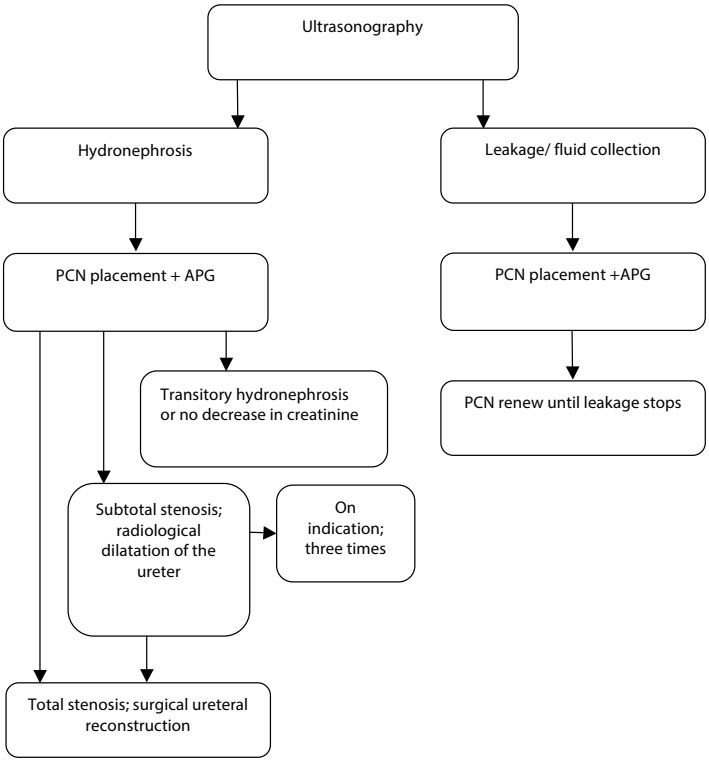

Figure 1 Flow-chart of assessing the urological complications.

Cost analysis

The direct medical costs due to urological complications after kidney transplantation were calculated combining data from the patient registry with in hospital costs. First, the total number of ultrasonographies, PCN placements, PCN replacements (or substitutions), antegrade pyelographies, radiological dilatation and surgical reconstructions of the ureter were collected and noted for each recipient. Hospital readmission because of urological complications (urinary tract infection, sepsis, PCN obstruction or dislocation) and hospital stay for radiological and surgical re-interventions were noted. Secondly, an independent financial advisor of the Erasmus MC, University Medical Center, provided the prices for all direct medical costs determined on real prices. Furthermore, costs were estimated by multiplying resource utilization with the cost per unit of resource (i.e., full costing in accordance with Dutch guidelines[24] for economic evaluations in health care). Finally, we determined the mean total direct medical costs per patient for urological complications after kidney transplantation. Costs were calculated in Euros (€). The base year for all costs was 2012; costs made in other years were converted to 2012 euros using the general price index. Costs of organ procurement were excluded because of the difference between deceased and living donation (incorporated by an independent organ procurement organization (Euro-transplant) or by the hospital). Costs of the kidney transplantation (including admission and non-urological complications, e.g. rejection) were not taken into account, since these should be equally distributed within these two groups. Costs made for rejection (radiological procedures, biopsies, medication and hospital admission) or costs related to primary non-function (dialysis, medication, admission, and transplant nephrectomy) were also not included. Overhead and housing were also excluded.

Statistical analysis

Statistical analysis was performed using IBM SPSS version 20.0 (IBM Corp., Armonk, NY, USA). Categorical variables are presented as number (percentage) and were compared using the Chi-square test. Continuous variables are presented as mean with standard deviation (SD) and were compared using an independent sample T-test. A p-value <0.05 was considered statistically significant.

RESULTS

Baseline characteristics of the 809 kidney transplant recipients (252 deceased donors and 557 living donors), transplanted between January 2007 and January 2012 are presented in table 1. In total 190 patients (23.4%) had a urological complication as defined by PCN insertion or surgical reconstruction of the ureter. The mean age of donors in the

group with urological complications was significantly higher (p<0.001) compared to the group without urological complications. In addition there were significantly more male recipients (p<0.001) and recipients of a living donor kidney transplantation (p=0.029) in the group with urological complications. There were no significant differences in type of anastomosis (intravesical or extravesical) or in the prevalence of stent placement between the groups with and without PCN. At 1 year serum creatinine level was significantly higher but there was no difference in graft survival between the groups with and without urological complications (Table 1). Follow-up was performed until April 2013, with a mean of 36 months after transplantation (SD 20 months). Hospital stay of patients after living donor kidney transplantation was significantly shorter (p=0.022); also, graft survival after a living donor transplantation was significantly longer (p=0.004) compared to patients with a deceased donor graftIn the group with urological complications (190 ripients), 47 patien received an organ from a deceased donor and 143 from a living donor. No significant differences in the number of PCN placements, radiological ureter dilatations or surgical ureter reconstructions between recipients with a deceased or living donor kidney transplantation were found (Table 2). Out of 809 kidney transplantations, 188 recipients (23.2%) required a PCN, 42 due to fluid collections or leakage, and 146 due to hydronephrosis on ultrasonography. In 18 of the 190 recipients (9,5%), a radiological percutaneous dilatation of the ureter was performed, in 3 patients due to stenosis after primary leakage and in 15 patients due to primary subtotal stenosis. Eight recipients of these 18, required an additional surgical ureter reconstruction after radiological ureter dilatation; all had hydronephrosis as primary diagnosis**.** This means that 10 patients had been treated successfully with a

Table 1 Baseline characteristics (donor and recipient) of 809 kidney transplants in recipients with and without urological complications. A urological complication is defined as the need for a percutaneous nephrostomy or surgical ureter reconstruction within the first 3 months after kidney transplantation.

	Without urological complications n=619	**With urological complications n=190**	**p-value**
Donor male sex(%)	289 (46.7)	82 (43.2)	0.393
Mean donor age (SD)	51.2 (12.96)	55.6 (13.04)	<0.001
Living donor(%)	414 (66.9)	143 (75.3)	0.029
Recipient male sex(%)	390 (63.0)	146 (76.8)	<0.001
Mean age KTx (SD)	51.6 (14.49)	51.3 (14.91)	0.797
Extravesical anastomosis (%)	207 (33.4)	61 (32.1)	0.732
Stent placement (%)	515 (83.2)	164 (86.3)	0.306
Functioning graft in months (SD)	35.3 (20.30)	38.33 (18.90)	0.062
Mean creatinine 1 year KTx (µmol/L) (SD)	131.5 (50.20)	159.4 (60.34)	<0.001

SD: standard deviation, KTx: kidney transplantation

radiological dilatation (1,2%). A total of 37 patients (4,6%) required a surgical ureteral reconstruction; 30 due to hydronephrosis and 5 after primary leakage followed by stenosis. In two patients (0,25%), a surgical reconstruction of the ureter anastomosis was performed within 2 days after transplantation due to leakage (Figure 2). In total, 5.8% of the recipients underwent radiological or surgical treatment because of urological complications.

Table 2 Characteristics of the 190 recipients with a urological complication. Sub-analyses were based on deceased or living donor kidney transplantation.

	Deceased donor n=47	Living donor n=143	p-value
Percutaneous nephrostomy(%)	46 (97.9)	142 (99.3)	0.405
- Leakage(%)	7 (14.9)	37 (25.9)	0.122
- Hydronephrosis(%)	40 (85.1)	106 (74.1)	0.122
Radiological ureter dilatation(%)	4 (8.5)	14 (9.8)	0.795
Surgical ureter reconstruction(%)	11 (23.4)	26 (18.2)	0.433
Functioning graft in months (SD)	36.9 (20.88)	38.8 (18.26)	0.557

SD: standard deviation

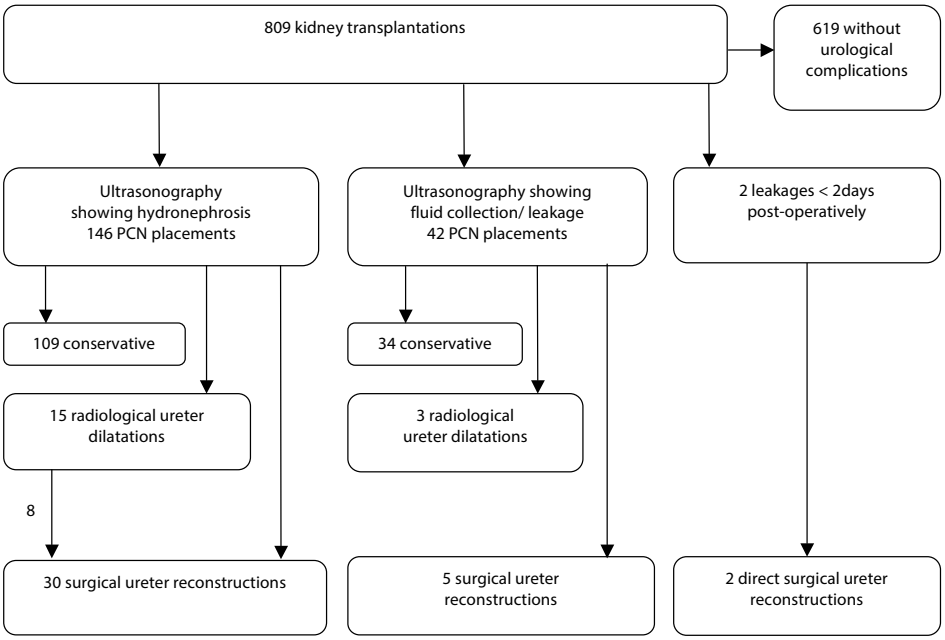

Figure 2 Flow-chart of all kidney transplantations performed, showing prevalence and treatment of urological complications.

Characteristics of the 47 recipients who requed a radiological or rgical ureter intervention are presented in table 3. In this subgroup, no significant differences were found in technique of ureteroneocystostomy (p=0.281) or prevalence of stent placement (p=0.796) between the deceased and living donor kidney transplantation groups. In patients that underwent a surgical reconstruction of the ureteroneocystostomy, urinary continuity was established in 30 patients (81.1%) by re-implantation of the transplant ureter onto the bladder. In 2 patients (5.4%), the transplant pelvis was connected directly to the bladder. In the remaining 5 patients (13.5%), other reconstruction techniques were used; in 3 patients the native ureter was used, one patient had a reconstruction with the use of the Boari technique and in one patient a reconstruction was not possible because of complete fibrosis of the ureter and the pelvic system. This patient remained PCN dependent.

Table 3 Characteristics of the 47 recipients with radiological ureter dilatation or surgical ureter reconstruction.

	Deceased n=14	**Living n=33**	**p-value**
Extravesical anastomosis of KTx(%)	4 (28.6)	15 (45.5)	0.281
Stent placement during KTx(%)	11 (78.6)	27 (81.8)	0.796
Radiological ureter dilatation(%)	4 (28.6)	14 (42.4)	0.372
Surgical ureter reconstruction type(%)	11 (78.6)	26 (78.8)	0.987
-Ureteroneocystostomy(%)	7 (50.0)	23 (69.7)	0.199
-Pyelocystostomy(%)	0 (0.0)	2 (6.1)	0.347
-Other*(%)	4 (28.6)	1 (3)	0.009
Functioning graft in months (SD)	39.6 (23.08)	37.9 (17.16)	0.785

KTx: kidney transplantation, SD: Standard Deviation; %: percentages; *3 with native ureter, 1 Boari technique, 1 reconstruction was not possible

The total direct medical costs related to urological complications after kidney transplantation were €2.322 on average per patient (Table 4). In more detail, in 694 patients (85.8%) one or more additional ultrasonography(ies) were performed to evaluate transplant function or to verify PCN position. A total of 1948 ultrasonographies were performed accounting for €158.353. In 188 patients (23.2%), 275 PCN insertions were performed accounting for €91.418. In 102 patients (12.6%), 295 PCNs were replaced accounting for €59.891. A total of 331 antegrade pyelographies were performed in 167 patients (20.6%) accounting for €48.965. Radiological ureter dilatation was performed 22 times in 18 patients (2.2%); costs were €15.313. Surgical ureteral reconstruction was performed 41 times in 37 patients (4.6%). Total costs for the surgical reconstruction were €82.030. One hundred forty seven patients (18.2%) were hospitalized with urological

complications (urinary tract infection, urosepsis, PCN obstruction of dislocation). They were in the hospital for 2382 days with a total cost of €1.131.045. Total hospital stay for patients that underwent a surgical ureteral reconstruction was 614 days for 31 patients (3.8%). The other 6 patients had a ureter reconstruction during the initial admission for the transplant. Costs on hospital admission related to the ureter reconstruction were € 291.546. Total costs incurred for the interventions were € 455.970 and for the admission days € 1.422.591. This equates € 2.322 per patient.

Table 4 An overview of direct medical costs of interventions related to urological complications after kidney transplantation.

	Recipients n=809	Sumof all interventions	Intervention costs	Total costs
Ultrasonography	694 (85.8%)	1948	€ 81	€ 158.353
PCN placement	188 (23.2%)	275	€ 332	€ 91.418
PCN replacement	102 (12.6%)	295	€ 203	€ 59.891
APG	167 (20.6%)	331	€ 148	€ 48.965
Radiological ureteral dilatation	18 (2.2%)	22	€ 696	€ 15.313
Surgical ureteral reconstruction	37 (4.6%)	41	€ 2001	€ 82.030
Hospitality days of re-admission	147 (18.2%)	2382	€ 475	€ 1.131.045
Hospitality days for ureteral reconstruction	31 (3.8%)	614	€ 475	€ 291.546
Total costs				€ 1.878.561
Average costs per patient				€ 2.322

PCN: Percutaneous Nephrostomy; APG: antegrade pyelography

DISCUSSION

In this retrospective single-center study, we present the incidence of urological complications in a cohort of 809 kidney transplantations performed between January 2007 and January 2012. Significantly more urological complications occurred in patients with an older donor ($p<0.001$), a living donor ($p=0.029$) and in male recipients ($p<0.001$). Importantly, no grafts were lost due to the need of supplementary radiological or surgical interventions. A number of issues related to these findings should be discussed. The surgical approach of kidney procurement in living donor nephrectomy is totally different from decreased donor nephrectomy. An excessive dissection of peri-ureteral tissue or tension on the ureter during living donor nephrectomy could be an explanation for the higher number of urological complications in these recipients.[10, 11, 25] Trauma during donor nephrectomy might be the reason for ureter edema causing functional hydronephrosis that resolves spontaneously without treatment. This might explain the difference between 23.2% of patients requiring a PCN and 5.8% that actually

required radiological or surgical intervention. The relatively high numbers of urological complications in male recipients could have an anatomical cause. The crossing funiculus might be an explanation for ureter obstruction in males, considering that the ligamentum rotundum is ligated during transplantation in females. Another explanation for the increased obstruction in males, is that they have a thicker bladder wall compared to women.[26]

Of the 809 kidney transplantations performed, 188 recipients (23.2%) required PCN placement, which is higher than reported in the literature.[9] When graft function deteriorates, the threshold to use a PCN for the indication of dilated pyelum or ureter is low in our center. Alberts et al. report an incidence of 12.3% of PCN placement and a surgical reconstruction in 5.2%.[9] In our population, 37 recipients (4.6%) (including 2 recipients within two days) required a surgical ureter reconstruction after kidney transplantation, which is comparable to the literature.[9, 10, 20] Although 1 year graft survival shows no difference between the group with PCN and the group without PCN, at 1 year, serum creatinine levels are significantly higher in the group with urological complications (Table 4). Although increased numbers of urological complications occurred in the living donor group, a sub-analysis of the group with a urological complication showed no differences in incidence of PCN placement when comparing transplantations from a deceased and living donors. As published before, no differences between DBD and DCD donors were found.[27]

This study was performed in a high volume kidney transplant center. Although it is not common in the literature to appoint the number of PCN placements, this intervention is related to urological complications. The percentage of PCN placements is rather high in our center, but even a slight hydronephrosis leads to a PCN, even as a diagnostic tool. In the event that the PCN insertion did not lead to improvement of graft function, mechanical factors were unlikely to be the cause. The PCN was then removed, and a kidney biopsy was performed.

Our study has some limitations. Firstly, a retrospective design was used, which might have caused some bias in data collection. Secondly, we were only able to capture direct medical costs during our cost analysis. Indirect costs (such as housing and overhead) and direct non-medical costs (as absence from work) were not included in our study. The consequence of the retrospective study design resulted in an estimated amount of cost, which is likely an underestimation. Total direct medical costs made for urological complications after kidney transplantation were € 2.322 per patient on average. Although, this is an underestimation of the total costs related to all complications after kidney transplantation (rejection and non-functioning of the graft were not included),

this study provides specific insights in costs related to ureteral complications after kidney transplantation.

Kidney transplantation has an economic benefit with a significant cost reduction as compared to dialysis.[3, 28, 29] Urological complications after kidney transplantation are a major concern and associated with morbidity, decreased quality of life and additional costs. Despite the relatively large number of PCN placements after kidney transplantation in these series, only a small number of patients required a revision of the ureter anastomosis. Overall urological complications do not influence one year graft survival.

REFERENCES

1 Evans RW, Manninen DL, Garrison LP, Jr., et al. The quality of life of patients with end-stage renal disease. N Engl J Med (1985);312:553-559.

2 Port FK, Wolfe RA, Mauger EA, Berling DP, Jiang K Comparison of survival probabilities for dialysis patients vs cadaveric renal transplant recipients. JAMA (1993);270:1339-1343.

3 Russell JD, Beecroft ML, Ludwin D, Churchill DN The quality of life in renal transplantation--a prospective study. Transplantation (1992);54:656-660.

4 Hariharan S, Johnson CP, Bresnahan BA, Taranto SE, McIntosh MJ, Stablein D Improved graft survival after renal transplantation in the United States, 1988 to 1996. N Engl J Med (2000);342:605-612.

5 Cimic J, Meuleman EJ, Oosterhof GO, Hoitsma AJ Urological complications in renal transplantation. A comparison between living-related and cadaveric grafts. Eur Urol (1997);31:433-435.

6 Helfand BT, Newman JP, Mongiu AK, Modi P, Meeks JJ, Gonzalez CM Reconstruction of late-onset transplant ureteral stricture disease. BJU Int (2011);107:982-987.

7 Dreikorn K Surgical aspects of donor nephrectomy in living related and cadaver donors. World J Urol (1988);6:70- 74.

8 Benoit G, Blanchet P, Moukarzel M, et al. Surgical complications in kidney transplantation. Transplant Proc (1994);26:287-288.

9 Alberts VP, Minnee RC, Bemelman FJ, van Donselaar-van der Pant KA, Laguna Pes P, Idu MM Ureteral reconstruction after renal transplantation: clinical outcome and risk factors. Urol Int (2012);88:333-337.

10 Dinckan A, Tekin A, Turkyilmaz S, et al. Early and late urological complications corrected surgically following renal transplantation. Transpl Int (2007);20:702-707.

11 Neri F, Tsivian M, Coccolini F, et al. Urological complications after kidney transplantation: experience of more than 1,000 transplantations. Transplant Proc (2009);41:1224-1226.

12 Dols LF, Terkivatan T, Kok NF, et al. Use of stenting in living donor kidney transplantation: does it reduce vesicoureteral complications? Transplant Proc (2011);43:1623-1626.

13 Faenza A, Nardo B, Catena F, et al. Ureteral stenosis after kidney transplantation. A study on 869 consecutive transplants. Transpl Int (1999);12:334-340.

14 Breda A, Bui MH, Liao JC, Gritsch HA, Schulam PG Incidence of ureteral strictures after laparoscopic donor nephrectomy. J Urol (2006);176:1065-1068.

15 Fuller TF, Deger S, Buchler A, et al. Ureteral complications in the renal transplant recipient after laparoscopic living donor nephrectomy. Eur Urol (2006);50:535-540; discussion 540-531.

16 Lehmann K, Muller MK, Schiesser M, et al. Treatment of ureteral complications after kidney transplantation with native ureteropyelostomy reduces the risk of pyelonephritis. Clin Transplant (2011);25:201-206.

17 Carter JT, Freise CE, McTaggart RA, et al. Laparoscopic procurement of kidneys with multiple renal arteries is associated with increased ureteral complications in the recipient. Am J Transplant (2005);5:1312-1318.

18 Dunkin BJ, Johnson LB, Kuo PC A technical modification eliminates early ureteral complications after laparoscopic donor nephrectomy. J Am Coll Surg (2000);190:96-97.

19 Kuo PC, Cho ES, Flowers JL, Jacobs S, Bartlett ST, Johnson LB Laparoscopic living donor nephrectomy and multiple renal arteries. Am J Surg (1998);176:559-563.

20 Streeter EH, Little DM, Cranston DW, Morris PJ The urological complications of renal transplantation: a series of 1535 patients. BJU Int (2002);90:627-634.

21 Slagt IK, Klop KW, IJzermans JN, Terkivatan T Intravesical versus extravesical ureteroneocystostomy in kidney transplantation: a systematic review and meta-analysis. Transplantation (2012);94:1179-1184.
22 Politano VA, Leadbetter WF An operative technique for the correction of vesicoureteral reflux. J Urol (1958);79:932-941.
23 Gregoir W the Surgical Treatment of Congenital Vesico-Ureteral Reflux Le Traitement Chirurgical Du Reflux Vesico-Ureteral Congenital. Acta Chir Belg (1964);63:431-439.
24 Hakkaart - Roijen L, Tan SS, Bouwmans CAM Handleiding voor kostenonderzoek 2010.
25 Krol R, Ziaja J, Chudek J, et al. Surgical treatment of urological complications after kidney transplantation. Transplant Proc (2006);38:127-130.
26 Hakenberg OW, Linne C, Manseck A, Wirth MP Bladder wall thickness in normal adults and men with mild lower urinary tract symptoms and benign prostatic enlargement. Neurourol Urodyn (2000);19:585-593.
27 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:e91211.
28 Mullins CD, Thomas SK, Pradel FG, Bartlett ST The economic impact of laparoscopic living-donor nephrectomy on kidney transplantation. Transplantation (2003);75:1505-1512.
29 Cecka JM The OPTN/UNOS Renal Transplant Registry. Clin Transpl (2005)1-16.

Chapter 6

Long-term outcome of kidney transplantation in patients with a urinary conduit: A case-control study

Inez K.B. Slagt[1], Jan N.M. IJzermans[1], Mustafa Alamyar[1], Paul C.M.S. Verhagen[2], Willem Weimar[3], Joke I. Roodnat[3], Türkan Terkivatan[1]

1 Department of Surgery, Erasmus MC, University Medical Center, Rotterdam, The Netherlands
2 Department of Urology, Erasmus MC, University Medical Center, Rotterdam, The Netherlands
3 Department of Nephrology, Erasmus MC, University Medical Center, Rotterdam, The Netherlands

International Urology and Nephrology 2013 Apr;45(2):405-11.

ABSTRACT

Introduction

To study the short- and long-term outcomes of kidney transplantation in patients with a bladder augmentation or urinary diversion compared to patients with a kidney transplantation in a normal functional bladder.

Patients and Methods

Between January 2000 and March 2011, 13 patients received 16 grafts into a reconstructed urinary tract. We performed a retrospective case-control study and matched each patient to 4 controls for donor and recipient gender and year of transplantation.

Results

Short- en long-term complications of kidney transplantation occurred in 12 patients, varying from urinary tract infections to medical hospitalization with or without surgical or radiological intervention. In 5 patients a percutaneous nephrostomy (PCN) was placed followed by surgical re-intervention. In three patients the grafts failed as a result of chronic rejection and were re-transplanted. There was no graft loss as a result of surgical complications or the reconstructed urinary tract. One-year patient and graft survival was 100%. After five years all patients were alive and seven of nine grafts (77.8%) were functioning. Mean follow up time was 4.3 years. Among the controls, 55 grafts were transplanted in 52 patients. Ten patients received a PCN. Five patients needed surgical re-intervention. In three patients transplantectomy was performed for ongoing rejection. Three patients were re-transplanted. One patient had a failing graft 7.5 years post transplantation and became dialysis dependent.

Conclusion

Kidney transplantation in patients with a reconstructed urinary tract has an increased complication rate. Nevertheless, the long-term results are comparable to patients with a normal urinary bladder.

INTRODUCTION

In the past, patients with untreatable lower urinary tract disease have been excluded from kidney transplantation, because it was thought that the bladder that contributed to the destruction of the native kidneys would threaten a kidney allograft.[1, 2] Complex urinary reconstructive procedures like bladder augmentation, Bricker[3], Indiana Pouch[4] and Mitrofanoff[5] are increasingly used due to advanced possibilities and kidney transplantation is nowadays offered to individuals without a functional bladder.[1, 6]

The first successful kidney transplantation connected to an augmented bladder was performed and reported by Kelly[6], twelve years after the first kidney transplantation. There is controversy about the safety of kidney transplantation for patients with a reconstructed urinary tract, due to the risk of complications potentially leading to graft loss. For the small group of kidney transplantation recipients with urinary diversion a higher incidence of surgical complications, wound healing problems and urinary tract infections, are reported.[7-9] However, long-term graft and patient survival seem to be similar to results of kidney transplantation for patients with a functionally innate bladder.[7-11]

Data in the literature about adult patients, with an augmented bladder in situ, receiving a kidney transplantation are scarce. Kidney transplantation in patients with a urinary conduit or reconstructed urinary diversion is reported to be 0,2% to 2,3% of the total number of procedures in single center studies.[7-9] Thereby, most series are published before the surgical technique and immunosuppressive medication were well developed. In this manuscript, the short- and long-term results of adult patients who received a kidney transplantation connected to a reconstructed urinary tract in the Erasmus Medical Center from January 2000 until March 2011 will be presented.

PATIENTS AND METHODS

Study population and data selection

The hospital data-base showed a total of 1427 patients who have been identified as kidney transplantation recipients between January 2000 and March 2011. These patients were screened for having a reconstructed urinary tract at the time of transplantation, which resulted in thirteen suitable patients. Those thirteen patients were matched to four patients with an innate urinary bladder who underwent a kidney transplant. The criteria for the matching process were donor gender and the gender of the recipient, living or deceased donor, and year of the transplantation in order to have a comparable

follow-up time. All records were reviewed for functional outcome, surgical and medical complications.

All percutaneous nephrostomy drainages (PCN), surgical re-interventions, acute rejection episodes, urinary tract infections and graft- and patient survival were registered. Rejection was biopsy proven and urinary tract infection was defined positive if medication was administered. Graft survival was defined by a functioning kidney transplant without the need for dialysis or graft removal during follow up. Follow up was performed until August 2011 for all cases and controls.

Operative technique

All kidney transplantations were performed by dedicated transplant surgeons whereas the anastomosis of the transplant ureter was performed by an experienced urologist. An extraperitoneal approach, using a half moon-shaped incision, preferably on the right side was performed. In case of contra-indications, like medical history with an urostoma or vascular abnormality, the kidney was engrafted in the left iliac fossa. Vascular connection of the artery and renal vein were performed end-to-side to the iliac vessels. The ureter was led to the reconstructed urinary tract without any kinking, spatulated distally and tension free anastomosed. Both intravesical and extravesical anastomosis were performed with resorbable sutures (PDS 5-0). Depending on the personal preference of the surgeon, a silicone stent (5 or 8-French) was used to relieve the new made anastomosis of the ureter.[12, 13]

In case of a Bricker and Indiana Pouch, described by Bricker[3] and Rowland[4] respectively, a ureter anastomosis was performed end-to-side to the terminal ileum or teniae of the caecum. The native bladder is left intact. In case of a Mitrofanoff[5] or a trans-appendicular continent conduit, in which a normal functional bladder is present, an intra- or extravesical ureter anastomosis was performed depending on the preference of the urologist. One patient (patient 11) had a bladder augmentation performed by pediatric surgeons with the native extended left ureter to avoid involvement of the intestine tract. Post operatively, immunosuppressive medication consisted of tacrolimus and methylprednisolon, and antibiotics (Co-trimoxazol) were provided to the patient. A PCN drain was placed in case of declining kidney function and signs of hydronephrosis on ultrasonography. The functioning of the PCN was checked by an antegrade pyelography (APG), visualizing the location of the PCN, a leakage or a stenosis.

Statistical analysis

Median and inter quartile ranges (IQR) are presented unless otherwise stated. Statistical analyses were performed by Mann-Whitney U and cross-tabs, using SPSS. Recipient and graft survival was analyzed by a Kaplan-Meier curve. Estimates between the case and control group were compared using the long rank test.

RESULTS

From a total of 1427 transplanted kidney grafts between January 2000 and March 2011, thirteen patients were transplanted with a reconstructed urinary tract in situ. Of those thirteen patients (Table 1 and 2), three received a re-transplantation and represent 1% of the total number of kidney transplantations. Ten patients had a living (un)related donor and three had a deceased donor, with a gender ratio (male:female) of 6:7. The median age of the recipients at the time of the renal transplantation was 23 years (IQR 20-45) (Table 2) with a gender ratio (male:female) of 8:5.

All reconstructed urinary tracts were performed with a median of 96 months (IQR 24 - 138 months) prior to the transplantation. The median age of the recipients at the time of the bladder reconstruction was 22 years (IQR 12-30) (Table 2). Type of the reconstruction (with or without an augmentation) and indication for urinary deviation are lined out in table 1. Complications occurred in twelve patients, varying from minor complications like urinary tract infections to major complications which needed surgical intervention or medical hospitalization (Table 1). Nine patients (patients 1, 3, 4, 7, 8, 9, 10, 12 and 13) developed a urinary tract infection that was medically treated in a timeframe to three months postoperatively. Five patients (patients 2, 4, 6, 9 and 12) required a PCN drain placement, between three weeks and two months postoperatively. All of these patients underwent a surgical re-intervention.

Three of five patients that received a PCN had a ureter re-implantation. In two cases (patients 4 and 9) a new ureteral anastomosis was created and in one case (patient 2) the graft pyelum was connected to the conduit. Patient 6 developed an avascular part of her Bricker which was revised two months after the transplantation and patient 12 developed a seroma. Surgical re-interventions were performed at a median time frame of seven months post transplantation (between 2-52 months). Acute rejection episodes that were treated successfully by immune suppressive medication occurred in four patients (patients 3, 4, 7 and 10), all were biopsy proven. After four years patient 4 required a surgical ureter revision but unfortunately dialysis was needed seven years post transplantation due to recurrent urinary tract infections.

Table 1 Clinical characteristics of the patients (n=13)

Patient no.	Sex	Type conduit	Age conduit	Reason conduit	Age ktx (year)	L/ D donor	Type anast.	Percutaneous/ surgical re-intervention (year)	GS-1	GS-5	Failure
1	M	IP	22	RN	23 (2002)	L	Extra	-	1	1	-
2	M	B	26	RN	39 (2002)	L	Extra	PCN (2002) stenose; pyelolisostomy	1	0	August 2003
					41 (2004)	L	Extra	Encrusted pyelitis (2009) PCN (2009), PNL (2009)	1	1	†
3	F	IS	5	NB	20 (2002)	L	Intra	-	1	1	March 2010
					28 (2010)	L	Extra	PCN (2010)	1	-	-
4	M	B	25	NB	27 (2002)	D	?	PCN (2002) R U-B (2006)	1	1	November 2009
5	F	IP	46	RI	51 (2003)	L	Extra	-	1	1	-
6	M	B	45	RI	55 (2003)	L	?	PCN (2003) Revision Bricker (2003)	1	1	-
7	M	M	9	RN	19 (2006)	L	Intra	-	1	0	July 2008
					22 (2009)	L	Extra	PCN (2009) R U-B (2009)	1	-	-
8	M	B	26	RI	28 (2006)	L	Extra	-	1	1	-
9	F	IP	14	RI	20 (2007)	L	Extra	PCN (2007) R U-B (2008)	1	-	-
10	M	M	19	NB	21 (2008)	D	?	-	1	-	-
11	F	EU	10	NB	16 (2009)	D	Extra	-	1	-	-
12	F	M	15	NB	24 (2010)	L	Intra	PCN (2010); lymfocele – seroom diagn laparosc + mesh removal	1	-	-
13	M	B	56	TBC-C	64 (2011)	L	Extra	-	-	-	-

IP: Indiana Pouch, B: Bricker, M: Mitrofanoff, IS: Isolated Sigmoid, EU: Extended Ureter,
RI: Recurrent Infections, NB: Neurogenic Bladder, RN: Reflux Nefropathie, TBC-C: Tuberculose Cystitis,
L: Living, D: Deceased, PCN: Percutaneous Nephrodrain, R U-B: Revision Ureter-Bladder anastomosis,
GS-1: Graft Survival 1 year, GS-5: Graft Survival 5 years, 0: non functional graft,
1: functional graft, -: no follow-up yet, ktx: Kidney Transplantation, PNL: Percutaneous Nephrolithotomy,
†: deceased, ?: unknown

Four patients (2, 3, 4 and 7) had graft failure as a result of chronic rejection after respectively one, eight, seven and two years. Three patients (2, 3, 7) were re-transplanted after respectively two, eight and three years and all those re-transplantations had a PCN placement due to hydronephrosis. In two cases a surgical intervention followed. One patient (2) had long-term antibiotic management due to encrusted pyelitis with a percutaneous nephrolithotomy (PNL) 5 years post transplantation[14] and one patient (7) underwent a revision of the ureterovesical anastomosis. In the third patient (3), the PCN was removed without any additional intervention.

One-year patient and graft survival was 100%. After five years all patients were alive and seven of the nine grafts (78%) were functioning. Median graft survival of the 16 transplanted kidney grafts was 43.25 months (IQR 20-95). One patient (patient 2) died because of a metastasized malignancy with a functioning graft six years after transplantation. There was no graft loss as a result of complications that were directly related to the reconstructed urinary tract.

In the control group with 52 transplanted patients, the male:female ratio was 32:20. The median age at the time of the transplantation was 45 years (IQR 39-60) (Table 2). In ten grafts a PCN drain was placed between 3 and 75 days postoperatively. A total of five surgical re-interventions were performed in a timeframe ranging between three days till ten months after transplantation. In two patients, a new ureterovesical anastomosis was constructed and three patients were operated on account of bleeding, leakage or a lymphocele. For two patients a percutaneous dilatation of the ureter was performed successfully whereas one patient was treated with a percutaneous drainage of a lymphocele.

Table 2 Characteristics case-control group characteristics

Match characteristics	**Case (n=13)**	**Control (n=52)**	**p-value**
Living - Deceased	10 – 3	40 – 12	1
Donor gender male – female	6 – 7	24 – 28	1
Recipient gender male - female	8 - 5	32 - 20	1
Median follow up time, months (IQR)	53 (20-94)	56 (16-97)	0.941
Baseline characteristics			
Re-transplantation(%)	3 (23)	4 (8)	0.136
Median age (years) ktx (IQR)	23 (20-45)	45 (39-60)	0.001
Median age (years) bladder reconstruction (IQR)	22 (13-30)	-	-
Median time (months) conduit before ktx (IQR)	87 (24-135)	-	-

IQR: Inter Quartile Range, ktx: kidney transplantation

Acute rejection occurred in sixteen patients in the control group which had been treated with immunosuppressive medication. In three of those sixteen patients rejection proceeded and transplantectomy was performed one, three and five months after transplantation. A second kidney transplantation was performed in four patients, respectively two, two and a half, three and six years after the initial transplantation. If those were not re-transplanted, a total of seven patients were dialyzing because of chronic transplant failure. Five patients deceased as a consequence of diseases unrelated to the kidney whereas three were lost to follow up due to migration or did not visit the outdoor department (Table 3).

There was no significant difference in the total amount of PCN placements between the group with a reconstructed urinary tract and the control group (p=0.268). Five patients (38%) in our study group underwent a surgical re-intervention versus 5 (10%) in the control group (p=0.022). We could not detect a significant difference in both groups when we studied surgical re-interventions in detail analyzing ureter revisions or other re-interventions separately (respectively p=0.051 and p=0.574). Medically treated acute rejections occurred in idem 31% of the patients in both groups, without significant difference. Additionally, no significant difference was found for transplantectomy, dialysis and death unrelated to the kidney transplantation in both groups. Long-term outcome of graft survival censored for death or loss to follow-up was analyzed by a Kaplan Meier curve and no significant difference found (p=0.189).

Table 3 Case – control complications overview

	Case (n=13)	**Control (n=52)**	**p-value**
PCN(%)	5 (38)	10 (19)	0.268
Surgical re-intervention total(%)	5 (38)	5 (10)	0.022
Surgical re-intervention ureter(%)	3 (23)	2 (4)	0.051
Surgical re-intervention other(%)	2 (15)	3 (6)	0.574
Dilatation ureter(%)	0	2 (4)	1
Graft loss			
Rejection (medically treated)(%)	4 (31)	16 (31)	1
Transplantectomy (rejection/ no perfusion)(%)	0	3 (6)	0.605
Death not ktx related/ unknown cause(%)	1 (8)	5 (10)	1
Dialysis(%)	1 (8)	7 (13)	0.685
Loss to follow-up(%)	0	3 (6)	0.605
Graft survival(%) (censored for death and re-transplantation)	9 (69)	41 (79)	0.189

IQR: Inter Quartile Range, ktx: kidney transplantation

DISCUSSION

Urological complications, including urinary tract infections in kidney transplantation patients are mentioned in up to 30% in the literature. These complications contribute significantly to morbidity and mortality rates, prolonged hospital stay and a second surgical intervention.[15] The first successful transplantation with a reconstructed urinary tract was described by Kelly[6] and multiple publications thereafter demonstrate acceptable long-term results in this kind of transplantation.[7-11, 16, 17] Still, a higher complication rate was mentioned and major surgical complications are reported between 5%-47%, mostly related to the ureteral anastomosis.[1, 2, 9, 11, 17, 18] However, kidney transplantations with a urinary drainage into a reconstructed urinary tract are rare and data has mostly not been standardized.[1, 7, 8, 18]

Surange[9] described a series of 59 kidney transplantations with an ileal conduit in 54 patients of which 13 were children. The surgical complication rate was 47% and the total number of complications was 60%. Graft survival was 90% after one year, 63% after five years, 52% after ten years and 52% after fifteen years. Patient survival was 95% after one year, 83% after five years, 69% after ten years and 69% after fifteen years. Hatch[11] reviewed the experience of sixteen transplant centers, which transplanted 31 kidneys for 30 children. Patients had been included during a 28-year period. The authors report six major surgical complications postoperatively; stomal stenosis, stomal prolapse, renal artery stenosis, urinary leak, enterovesical fistula and wound dehiscence. Graft survival was 90% after one year, 78% after five years, and 60% after ten years in this group of children with a urinary diversion or a bladder augmentation. Hatch[11] concluded that graft survival is not adversely affected compared to historical controls when a kidney transplantation is drained into a urinary conduit or augmented bladder.

Bladder reconstruction and transplantation are major interventions which require a high level of surgical expertise and the timing of bladder reconstructive surgery related to kidney transplantation is of great importance.[1] An extensive medical and surgical history on the urinary tract may influence the results of a ureter anastomosis of recipients with a urinary conduit. Concerning the timing of the kidney transplantation, it is important to realize that when a urinary tract reconstruction is performed prior to the kidney transplantation, immunosuppressive medication will not influence the healing of the reconstructed urinary tract.[19] On the other side, bladder reconstruction after transplantation with a stable renal function and reduced immunosuppressive therapy may be preferred because of optimal pre- and perioperative circumstances. Most centers advocate creation of the urinary conduit at least 6 weeks prior to the transplantation.[1, 8, 10, 20]

During the transplantation an extravesical, single layer, end-to-side anastomosis of the graft ureter into the intestinal loop is recommended for the ureterovesical anastomosis. Furthermore, implantation into the native bladder portion of the reconstructed bladder is to be preferred.[2, 9, 11] Prospective comparative studies of recent years demonstrate the benefits of routine stent placement.[13] This may have influenced our data especially due to PCN placement.

Notwithstanding the relatively limited number of patients and the presence of high heterogeneity of reconstructions that are described in our study group, this manuscript reveals important data and report to our knowledge the largest series in literature about this topic. More percutaneous and surgical interventions were performed in patients that underwent a kidney transplantation into a reconstructed urinary tract. However, when compared to the matched group of kidney transplant patients with an anatomically and functionally native bladder, no higher graft loss was seen due to those interventions. Finally, it should be noted that important advances have been made in the entire medical and surgical techniques over the past decade. This includes immunosuppressive medication, diagnostic tests, percutaneous and surgical intervention, which has significantly improved the postoperative outcomes. Still it is highly recommended to perform kidney transplantation in patients with a reconstructed urinary tract in an experienced center, because of the low incidence of these cases.

CONCLUSION

Kidney transplantation on patients with bladder augmentation or urinary diversion is an appropriate management strategy in case of end stage renal failure. It achieves similar graft and patient survival. Despite an increased risk of complications and surgical interventions, the long-term results are encouraging.

REFERENCES

1 Rigamonti W, Capizzi A, Zacchello G, et al. Kidney transplantation into bladder augmentation or urinary diversion: long-term results. Transplantation (2005);80:1435-1440.

2 Sheldon CA, Gonzalez R, Burns MW, Gilbert A, Buson H, Mitchell ME Renal transplantation into the dysfunctional bladder: the role of adjunctive bladder reconstruction. J Urol (1994);152:972-975.

3 Bricker EM Bladder substitution after pelvic evisceration. Surg Clin North Am (1950);30:1511-1521.

4 Rowland RG, Mitchell ME, Bihrle R, Kahnoski RJ, Piser JE Indiana continent urinary reservoir. J Urol (1987);137:1136-1139.

5 Mitrofanoff P Trans-appendicular continent cystostomy in the management of the neurogenic bladder Cystostomie continente trans-appendiculaire dans le traitement des vessies neurologiques. Chir Pediatr (1980);21:297-305.

6 Kelly WD, Merkel FK, Markland C Ileal urinary diversion in conjunction with renal homotransplantation. Lancet (1966);1:222-226.

7 Blanco M, Medina J, Pamplona M, et al. Outcome of renal transplantation in adult patients with augmented bladders. Transplant Proc (2009);41:2382-2384.

8 Coosemans W, Baert L, Kuypers D, et al. Renal transplantation onto abnormal urinary tract: ileal conduit urinary diversion. Transplant Proc (2001);33:2493-2494.

9 Surange RS, Johnson RW, Tavakoli A, et al. Kidney transplantation into an ileal conduit: a single center experience of 59 cases. J Urol (2003);170:1727-1730.

10 Hatch DA, Belitsky P, Barry JM, et al. Fate of renal allografts transplanted in patients with urinary diversion. Transplantation (1993);56:838-842.

11 Hatch DA, Koyle MA, Baskin LS, et al. Kidney transplantation in children with urinary diversion or bladder augmentation. J Urol (2001);165:2265-2268.

12 Chaykovska L, Deger S, Wille A, et al. Kidney transplantation into urinary conduits with ureteroureterostomy between transplant and native ureter: single-center experience. Urology (2009);73:380-385.

13 Wilson CH, Bhatti AA, Rix DA, Manas DM Routine intraoperative ureteric stenting for kidney transplant recipients. Cochrane Database Syst Rev (2005)CD004925.

14 Darbas A, van Agteren M, Roodnat J, Betjes MG, Weimar W Quiz page January 2011. A kidney transplant patient with rapidly progressive kidney failure and a radiopaque pyelum wall. Am J Kidney Dis (2011);57:A25-27.

15 Dols LF, Terkivatan T, Kok NF, et al. Use of stenting in living donor kidney transplantation: does it reduce vesicoureteral complications? Transplant Proc (2011);43:1623-1626.

16 Luke PP, Herz DB, Bellinger MF, et al. Long-term results of pediatric renal transplantation into a dysfunctional lower urinary tract. Transplantation (2003);76:1578-1582.

17 Glass NR, Uehling D, Sollinger H, Belzer F Renal transplantation using ileal conduits in 5 cases. J Urol (1985);133:666-668.

18 Power RE, O'Malley KJ, Khan MS, Murphy DM, Hickey DP Renal transplantation in patients with an augmentation cystoplasty. BJU Int (2000);86:28-31.

19 Warholm C, Berglund J, Andersson J, Tyden G Renal transplantation in patients with urinary diversion: a case-control study. Nephrol Dial Transplant (1999);14:2937-2940.

20 Rischmann P, Malavaud B, Bitker MO, et al. Results of 51 renal transplants with the use of bowel conduits in patients with impaired bladder function: a retrospective multicenter study. Transplant Proc (1995);27:2427-2429.

Chapter 7
General discussion and future perspectives

Inez K.B. Slagt, Jan N.M. IJzermans, Türkan Terkivatan

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

GENERAL DISCUSSION

In the last decades, several developments in the field of kidney transplantation have accelerated leading to an optimal, multidisciplinary approach. Nevertheless, urological complications still occur and increase the morbidity, mortality and costs.[1] This thesis is focused on urological complications, but also donor characteristics, immunosuppression and graft survival on the long term are important areas, which require optimum care. The eminent question of this thesis is which adjustments can prevent urological complications in kidney transplantation in the surgical field.

Ureteroneocystostomy technique

Kidney transplantation is worldwide accepted as the best medical care in patients with end stage kidney disease. Optimizing transplantation and thereby the urinary continuity by a ureteroneocystostomy providing a watertight, tension-free, and nonrefluxing anastomosis with good passage of urine production and without obstruction is still a challenge we pursue.[2] Surgical techniques have been thoroughly studied and developed over the past.

In a systematic review and meta-analysis we reached level 2 of evidence by comparing all existing literature. In this review the extravesical technique is considered superior on stenosis, leakage and total number of urological complications. Though only two randomized controlled trials were performed by that time and showed a different preference for the intravesical or extravesical anastomosis and the use of a prophylactic ureteric stent.[3, 4] Other studies that were included, were performed in different eras of immunosuppressive medication and had a retrospective design with additional biases.

To reach the best level of evidence we performed a randomized controlled trial comparing the intravesical and extravesical anastomosis in 200 consecutive kidney transplantations from a living donor. No differences were found regarding percutaneous nephrostomy placement, which is often the first sign of leakage or stenosis.[1, 5] However, the extravesical anastomosis was performed significantly faster with fewer urinary tract infections compared to the intravesical anastomosis. In this study 20% of the patients required a percutaneous nephrostomy placement independent of the type of ureteroneocystostomy technique, which is rather high. This might be explained by the post-operative care of our kidney transplant recipients. A low threshold is taken to account to place a percutaneous nephrostomy, as this is considered to be minimally invasive. Even a slight hydronephrosis on ultrasonography leads to a percutaneous nephrostomy placement, either for therapeutically benefit or as diagnostic tool before performing a biopsy. Despite the high number of percutaneous nephrostomies, only 10

recipients (5%) required a radiological dilatation or surgical ureter intervention, which is comparable to the worldwide literature.[6]

Identification of risk factors and costs of urological complications

A higher percentage of urological complications have been reported after deceased donor kidney donation when compared to living donor kidney donation.[7, 8] Identifying the risk factors for urological complications is necessary to optimize the transplantation procedure and reduce these complications. Factors that may provoke urological complications, such as leakage and stenosis have not been identified in the literature. A possible factor may be the insufficient blood supply to the ureter after retrieval of the kidney.[9-11] The 'golden triangle' is believed to be important for the blood supply of the ureter. Excessive dissection during organ retrieval should therefore be avoided and a short ureter would be favorable during transplantation to avoid necrosis of the distal ureter.[7, 9, 11] In our study, arterial reconstruction was highly associated with urological complications, which is confirmed by literature.[12-14] Although the type of ureteroneocystostomy and stent placement seem to be of influence[6, 15-19] this could not be supported by our data. There were no differences on long-term graft survival between Donation after Brain Death (DBD) and Donation after Circulatory Death (DCD), which is also confirmed by literature.

To evaluate the additional costs caused by urological complications we identified all percutaneous nephrostomies, ultrasonographies, and radiological or surgical interventions of 809 kidney transplantations. That way we created an overview of all additional costs. Our serie described an increased amount of percutaneous nephrostomies, especially in male patients, when compared to literature.[6] Trauma during graft retrieval could lead to edema of the ureter causing (temporarily) hydronephrosis requiring a percutaneous nephrostomy, without further intervention. The high number of urological complications in male recipients could have an anatomical cause. The crossing funiculus might be an explanation for ureter obstruction in males, considering that the ligamentum rotundum is ligated during transplantation in females. Our series requires the same amount of radiological or surgical interventions when compared to the literature.[6] Total direct medical costs made for urological complications after kidney transplantations were on average €2.322 per patient. This amount is probably an underestimation of the total amount of costs due to included areas. Rejection, intervention regarding arterial complications, or intervention regarding non-functioning grafts was not taken into account. Although urological complications are a major concern with morbidity, decreased quality of life and additional costs, kidney transplantation has an economic benefit with a significant decrease in costs as compared to dialysis.[20-22]

Kidney transplantation in a reconstructed urinary tract

The first successful transplantation with a reconstructed urinary tract was described by Kelly,[23] and multiple studies demonstrate acceptable long-term results.[24-27] Still, a higher rate of complications is mentioned as supported by our study. Bladder reconstruction and transplantation are major interventions, which require a high level of surgical experience. The timing of bladder reconstruction related to the kidney transplantation is of great importance.[28] Previous surgical interventions on the urinary tract may influence the results of a ureter anastomosis of recipients with a urinary conduit. Concerning the timing of the kidney transplantation, when a urinary tract reconstruction is performed on advance, immunosuppressive medication will not influence the healing of the reconstructed urinary tract.[29] On the other hand, if the transplantation is performed first, optimal pre- and peri-operative circumstances are established with stable renal function and reduced immunosuppressive therapy. In our study, more percutaneous and surgical interventions were performed in patients that underwent a kidney transplantation with a reconstructed urinary tract. When compared to a matched group with an anatomically and functionally native bladder, there was no higher graft loss due to those interventions.

Future perspectives

Although we all agree that kidney transplantation is the optimal kidney replacement therapy for patients with end stage kidney disease, this field still needs further research. For the near future it is necessary to optimize the surgical technique in kidney transplantation recipients. Prospective randomized clinical trials analyzing the need of prophylactic stenting, type and time of removal of the stent should be of future interest. A decrease in urological complications will improve the quality of live, diminish morbidity and reduce additional costs. Future directions include an indisputable opinion concerning stent use, ureteral length and processes on cell level like ischemia or inflammation.

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);43:1623-1626.

2 Jindal RM, Carpinito G, Bernard D, et al. Trial of intravesical versus extravesical ureteroneocystostomy in renal transplant recipients. Clin Transplant (1994);8:396-398.

3 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);27:1091-1092.

4 Waltke EA, Adams MB, Kauffman HM, Jr., et al. Prospective randomized comparison of urologic complications in end-to-side versus Politano-Leadbetter ureteroneocystostomy in 131 human cadaver renal transplants. J Urol (1982);128:1170-1172.

5 Tan EC, Lim SM, Rauff A. Techniques of ureteric reimplantation in kidney transplantation and its related urological complications. Ann Acad Med Singapore (1991);20:524-528.

6 Alberts VP, Minnee RC, Bemelman FJ, et al. Ureteral reconstruction after renal transplantation: clinical outcome and risk factors. Urol Int (2012);88:333-337.

7 Dinckan A, Tekin A, Turkyilmaz S, et al. Early and late urological complications corrected surgically following renal transplantation. Transpl Int (2007);20:702-707.

8 van Roijen JH, Kirkels WJ, Zietse R, et al. Long-term graft survival after urological complications of 695 kidney transplantations. J Urol (2001);165:1884-1887.

9 Neri F, Tsivian M, Coccolini F, et al. Urological complications after kidney transplantation: experience of more than 1,000 transplantations. Transplant Proc (2009);41:1224-1226.

10 Khauli RB, Ayvazian PJ. Modified extravesical ureteroneocystostomy and routine ureteral stenting in renal transplantation: experience in 300 consecutive cases. Transplant Proc (2001);33:2665-2666.

11 Krol R, Ziaja J, Chudek J, et al. Surgical treatment of urological complications after kidney transplantation. Transplant Proc (2006);38:127-130.

12 Kuo PC, Cho ES, Flowers JL, et al. Laparoscopic living donor nephrectomy and multiple renal arteries. Am J Surg (1998);176:559-563.

13 Dunkin BJ, Johnson LB, Kuo PC. A technical modification eliminates early ureteral complications after laparoscopic donor nephrectomy. J Am Coll Surg (2000);190:96-97.

14 Carter JT, Freise CE, McTaggart RA, et al. Laparoscopic procurement of kidneys with multiple renal arteries is associated with increased ureteral complications in the recipient. Am J Transplant (2005);5:1312-1318.

15 Butterworth PC, Horsburgh T, Veitch PS, Bell PR, Nicholson ML. Urological complications in renal transplantation: impact of a change of technique. Br J Urol (1997);79:499-502.

16 Kayler L, Kang D, Molmenti E, Howard R. Kidney transplant ureteroneocystostomy techniques and complications: review of the literature. Transplant Proc (2010);42:1413-1420.

17 Mangus RS, Haag BW. Stented versus nonstented extravesical ureteroneocystostomy in renal transplantation: a metaanalysis. Am J Transplant (2004);4:1889-1896.

18 Slagt IK, Klop KW, IJzermans JN, Terkivatan T. Intravesical versus extravesical ureteroneocystostomy in kidney transplantation: a systematic review and meta-analysis. Transplantation (2012);94:1179-1184.

19 Wilson CH, Bhatti AA, Rix DA, Manas DM. Routine intraoperative ureteric stenting for kidney transplant recipients. Cochrane Database Syst Rev (2005):CD004925.

20 Russell JD, Beecroft ML, Ludwin D, Churchill DN. The quality of life in renal transplantation--a prospective study. Transplantation (1992);54:656-660.
21 Mullins CD, Thomas SK, Pradel FG, Bartlett ST. The economic impact of laparoscopic living-donor nephrectomy on kidney transplantation. Transplantation (2003);75:1505-1512.
22 Cecka JM. The OPTN/UNOS Renal Transplant Registry. Clin Transpl (2005):1-16.
23 Kelly WD, Merkel FK, Markland C. Ileal urinary diversion in conjunction with renal homotransplantation. Lancet (1966);1:222-226.
24 Blanco M, Medina J, Pamplona M, et al. Outcome of renal transplantation in adult patients with augmented bladders. Transplant Proc (2009);41:2382-2384.
25 Coosemans W, Baert L, Kuypers D, et al. Renal transplantation onto abnormal urinary tract: ileal conduit urinary diversion. Transplant Proc (2001);33:2493-2494.
26 Surange RS, Johnson RW, Tavakoli A, et al. Kidney transplantation into an ileal conduit: a single center experience of 59 cases. J Urol (2003);170:1727-1730.
27 Hatch DA, Koyle MA, Baskin LS, et al. Kidney transplantation in children with urinary diversion or bladder augmentation. J Urol (2001);165:2265-2268.
28 Rigamonti W, Capizzi A, Zacchello G, et al. Kidney transplantation into bladder augmentation or urinary diversion: long-term results. Transplantation (2005);80:1435-1440.
29 Warholm C, Berglund J, Andersson J, Tyden G. Renal transplantation in patients with urinary diversion: a case-control study. Nephrol Dial Transplant (1999);14:2937-2940.

Chapter 8
Summary and conclusions in English and Dutch

Inez K.B. Slagt

SUMMARY

This thesis describes the fundamentals of the surgical technique to perform the ureter-bladder anastomosis and urological complications after kidney transplantation.

In **chapter one** a historical overview of kidney transplantation and the development in establishing urinary continuity is presented. Worldwide, the most accepted anastomosis is the ureteroneocystostomy. The two most commonly used techniques are the intravesical (Politano-Leadbetter) and the extravesical (Lich-Gregoir). Failure in this anastomosis leads to major urological complications, like leakage or obstruction requiring additional radiological or surgical intervention.

Chapter two describes the existing literature in a systematic review and meta-analysis comparing the intravesical anastomosis to the extravesical anastomosis. The PRISMA statement is used to demonstrate the relative risk regarding stenosis, leakage, and total number of urological complications, haematuria and urinary tract infections. After having included a total of 19 studies, the extravesical anastomosis was superior to the intravesical with less stenosis, leakage and total number of urological complications.

In **chapter three** we describe our performed randomized controlled trial comparing the intravesical anastomosis with the extravesical as described respectively by Politano-Leadbetter and Lich-Gregoir. Two hundred consecutive recipients of a living donor kidney were randomized for either intravesical or an extravesical anastomosis. Percutaneous nephrostomy placement was the primary outcome of this study. Comparing the outcomes, there was no difference in major urological complications like leakage or stenosis. However, the extravesical anastomosis was superior with significantly fewer urinary tract infections compared with the intravesical anastomosis. Furthermore, the extravesical anastomosis was performed significantly faster as this technique is surgically less complex.

In **chapter four** we defined independent risk factors for developing urological complications after 566 deceased donor kidney transplantations. Our univariate analysis showed an increased amount of urological complications in male donors, male recipients, pre-emptive transplantation, and arterial reconstruction. The multivariate analysis showed that male recipients and arterial reconstructions were independent risk factors to develop urological complications after deceased donor kidney transplantation.

In **chapter five** we present a retrospective study, which is performed to analyze the clinical outcome after kidney transplantation in 809 recipients. A total of 188 recipients

(23.4%) required a percutaneous nephrostomy placement while only 47 recipient (5.8%) required an additional radiological and/ or surgical intervention. Urological complications after kidney transplantation lead to an increase of costs up to on average €2.322 per recipient, but these complications did not influence the graft survival.

Chapter six describes our experience on kidney transplantation in patients with a urinary conduit. The case-control design ensured an equal comparison of patients with a reconstructed urinary tract, i.e. Bricker, Indiana Pouch, Mitrofanoff with recipients with a native bladder. An increased risk of urological complications and surgical interventions in the recipients with a reconstructed urinary tract was noticed. More percutaneous nephrostomies were placed and more surgical ureter re-interventions were performed. However, comparing the long term outcomes and graft survival no differences were found between the cases and controls. Therefore, kidney transplantation on patients with a reconstructed urinary tract is an appropriate management in case of end stage kidney disease.

In **chapter seven** the studies performed in **chapter two-six** are discussed. In addition, directions for further studies are pointed out.

CONCLUSIONS

Chapter two: The systematic review and meta-analysis shows superiority of the extravesical ureteroneocystostomy based on stenosis, leakage and total number of urological complications.

Chapter three: The randomized controlled clinical trial shows no differences in the number of urological complications comparing the two most commonly used intravesical and extravesical ureteroneocystostomy anastomoses. However, as the extravesical approach is associated with fewer urinary tract infections and with a time-sparing simplicity of the surgical technique, it may be advocated as first choice.

Chapter four: Independent risk factors to develop urological complications in deceased donor kidney transplantation are recipient's gender and arterial reconstruction of the graft. There were no differences in urological complications between DBD or DCD donors.

Chapter five: In 5.2% of all kidney transplantations a surgical ureter reconstruction is required with additional morbidity, decreased quality of life and additional costs. Nevertheless, costs made for urological complications do not outweigh the benefits of a kidney transplantation.

Chapter six: Kidney transplantation in patients with a bladder augmentation or urinary diversion is an appropriate management strategy in case of end-stage renal failure with similar graft and patient survival compared to patients with a native bladder. Despite an increased risk of complications and surgical interventions, the long-term results are promising.

SAMENVATTING

In dit proefschrift worden de verschillende aspecten van de chirurgische techniek voor de ureter-blaas anastomose en urologische complicaties na een nier transplantatie uiteengezet.

Hoofdstuk één bevat een historisch overzicht van de niertransplantatie en de ontwikkelingen rondom de chirurgische techniek in het vervaardigen van de continuïteit van de urinewegen. Wereldwijd zijn de twee meest gebruikte technieken de intravesicale (Politano-Leadbetter) en de extravesicale (Lich-Gregoir) ureter-blaas anastomose. Falen van deze anastomose leidt tot grote urologische complicaties zoals lekkage of obstructie waarvoor vaak meerdere radiologische en/of chirurgische interventies noodzakelijk zijn.

Hoofdstuk twee beschrijft de bestaande literatuur in een systematisch review met meta-analyse waarin de intravesicale anastomose met de extravesicale anastomose wordt vergeleken. De PRISMA richtlijnen zijn gebruikt om het relatieve risico van stenose, lekkage, totale aantal urologische complicaties, hematurie en urine weg infecties te beschrijven. In deze analyse waarin 19 studies geïncludeerd zijn, leek de extravesicale anastomose betere resultaten op te leveren ten opzichte van de intravesicale met minder stenose, lekkage en totaal aantal urologische complicaties.

In **hoofdstuk drie** beschrijven wij onze prospectieve gerandomiseerde studie waarin de intravesicale met de extravesicale ureter-blaas anastomose is vergeleken. Tweehonderd opeenvolgende ontvangers van een nier van een levende donor werden gerandomiseerd voor een intravesicale of een extravesicale anastomose, met het plaatsen van een percutane nefrostomie katheter als primaire uitkomst maat. Bij het vergelijken van de uitkomsten waren er geen verschillen tussen de twee groepen wat betreft de plaatsing van een nefrostomie katheter. De extravesicale anastomose was echter geassocieerd met significant minder urineweginfecties ten opzichte van de intravesicale anastomose. Ook was de gemiddelde tijdsduur om een extravesicale anastomose aan te leggen significant korter, hetgeen verklaard kan worden door de minder complexe chirurgische handeling.

In **hoofdstuk vier** van dit proefschrift presenteren wij een studie waarin onafhankelijke risicofactoren voor het ontwikkelen van urologische complicaties na een niertransplantatie van een overleden donor worden vastgesteld. De univariate analyse, verricht bij 566 niertransplantaties, liet toegenomen urologische complicaties zien bij mannelijke donoren, mannelijke ontvangers, pre-emptieve transplantaties en arteriële reconstructies. Aanvullende multivariate analyse op genoemde factoren toonde dat

mannelijker ontvangers en arteriële reconstructies onafhankelijke risicofactoren waren voor het ontwikkelen van urologische complicaties na een niertransplantatie van een overleden donor.

In **hoofdstuk vijf** wordt een retrospectieve studie beschreven die de klinische uitkomsten van 809 niertransplantaties toont. Aanvullend verrichten wij een kosten analyse in geval van urologische complicaties. In 188 ontvangers (23.4%) van een niertransplantatie is een percutane nefrostomie katheter geplaatst terwijl bij 47 ontvangers (5.8%) een aanvullende radiologische of chirurgische interventie nodig was. Urologische complicaties na niertransplantatie leiden tot toegenomen kosten van gemiddeld €2.322 per ontvanger. Echter deze complicaties zijn niet van invloed op de overlevingsduur van het transplantaat.

Hoofdstuk zes beschrijft onze ervaringen van niertransplantaties bij patiënten met gereconstrueerde urinewegen. Een case-control ontwerp werd gecreëerd om ontvangers met een gereconstrueerde urineweg, zoals een Bricker, Indiana Pouch of een Mitrofanoff, te vergelijken met ontvangers met een natieve blaas. Een toegenomen aantal urologische complicaties en chirurgische interventies werd gezien in ontvangers van een niertransplantatie met een blaasreconstructie. In deze groep werden meer percutane nefrostomie katheters geplaatst en meer chirurgische ureter-interventies verricht. De lange termijn uitkomsten en de overlevingsduur van het transplantaat kwamen overeen tussen de twee patiënten groepen.

In **hoofdstuk zeven** worden de bevindingen uit de **hoofdstukken twee-zes** bediscussieerd. Tevens worden enkele aanknopingspunten voor verder onderzoek gegeven.

CONCLUSIES

Hoofdstuk twee: Het systematisch review met meta-analyse toont betere resultaten van de extravesicale ureter-blaas anastomose, gebaseerd op het aantal stenoses, lekkages en totaal aantal urologische complicaties.

Hoofdstuk drie: Onze gerandomiseerde klinische studie toont geen verschil in urologische complicaties wanneer de intravesicale en extravesicale anastomose, respectievelijk volgens Politano-Leadbetter en Lich-Gregoir, met elkaar vergeleken worden. Desondanks had de groep met de extravesicale anastomose minder urineweginfecties en een kortere operatieduur door de chirurgische eenvoud van de anastomose.

Hoofdstuk vier: Onafhankelijke risicofactoren voor het ontwikkelen van urologische complicaties bij niertransplantaties van een post mortale donor zijn donor geslacht en arteriële reconstructie in de donor nier. Er zijn geen verschillen in het aantal urologische complicaties bij niertransplantaties afkomstig van een 'heart-beating' of een 'non-heart-beating' donor.

Hoofdstuk vijf: In 5.2% van alle niertransplantaties is een chirurgische ureter-reconstructie noodzakelijk met bijkomende morbiditeit, verminderde kwaliteit van leven en aanvullende kosten. Kosten in het kader van urologische complicaties wegen echter niet op tegen de voordelen van een niertransplantatie.

Hoofdstuk zes: Een niertransplantatie in patiënten met een blaas augmentatie of een gereconstrueerde urineweg is een geschikte behandeling in het geval van eind stadium nier falen. Hoewel er meer urologische complicaties optreden, zijn de orgaan-, en patiënt overleving vergelijkbaar met die van patiënten met een natieve blaas.

Chapter 9
Appendices

CONTRIBUTING AUTHORS

Dr. F.J.M.F. Dor
Department of Surgery
Erasmus MC University Medical Center
Rotterdam

Prof.dr. J.N.M. IJzermans
Department of Surgery
Erasmus MC University Medical Center
Rotterdam

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

Dr. K.W.J. Klop
Department of Surgery
Erasmus MC University Medical Center
Rotterdam

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

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

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

Dr. P.C.M.S. Verhagen
Department of Urology
Erasmus MC University Medical Center
Rotterdam

Prof.dr. W. Weimar
Department of Internal Medicine
Erasmus MC University Medical Center
Rotterdam

DANKWOORD

Het is zover, het is af! Velen hebben bijgedragen aan het tot stand komen van dit proefschrift. Graag wil ik iedereen bedanken voor alle hulp, interesse en steun. Een aantal personen wil ik in het bijzonder bedanken.

Mijn promotor, prof.dr. J.N.M. IJzermans. Beste Jan, toen ik kwam praten over een onderzoekstraject van een jaar, bood je mij een promotietraject aan. Wat een onverwachte, maar welkome uitdaging. Bedankt voor alle vrijheid tijdens het onderzoek en alle motiverende en enthousiaste besprekingen die we hadden.

Mijn co-promotor, dr. T. Terkivatan. Beste Türkan, heel veel dank voor alle begeleiding en je immer kritische blik. Tijdens mijn promotietraject ben je maar liefst twéé keer met zwangerschapsverlof geweest en toch was er altijd ruimte voor advies en overleg. Dat corrigeren op papier je beter afgaat dan digitaal is een feit. Ik zal mijn volledig rood doorstreepte documenten missen. Dankjewel voor je onuitputtende inzet.

Graag wil ik de leescommissie, prof.dr. H.W. Tilanus, prof.dr. W. Weimar en prof.dr. C.H. Bangma, bedanken voor het beoordelen van dit proefschrift en deelname in de oppositie.

Beste Frank, Khe en Diederik, dank voor jullie hulp, tijd en vooral alle geduld tijdens de uitvoering van de INEX studie. Door jullie telefoontje voor aanvang van de operatie kon ik op tijd paraat staan, dit geeft jullie nauwe betrokkenheid aan! Frank, altijd geïnteresseerd en enthousiast. Ik klopte bij jou aan om onderzoek te doen en rolde zo een promotietraject in. Fijn dat je zo meedenkend bent geweest gedurende mijn promotie. Khe, welk lootje we ook trokken, je had liever de andere gehad. Gelukkig is het altijd wel goed gekomen! Diederik, was het wennen om de INEX studie niet meer uit te hoeven voeren toen alle patiënten geïncludeerd waren? Dankjewel voor de gezelligheid en mooie verhalen tijdens de operaties.

Aan alle onderzoekers van de Heelkunde in het Erasmus MC; bedankt voor alle betrokkenheid. Gelukkig was de afstand nooit te groot om koffie te drinken, verjaardagstaart te eten, langs te komen voor een gezellige babbel of hulp bij het onderzoek. Succes met alle onderzoeken en de verdere carrière, het komt goed!

Mijn paranimfen verdienen een bijzondere vermelding. Lieve broer, lieve Ruben. Omdat je geen medische achtergrond hebt, is praten met jou een feest. Jouw nieuwe inzichten en opmerkingen als: 'dan doe je toch gewoon zo….', geven onderzoek doen een nuance

die niemand anders eraan kan geven. Dankjewel voor de steun en toeverlaat die je bent geweest de afgelopen jaren. Natuurlijk ook veel succes met je eigen carrière en geluk met Mariska. Ik had me geen betere grote broer kunnen wensen! Lieve Anna, mijn beste vriendinnetje, vanaf de dag dat we elkaar leerde kennen zat het goed! Ondanks onze overvolle agenda's werd onze vriendschap niet minder hecht. Dankjewel voor alle gezellige etentjes, drankjes en avondjes uit. Veel succes met de laatste loodjes van je eigen proefschrift en je opleiding. We moeten die stedentrip nog altijd boeken (en dat gaat echt gebeuren!), wat een geluk dat jij naast mij staat als paranimf op deze dag!

Niet te vergeten al mijn lieve vrienden en vriendinnen, medisch en niet medisch, jullie gezelligheid heeft het de afgelopen jaren makkelijker gemaakt! De opvang als het 'even tegenzit' en de vreugde bij goede ontwikkelingen waren heerlijk om met jullie te delen. Ik heb naar alle etentjes, borrels, feestjes en uitstapjes uitgekeken en hoop dat er nog heel veel gaan volgen!

Lieve familie, lieve papa, met jouw kennis op veel verschillende vlakken geeft een advies van jou altijd een fijn gevoel! Het vertrouwen en de mogelijkheden die jij creëerde zijn onmisbaar geweest! Dankjewel voor de nooit eindigende support, zelfs als het niet precies te volgen is wat ik doe. Lieve mama, dank voor jouw onvoorwaardelijke liefde en interesse. Zolang ik het me kan herinneren sta je voor ons klaar. Wat een geluk hebben Ruben en ik met jou gehad! Zelfs nu we uitgevlogen zijn, is de interesse oneindig aanwezig. En lieve oma, altijd nauw betrokken bij het avontuur van de kleinkinderen! Opleiding is voor u altijd heel belangrijk en dat staat bovenaan. Gelukkig staan vakantie vieren en leuke dingen doen op een gedeelde eerste plaats. Ik hoop u nog veel ansichtkaarten van toekomstige vakantiebestemmingen te kunnen sturen!

Liefste Wouter, wat fijn dat jij mij hebt gevonden! Sindsdien vieren wij de hoogtepunten en vang je mij op bij tegenslag. Dankjewel voor het maken van de kaft, het is prachtig geworden! Ik ben trots op hoe jij het leven aanpakt en op je altijd open en vriendelijke benadering! Wat de toekomst ook gaat brengen, het wordt een mooi avontuur!

LIST OF PUBLICATIONS

Urological complications after kidney transplantation clinical outcome and cost analysis
Slagt IKB, IJzermans JNM, Verhagen PCMS, Roodnat JI, Tran TCK, Weimar W, Dor FJMF, Terkivatan T
Submitted

Independent risk factors for urological complications after deceased donor kidney transplantation
Slagt IKB, IJzermans JNM, Visser LJ, Weimar W, Roodnat JI, Terkivatan T
PLoS One, March 2014

Intravesical or extravesical ureteroneocystostomy in living donor kidney transplantation recipients; A randomized controlled trial
Slagt IKB, Dor FJMF, Tran TCK, Kimenai HJAN, Weimar W, IJzermans JNM, Terkivatan T
Kidney International, February 2014

Long-term outcome of kidney transplantation in patients with a urinary conduit: a case-control study
Slagt IKB, IJzermans JNM, Alamyar M, Verhagen PCMS, Weimar W, Roodnat JI, Terkivatan T
International Urology and Nephrology, April 2013

Intravesical versus extravesical ureteroneocystostomy in kidney transplantation: systematic review and meta-analysis
Slagt IKB, Klop KWJ, IJzermans JNM, Terkivatan T
Transplantation, December 2012

Other publications

Hydroxylated collagen peptide in urine improves the detection of colorectal liver metastases
Bröker ME, Lalmahomed ZS, Huizen NA, Dekker LJ, Ayez N, Alberda WJ, Slagt IKB, Tetteroo GW, Vrijand WW, Coene P, Verhoef C, Steijerberg EW, Luider TM, IJzermans JNM
Submitted

Differences in cartilage forming capacity of expanded human chondrocytes from ear and nose and their gene expression profiles
Hellingman CA, Verwiel ETP, Slagt IKB, Koevoet W, Poublon RML, Nolst-Trenité GJ, Baatenburg de Jong RJ, Jahr H, van Osch GJVM
Cell Transplantation, 2011

PHD PORTFOLIO

Name PhD-candidate:	Inez Kirsten Beatrice Slagt, MD
Erasmus MC Department:	Surgery
PhD period:	October 2010- October 2013
Research group:	Erasmus Medical Center, Department of Surgery, Division of Transplant Surgery
Supervisor:	T. Terkivatan, MD PhD
Promotor:	professor J.N.M. IJzermans, MD PhD

1. PhD training	*Year*	*Workload (ECTS)*
General courses		
Basic Introduction Course on SPSS	2011	0.8
BROK ('Basiscursus Regelgeving Klinisch Onderzoek')	2011	1.5
Principles of research in medicine and epidemiology	2011	1.0
Regression analysis	2011	1.0
Biostatistics for clinicians	2012	1.0
Seminars and Workshops		
Journal Club	2010-2013	3.0
Presenting Skills for Scientists	2011	1.0
Biomedical English Writing and Communication	2012-2013	4.0
CPO Minicursus voor Methodologie van Patiëntgebonden Onderzoek en Voorbereiding van Subsidieaanvragen	2013	1.0
International conferences		
ESSR, Lille (poster + oral presentations)	2012	4.0
TTS, Berlin (poster + oral presentations)	2012	4.0
ESSR, Istanbul (oral presentation)	2013	4.0
National conferences		
Chirurgendagen (poster presentation)	2012	1.0
Bootcongres (2 poster presentations)	2012	1.0

2. Teaching	*Year*	*Workload (ECTS)*
Lecturing		
Teaching (medical students, nurses in training)	2010-2013	3.0
'Proefstuderen'	2010-2013	2.0
Supervising practicals and excursions		
Examination of Basic Life Support (EHBO) of medical students	2011-2013	1.0

CURRICULUM VITAE

Inez Kirsten Beatrice Slagt was born on May 26th of 1984 in Rotterdam. After graduation from high school at the Comenius College in Capelle aan den IJssel in 2002, she started Psychology at the Erasmus University Rotterdam. A year later she started her medical studies at Erasmus University Rotterdam. Her medical degree was obtained in October 2009, where after she took up a surgical residency at the Albert Schweitzer Hospital in Dordrecht (dr. R.J.P. Oostenbroek). In October 2010 she started her PhD project at the Department of Surgery at the Erasmus University Medical Center in Rotterdam, under supervision of dr. T. Terkivatan and prof.dr. J.N.M. IJzermans, which resulted in this thesis. From September 2013 until August 2014 she worked as a surgical resident at the Department of Surgery at the Ikazia Hospital in Rotterdam (dr. P.T. den Hoed). At present she works as urology resident at the St. Elisabeth Hospital in Tilburg (dr. P.J.M. Kil).