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Surgical Safety and Efficacy of Third Kidney Transplantation in the Ipsilateral Iliac Fossa

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Statistical Analysis C
Data Interpretation D
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Background: Kidney re-transplantation is a relevant option for patients who are returning to dialysis after graft failure. However, evidence is lacking to what extent a third kidney transplantation in the ipsilateral iliac fossa is safe and effective. The aim of this study was to investigate the outcomes of third kidney transplantations in the ipsilateral iliac fossa compared to first and second ipsilateral fossa kidney transplantations.

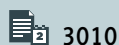
Material/Methods: There were 2074 kidneys transplanted at the Erasmus MC Rotterdam and at the University Medical Centre Groningen. Donor, recipient, and surgical data were collected. The cohort was divided into 3 groups: recipients of a first graft (I KTx; n=1744), recipients of a second graft (II KTx; n=44), and recipients of a third graft (III KTx; n=7).

Results: Recipients from the II KTx group had a significantly higher rate of primary non-function (PNF) compared to recipients in the I KTx group and recipients in the III KTx group (4.5% versus 0.7% and 0% respectively; $P=0.006$). The 1-year graft survival did not differ between groups: 96% for I KTx, 91% for II KTx, and 85% for III KTx ($P=0.214$). The 5-year graft survival did differ significantly between groups: 89% for I KTx, 82% for II KTx, and 68% for III KTx ($P=0.029$). There were no differences regarding hospital stay and rate of complications between groups.

Conclusions: Third kidney transplantation in the ipsilateral iliac fossa is feasible and viable. Short-term results are comparable to the first and the second kidney transplantation, however, long-term results are inferior but acceptable compared to dialysis.

MeSH Keywords: Delayed Graft Function • Graft Survival • Kidney Transplantation • Postoperative Complications

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Background

Kidney transplantation provides the best long-term outcome for patients with end-stage kidney disease [1]. There is continuous effort to increase the number of kidney transplantations by optimal utilization of donor kidneys. Kidney re-transplantation after graft loss is an option for patients returning to dialysis.

In general, little data on the results of kidney re-transplantation have been published showing contradictory findings. Most of the studies were case-control or cohort studies with a small number of cases. Moreover, long study inclusion times may cause significant biases due to changes in immunosuppression protocols over time, learning curve, variations in donor population, and the recipient complexity [2–4]. Some studies reported comparable or better outcomes of re-transplantation compared to the first transplantation [2,5–7], whereas others reported inferior outcomes of re-transplantation [3,8,9]. These studies mainly focused on graft and patient survival, while surgical aspects were not studied extensively.

Re-transplantation in the ipsilateral iliac fossa can be a surgical challenge as has been reported previously [10]. Surgical risks of a third dissection of the iliac fossa include prolonged duration of surgery [3,4], prolonged second warm ischemia time (WIT-2), greater amount of blood loss [3], and an increased risk of iliac vessels injury, due to the postsurgical adhesions. Combined with more comorbidity and higher sensitization grade of the recipient [9] this may lead to worse kidney transplantation outcomes [11]. Nonetheless, cohort studies focusing on the outcomes of a third kidney transplantation in the same iliac fossa are lacking.

The aim of this study was to investigate the outcomes of a third kidney transplantation in the ipsilateral iliac fossa in comparison to first and second ipsilateral kidney transplantation with a special emphasis on the surgical complications.

Material and Methods

Study design and parameters of interest

A retrospective 2-center study was conducted of all consecutive kidney transplant recipients (n=2074) who received kidney transplantation between 2011–2016 at either the Erasmus MC Rotterdam or the University Medical Centre Groningen. The kidney transplant databases of these 2 centers were analyzed and adult recipients who received a third or higher kidney transplantation in the ipsilateral fossa were extracted. Both deceased and living donor kidney transplantations were included. In case of re-transplantation(s), only the most recent transplantation was included in the analysis. Donor, recipient, and surgical data were collected and analyzed. The follow-up

was until the 31st of July 2017 for all cases or until death or graft loss occurred. Baseline characteristics consisted of recipient age, sex, and body mass index, type of donor (deceased or living), number of prior transplantations, number of veins and arteries of the donor kidney, side of surgery, cold ischemia time (CIT), WIT-2 and follow-up time (in months). The medical history of the recipient was collected and included the etiology of chronic kidney disease, dialysis modality (hemodialysis or peritoneal dialysis), history of hypertension and diabetes mellitus, as well as the anesthesiology risk classification according to the American Society of Anesthesiology. Immunologic data collected included blood group ABO-(in)compatibility, current and peak panel reactive antibodies (PRA) level, human leukocytes antigen (HLA) mismatches, and numbers of positive cross-match were collected and analyzed. Pediatric patients and patients with multiple organ transplantations were not included.

The cohort was divided into 3 groups: recipients of a first kidney transplantation (I KTx) (n=1744), second kidney transplantation to the ipsilateral iliac fossa (II KTx) (n=44) and third or subsequent kidney transplantation to the ipsilateral iliac fossa (III KTx) (n=7).

Short-term outcomes that were evaluated included operation time, estimated blood loss, the incidence of primary non-function (PNF) and delayed graft function (DGF), thrombotic events, bleeding events, urological complications, length of hospital stay, and the estimated glomerular filtration rate (eGFR) at 3 months after transplantation calculated with the Chronic Kidney Disease Epidemiology Collaboration (CKD-EPI) formula. PNF was defined as permanent dependence on dialysis post-transplantation. DGF was defined as the temporary need for dialysis starting the first week after kidney transplantation. PNF cases were not included in the DGF group. A bleeding event was defined as the need for red blood cells transfusion and/or the need of surgical re-intervention because of bleeding. A thrombotic event was defined as the thrombosis of the renal vein or renal artery of the kidney transplant diagnosed by imaging (ultrasound, nuclear scintigraphy, computed tomography) and confirmed during the surgical re-intervention. A urological complication was defined as the need for percutaneous nephrostomy placement or surgical re-intervention because of a urologic complication (ureteral stricture, urinary leakage). Long-term outcomes that were investigated included 1-year and 5-year patient and non-death censored graft survival. Graft survival was defined as the time between the kidney transplantation and date of graft failure (defined as return to hemodialysis or peritoneal dialysis return).

Surgical technique

Kidneys were routinely implanted in the iliac fossa. First, the renal vein was anastomosed to the external iliac vein. The renal

Table 1. Characteristic of the recipients of a first, second or third kidney transplanted to the same iliac fossa.

	First KTx (n=1744)	Second KTx (n=44)	Third KTx (n=7)	P	Tukey-Kramer		
					I vs. II	I vs. III	II vs. III
Mean age (years) (\pm SD)	55 \pm 14	46 \pm 17	46 \pm 11	.031	<.001	.218	1.00
Male sex (% , n)	61% (1055)	57% (25)	43% (3)	.566			
Median BMI (kg/m ²)	26 (15–45)	24 (16–40)	21 (20–41)	.082			
Hypertension (% , n)	59.5 (1038)	31.8 (14)	42.9 (3)	.791			
Diabetes (% , n)	21.4 (374)	9.1 (4)	0.0 (0)	.977			
Haemodialysis (% , n)	49.4 (862)	45.5 (20)	42.9 (3)	.525			
Median ASA risk classification	3 (0–4)	3 (1–4)	3 (2–3)	.989			
Median HLA mismatches	3 (0–6)	3 (0–6)	2.5 (2–4)	.700			
Mean current PRA (%) (\pm SD)	10 (\pm 3)	29 (\pm 17)	36 (\pm 11)	<.001	<.001	<.001	<.001
Mean peak PRA (%) (\pm SD)	16 (\pm 7)	42 (\pm 44)	100 (\pm 0)	<.001	<.001	<.001	.056
Positive crossmatch (% , n)	0.06 (1)	0	0	.203			
ABO-incompatible (% , n)	3.9 (69)	6.8 (3)	0	.227			
Living donor (% , n)	61.0 (1064)	52.3 (23)	42.9 (3)	.064			

KTx – kidney transplantation; BMI – body mass index; ASA – American Society of Anaesthesiology; HLA – human leukocyte antigen; PRA – panel reactive antibody.

artery was then anastomosed to the external iliac artery. All vascular anastomoses were performed in an end-to-side fashion and with running sutures. In the II KTx group and the III KTx group, the vascular anastomoses were performed proximally or distally of the previous anastomosis. There was 1 case in the III KTx group when the cava vein and common iliac artery were used for the anastomosis, as a typical anastomosis was not possible. The anastomosis between donor ureter and recipient bladder was an extravesical anastomosis [10]. There was no case in which the previous transplant (in the II KTx group and the III KTx group) was implanted intraperitoneally. Immunosuppression of the recipients consisted of prednisolone, tacrolimus, mycophenolate mofetil, and induction therapy with basiliximab.

Ethics

The study did not meet criteria for applying for the approval of the local or national ethics committee, as this is retrospective cohort study based on data from renal databases from 2 transplant centers. The study complies with the Declaration of Helsinki and the Declaration of Istanbul.

Statistical analyses

Data is presented as frequencies for categorical variables and mean with standard deviation or median with range for

continuous variables. One-way ANOVA or the Kruskal-Wallis tests were used for between-group comparisons as appropriate. Subsequent comparisons between 2 groups were done with Tukey's post hoc test. Survival analysis was performed using the Kaplan-Meier method and Log rank test. The Cox proportional hazard model was used to report hazard ratios of re-transplantation for patient and graft survival. A *P*-value below 0.05 was regarded as statistically significant. All data were analyzed with statistical software SPSS version 21 for Windows.

Results

The baseline characteristics of these patients are depicted in Table 1. Fifty-one out of 2074 total kidney transplantations were identified as a third or subsequent adult transplant (2.5%). In this group, 7 recipients received third or subsequent kidney to the ipsilateral iliac fossa.

The recipients in the I KTx group were older (55 \pm 14 years) in comparison to other groups (*P*=0.031). Patients receiving a second or third kidney transplantation had a higher peak and current PRA. There were fewer living donor kidneys in the II KTx group and the III KTx group (*P*=0.064).

Table 2. Intraoperative and short-term results of the first, second and third kidney transplanted to the same iliac fossa.

	First KTx (n=1744)	Second KTx (n=44)	Third KTx (n=7)	P	Tukey-Kramer		
					I vs. II	I vs. III	II vs. III
Median number of transplants	1 (0)	3 (3–4)	4 (3–7)	<.001	<.001	<.001	<.001
Right implantation side (% , n)	82.2 (1433)	54.5 (24)	85.7 (6)	.779			
Median number of arteries	1 (1–5)	1 (1–3)	1 (0)	.718			
Median number of veins	1 (1–3)	1 (1–2)	1 (1–4)	.084			
Median CIT (min)	167 (154–1589)	240 (160–1320)	543 (206–1420)	.030	.495	.043	.165
Median WIT 2 (min)	29(10–46)	23(11–53)	28(19–32)	.006	.005	.733	.887
Mean operation time (min) (±SD)	135±41	205±67	202±19	<.001	<.001	.005	.991
Median blood loss (ml)	200 (50–5200)	438 (100–2565)	600 (150–2100)	<.001	<.001	.018	.896
Median hospital stay (days)	13(8–143)	14 (7–27)	18 (8–27)	.943			
PNF (% , n)	0.7 (12)	4.5 (2)	0 (0)	.006	.004	.299	.976
DGF (% , n)	21.3 (371)	29.5 (13)	28.6 (2)	.167			
Thrombotic events (% , n)	1.8 (31)	9.1 (4)	0	.926			
Bleeding events (% , n)	5.3 (93)	6.8 (3)	0	.798			
Urological complications (% , n)	0.6 (11)	2.3 (1)	0	.203			
Transplant nephrectomy (% , n)	1.0 (17)	2.3 (1)	0	.582			
Median 3 months GFR (ml/min)	47(5–144)	52 (7–96)	46(5–101)	.419			
Median follow-up (months)	34 (0–83)	39 (0–82)	35 (6–80)	.554			

KTx – kidney transplantation; CIT – cold ischemia time; WIT 2 – second warm ischemia time (vascular anastomosis time); PNF – primary non-function; DGF – delayed graft function; GFR – glomerular filtration rate.

Surgical aspects

There were no differences between the 3 groups with regard to the number of donor kidney arteries and veins (Table 2). There was a significantly longer CIT in the III KTx group in comparison to I KTx group (543 minutes versus 167 minutes; $P=0.043$). Median WIT 2 was shorter in the II KTx group in comparison to the I KTx group and the III KTx group (23 minutes versus 29 minutes and 28 minutes, respectively), although significance was reached when the I KTx group and the II KTx group were compared ($P=0.005$). The mean duration of surgery was significantly longer in the II KTx group and the III KTx group in comparison to the I KTx group (205 minutes versus 202 minutes versus 135 minutes respectively; $P<0.001$ and $P=0.005$). Median blood loss was significantly higher in the II KTx group and III KTx group in comparison to the I KTx group (438 and 600 mL versus 200 mL respectively; $P<0.001$ and $P=0.018$).

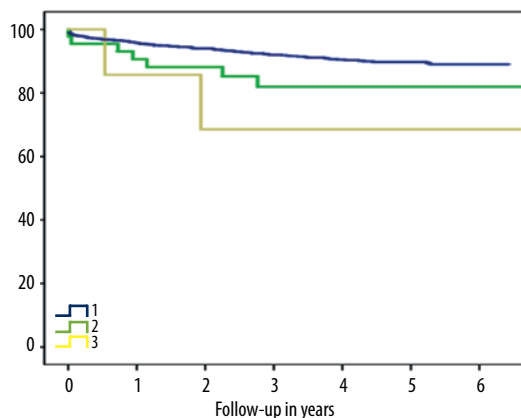
In the III KTx group (7 cases), there was 1 kidney transplantation (the fifth transplantation in the same patient and third transplantation to the same iliac fossa) performed intraperitoneally as the extra-peritoneal space was not accessible.

Short-term follow-up

There were no differences in the median hospital stay between groups (13 days, 14 days, and 18 days; $P=0.943$). Recipients in the II KTx group had a significantly higher rate of PNF compared to the I KTx group and the III KTx group (4.5% versus 0.7% versus 0%; $P=0.006$). Postoperative vascular and urological complications did not differ between groups. The median GFR at month 3 was similar between groups (Table 2).

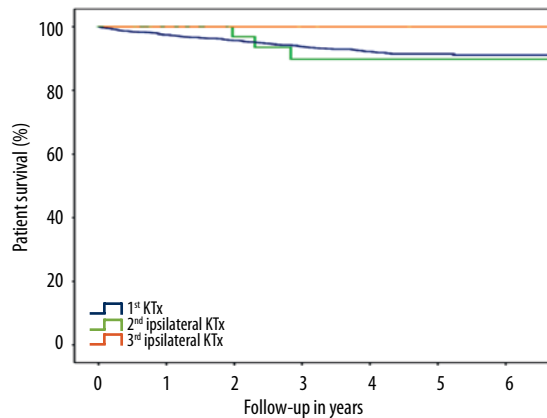
Long-term follow-up

There were no differences in the median follow-up of the recipients. One-year graft survival did not differ between groups: 96% for the I KTx group, 91% for the II KTx group, and 85% for the III KTx group ($P=0.214$). The 5-year graft survival differed between groups: 89% for the I KTx group, 82% for the II KTx group, and 68% for the III KTx ($P=0.029$) (Figure 1). The 1-year and 5-year patient survival did not differ between groups: 97% and 91% for the I KTx group, 100% and 90% for the II KTx group, and 100% and 100% for the III KTx group ($P=0.796$ and 0.856) (Figure 2).



TX	1 year	2 years	3 years	4 years	5 years	6 years	
1 st	1744	1478	1158	841	554	309	85
2 nd	44	37	31	23	16	10	6
3 rd	7	5	4	3	2	1	1

Figure 1. Graft survival.



TX	1 year	2 years	3 years	4 years	5 years	6 years	
1 st	1744	1478	1162	843	555	310	86
2 nd	44	37	31	23	16	10	6
3 rd	7	5	4	3	2	1	1

Figure 2. Patient survival.

Table 3. The hazard ratio for graft and patient survival.

	Graft survival		Patient survival	
	HR	p	HR	p
I KTx (control)	1.0	–	1.0	–
II KTx	1.97	0.080	1.09	0.881
III KTx	1.90	0.521	0.05	0.674

HR – hazard ratio; KTx – kidney transplantation.

The hazard ratios for graft and patient survival were calculated for the II KTx group and the III KTx group with the I KTx group as the reference group. No significant differences were found between the 3 groups (Table 3).

Discussion

In the present study, the results of the III KTx group in the ipsilateral iliac fossa were studied and compared with the outcomes of the I KTx group and the II KTx group in that same iliac fossa. Our main finding was that these outcomes were comparable, and the third kidney transplantation was a feasible and viable option for patients requiring a re-transplantation. Despite the longer duration of surgery and higher blood loss, the complication rate was the same compared to the first and second kidney transplantation. The median CIT was relatively short in all groups as living donors were a significant contribution to donor pool (61.0% and 52.3% in the I KTx group and the II KTx group, respectively). The median CIT was significantly longer in the III KTx group in comparison to the I KTx group

(543 minutes versus 167 minutes; $P=0.043$) which can be explained by the lowest rate of living donors in the donor pool (42.9%). The short-term outcomes were comparable. GFR was similar between the groups at 3 months post-transplantation (34 mL/min, 39 mL/min, and 35 mL/min in the I KTx group, the II KTx group, and the III KTx group, respectively, $P=0.419$). No differences were observed in patient survival at 1-year and 5-years post-transplantation. Although 5-year graft survival was inferior (68% for the III KTx group versus 89% for the I KTx group and 82% for the II KTx; $P=0.029$), the next transplantation to the same iliac fossa was not a risk factor for patient and graft survival.

To the best of our knowledge, there are no cohort studies reporting on third and subsequent kidney transplantations in the same iliac fossa. Mazzucchi et al. published a series of 21 cases after third and subsequent kidney transplantation [3]. They did not report the numbers of explorations of the iliac fossa. In this series, 1 patient received a fifth kidney transplant, meaning that 1 of the iliac fossa was used for the third time for kidney implantation. The duration of surgery was longer

for the whole group and they needed more blood transfusions compared to the first kidney transplantation. These findings were similar to ours.

Kidney re-transplantation in the ipsilateral iliac fossa is surgically challenging. The transplant surgeon is forced to explore an iliac fossa with 2 previous dissections (the prior transplantation and graft nephrectomy) in case of a second ipsilateral kidney re-transplantation and 4 previous dissections in the case of a third ipsilateral kidney re-transplantation. When there is atrophy of a previous graft, there is no necessity for graft nephrectomy and the same iliac fossa can be used again. It can be assumed that the timing of kidney graft nephrectomy is important. If it is an early kidney graft removal (with kidney capsule), the iliac fossa may look similar to the native one. If it is a late graft nephrectomy (sub-capsular), more adhesions may be expected in the iliac fossa. In our analyzed cohort of the III KTx group, all previous graft nephrectomies were done sub-capsular.

There is a lack of standards in management of patients for kidney re-transplantation due to the small numbers of reported cases in the literature. Ott et al. reported a longer operation time and higher surgical risk in third or fourth kidney transplantations [4]. Kienzl-Wagner et al. published good short-term and long-term results after third and fourth kidney transplantations [12]. Acute rejection was the predominant cause of graft loss in their series and the rate of surgical complications was on a reasonable level (7.1% severe complications). Izquierdo et al. did not find differences in the patient and graft survival after third kidney transplantation in comparison to the second [13].

According to the published literature, there is no linear relationship between the number of transplantations and graft survival. Patients receiving a fourth or fifth kidney transplant can have a better graft survival in comparison to those receiving a second or third [9]. There are many factors affecting the results of the next kidney transplantation. Heaphy et al. underlined that the survival of the primary graft can predict the outcomes of the re-transplantation [14]. And it appears that a poorly functioning first transplantation results in a higher chance of worse outcome after re-transplantation. Blanco et al. published similar findings [6].

If an ipsilateral approach is impossible, several other options are available. Some authors suggest transplanting the kidney intraperitoneally as a first choice for the third and subsequent kidney transplantation [15]. In our series, we used the intraperitoneal space only in 1 case. In our opinion, a retroperitoneal approach to the iliac fossa should always be considered as a first choice for kidney re-transplantation. First, the risk of twisting of the kidney on the vascular pedicle is

greater when the graft is placed intraperitoneally. Second, performing a kidney biopsy is much more difficult when the kidney is implanted intraperitoneally. In our experience, it is usually quite possible to reach iliac vessels more proximally to the previous anastomosis. Careful patient assessment, including a computed tomography (CT) scan visualizing the iliac vessels before transplantation and surgeon experience, are key factors to success [16].

Other options are placing the kidney in the subhepatic retroperitoneal space reached through a midline incision and Cattell-Braasch maneuver or performing an orthotopic kidney transplantation when the iliac fossa is inaccessible [13,17]. This latter technique consists, in most cases, of a left nephrectomy through the lumbotomy using the native renal vein and splenic artery for vascular anastomosis. Musquera et al. published the largest series of such cases (n=84) [18].

Three prior studies have reported performance of nephrectomy of the failed allograft [19–21]. Nghiem published a series of 6 cases of simultaneous pancreas and kidney (SPK) transplantation at the time of kidney transplant nephrectomy [9]. He used the vessels of previous renal graft for anastomosis after verifying sufficient blood flow. No complications (including renal artery stenosis) were observed and kidney function was excellent (average serum creatinine concentration 1.4 mg/dL) after an average of 39 months follow-up. LaMattina et al. presented a 9-case series of SPK re-transplantation in previous SPK recipients [20]. The previous transplant renal vein was reused in 3 cases and the previous transplant renal artery was reused in 1 case for the new kidney allograft anastomosis with good results. Chedid et al. reported a series of 6 cases of kidney re-transplantation after SPK transplantation using the renal vessels of the failed allograft [21]. The detailed technique with pre- and perioperative assessment of the remnant renal vessels were described with the utilization rate at the level of 83.3% (in 5 cases the previous renal vessels were used with success). In some instances, the utilization of the renal vessels of the failed allograft may not be possible in the event of severe atherosclerosis compromising the renal artery of the failed allograft. If the venous anastomosis is challenging due to thrombosis or stenosis of the iliac vein, the gonadal vein can be used for venous anastomosis [22]. An interesting point of view has been presented recently by Lejay et al. [23]. According to authors regarding both donor and recipient involvement, vascular surgeons should be more involved in kidney transplantation when complicated vascular status is presented.

The type of donor used for re-transplantation could be an important factor. When a surgical procedure is more demanding, graft quality should be as high as possible. Mazzucchi et al. showed that kidney re-transplantations have a better graft survival with a living kidney donor [3]. One-year graft survival for

re-transplantation was 75% and 46% for living and deceased donors respectively. The impact of donor type on patient survival after kidney re-transplantation revealed no survival benefits with donor kidneys from extended criteria donors [24]. There is lack of data regarding the use of kidneys for re-transplantation from donors after circulatory death.

Although re-transplantation is more frequent accompanied by complications and diminished graft survival, the results are superior to remaining dialysis dependent [25,26]. As compared to the outcomes of patients with end-stage renal failure who start dialysis therapy following allograft failure, transplantation of the third and subsequent kidney in the same iliac fossa seems to provide superior patient survival [27,28].

The limitations of our study were the small number of third ipsilateral kidney transplantations and the retrospective design of the study.

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Conclusions

The third and subsequent kidney transplantation in the ipsilateral iliac fossa is feasible and the short-term results may be comparable to the first and the second kidney transplant. In carefully selected recipients, a third or subsequent transplantation in the ipsilateral fossa is possible. Although this procedure is more technically, the short and long-term outcomes are fair.

Disclosures

None.