Outcomes in Pancreas Transplantation Alone versus Simultaneous Pancreas and Kidney Transplantation with Exocrine Drainage through a Duodenoduodenostomy

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Running title: PTA versus SPK transplantation with DD

Abbreviations:

DD	Duodenoduodenostomy
DJ	Duodenojejunostomy
DSA	Donor-Specific Antibody
IQR	Interquartile Range
PAD	Peripheral Artery Disease
PAK	Pancreas After Kidney
PRA	Panel Reactive Antibodies
PTA	Pancreas Transplantation Alone
PTA_{DD}	Pancreas Transplantation Alone with Duodenoduodenostomy
SPK	Simultaneous Pancreas and Kidney
SPK_{DD}	Simultaneous Pancreas and Kidney with Duodenoduodenostomy
SPK_{DJ}	Simultaneous Pancreas and Kidney with Duodenojejunostomy

Abstract

Until recently pancreas transplantation has been performed with exocrine drainage via duodenojejunostomy (DJ). Since 2012, DJ was substituted for duodenoduodenostomy (DD) in our hospital, allowing endoscopic access for biopsies. This study assessed (1) safety profiles with DD versus DJ procedures, and (2) graft rejection rate and graft loss with the DD technique in pancreas transplantation alone (PTA) compared with simultaneous pancreas and kidney (SPK) transplantation. (1) DD patients (n=117; 55 PTA_{DD} and 62 SPK_{DD} with median follow-up 2.2 years) were compared with SPK_{DJ} patients (n=167) transplanted in the period 1998-2012 (preDD era). Postoperative bleeding and pancreas graft vein thrombosis requiring reoperation occurred in 18% and 9% of DD patients, respectively, versus 10% (p=0.039) and 6% (p=0.28) in DJ patients. (2) More SPK_{DD} than PTA_{DD} patients were males (p=0.016), had longer history of diabetes (p=0.018) and more often coronary artery disease (p=0.025). Pancreas graft rejection rates were higher in PTA_{DD} transplants versus SPK_{DD} patients (p=0.003). Hazard ratio (HR) for graft loss was 2.25 (95% CI 1.00, 5.05; p=0.049) in PTA_{DD} versus SPK_{DD} recipients. In conclusion, DD patients were more often subject to bleeding requiring reoperation than DJ patients. PTA_{DD} was more likely to undergo rejection and graft loss compared with $SPK_{DD.}$

Introduction

The first clinical pancreas transplantation together with implantation of a kidney graft was performed in December 1966 by the transplant surgeons Kelly and Lillehei.[1] Initially, the success rate with pancreas transplantation was low,[2] but increased in the 1980s along with advances in surgical technique and immunosuppressive therapy.[3, 4]

Today, simultaneous pancreas and kidney (SPK) transplantation is an established curative treatment for patients with type 1 diabetes and end-stage renal disease, with the majority (75%) of pancreas transplantations performed worldwide being SPK transplants.[4] However, the role of pancreas transplantation alone (PTA) in the treatment of nonuremic brittle type 1 diabetic patients is still debated. The evident benefit of a functioning pancreas transplant is that patients obtain normoglycemia without use of exogenous insulin along with reduced risk of acute diabetic complications. However, the surgical procedure for pancreas transplantation has been associated with higher complication rates compared with the surgical procedure for single kidney transplantation. Furthermore, the pancreas graft survival rates in PTA transplants have been inferior to those compared with SPK transplants,[3, 4] probably due to higher immunologic graft failure rates.

In September 2012 we introduced the duodenoduodenostomy (DD)[5] for exocrine drainage of the duodenal segment of the pancreaticoduodenal transplant. Before that duodenojejunostomy (DJ) was standard procedure. The intention with the DD technique was to facilitate endoscopic access to the site of exocrine drainage and improve surveillance of rejection with protocol and clinical indication biopsies of the pancreas graft, and also to facilitate intervention (e.g., stenting of the pancreatic duct in cases of exocrine leakage). Theoretically, this could lead to early detection of rejection and reduced risk of pancreas graft loss.

The surgical technique of exocrine drainage through a DD has been reported by others, first in case reports[6-8] and later in larger patient cohorts,[5, 9-12] but few centers are currently using this surgical technique worldwide, and experience is limited.

In the present study, we addressed whether DD is associated with more or less frequent complications compared with DJ. Secondly, in light of improved endoscopic and histological surveillance of the pancreas graft, we investigated whether rejection and graft survival rates in PTA with DD (PTA_{DD}) are comparable with those of SPK with DD (SPK_{DD}).

Materials and Methods

Study population

All organ transplantations in Norway are performed at one single center, Oslo University Hospital, Rikshospitalet in Oslo, which serves the entire population of just over 5.2 million inhabitants. Currently between 30 and 40 pancreas transplantations are performed annually.

We retrospectively analyzed data from the Norwegian Renal Registry. Patient medical records served as an additional source to obtain more complete clinical data. These analyses included 117 eligible patients with type 1 diabetes who were recipients of a first PTA_{DD} (n=55) or SPK_{DD} (n=62) transplant from September 9, 2012 to July 26, 2016. Recipients of pancreas after kidney (PAK) transplants were not included. One hundred sixty-seven SPK_{DJ} transplants performed between March 3, 1998 and August 31, 2012 served as a historical control group prior to the change in surgical technique. Only ten PTA were performed with the DJ technique, and were therefore not included in the analysis. All transplant recipients were more than 18 years old. Cases were closed for analysis on October 25, 2016 to ensure a minimum follow-up length of three months or more. Causes of death were defined according to the European Renal Association-European Dialysis and

Transplant Association (ERA-EDTA) coding systems.[13] No patient was lost to follow-up. The study was approved by the Regional Committee for Medical and Health Research Ethics.

Pretransplant cardiac assessment

Since 1999, coronary angiography (CAG) has been included as part of the cardiac work-up of all patients with type 1 diabetes who were potential recipients of pancreaticoduodenal allografts.[14] Before 1999, patients were screened for ischaemic heart disease with a non-invasive cardiac stress test, and if judged clinically relevant, a CAG was perfomed. According to our protocol, we do not accept patients with a left ventricular ejection fraction of less than 30%.

Surgical techniques

The Norwegian pancreas transplantation program was initiated in June 1983.[15] Several techniques for exocrine drainage have been used. (1) Initially, a duct-occluded segmental pancreas was used for transplantation;[15] (2) in April 1988, this technique was replaced by a whole-organ pancreas graft with exocrine drainage by anastomosing the duodenal segment to the urinary bladder.[15] (3) In March 1998, bladder drainage was substituted with enteric drainage by anastomosing the duodenal segment of the pancreaticodudenal transplant to the proximal jejunum (DJ).[16] (4) The current technique is still enteric drainage, but since September 2012, DJ has been abandoned in favor of DD,[5] which also opened for more frequent PTA transplantations. The technique of the vascular and enteric anastomosis was kept unaltered with an aortic patch end-to-side on the right common iliac artery, elongated portal vein end-to-side on the cava/proximal iliac vein, and hand-sewn enteric side-to-side anastomosis.

Immunosuppressive agents

The immunosuppressive protocols used in our center have changed over time. In our study

population, the pancreaticoduodenal transplant recipients received maintenance immunosuppression with prednisolone, cyclosporine, and mycophenolate mofetil in the period from March 1998 to the end of 2001. Since 2002, cyclosporine has been substituted with tacrolimus as calcineurin inhibitor. In September 2003, lymphocyte-depleting induction therapy with anti-thymocyte globulin (ATG) was introduced on a regular basis.

Postoperative complications during the first three months

After reviewing descriptions of surgical procedures, radiological imaging, and other relevant examinations, complications were stratified in pancreas- or kidney-related complications. Postoperative surgical complications leading to reoperation within three months after transplantation were assessed in terms of pancreas graft-related bleeding, infection, anastomotic leak, and pancreas graft vein thrombosis. Patients transplanted after April 7, 2015 (*n*=38) are also included in an on-going prospective study exploring how microdialysis catheters, protocol ultrasound Doppler, and computed tomography can detect such complications (www.clinical.trials.gov [NCT01957696]). Since more subclinical complications may be detected by closer monitoring, only pancreas graft vein thrombotic complications leading to graft loss or requiring reoperation are reported in this study. Rejections were classified according to the Banff classification criteria.[17, 18] Only biopsy-proven rejection episodes are reported. In case of early pancreas graft loss due to pancreas vein thrombosis, histopathological analysis was used to rule out the possibility of a vascular rejection. Absence of pretransplant panel-reactive antibodies (PRA) was a prerequisite to receive a pancreas transplant in the DJ era, while PRA of 40% or less has been accepted in the DD era.

Defining pancreas graft failure

Pancreas graft failure was defined as patient death with functioning graft, graftectomy, need for

exogenous insulin therapy, and/or HbA_{1c} levels at or higher than 6.5% (48 mmol/mol) along with low C-peptide levels. Recurrence of autoimmune type 1 diabetes has not regularly been assessed. Pancreas graft survival was uncensored for patient death.

Statistical analysis

Demographic data are summarized and grouped by mode of treatment. Continuous variables are reported as the mean ± *SD* or median (interquartile range), depending on normal distribution of the data. Categorical data are described using frequencies and percentages. Student's *t* test for independent samples or the Mann-Whitney *U* (Wilcoxon) test were used to compare continuous variables as appropriate. Categorical variables were compared with the use of the Pearson chi-square test (Fisher's exact test was applied if the number of observations per cell was fewer than five). Kaplan-Meier curves were used to construct the probability of pancreas graft loss (percentage) by transplant type (PTA_{DD} or SPK_{DD}). The difference in pancreas graft survival between the groups was compared using Cox regression analysis. Cox proportional hazard models were used to calculate hazard ratio (HR) for pancreas graft loss in relation to transplant type. The proportional hazards assumption was tested using graphical checks. All reported *p* values were two-tailed, and *p* values of <0.05 were considered significant. Statistical analysis was conducted using IBM SPSS Statistics for Windows, version 21 (IBM, Armonk, NY, USA) or Stata version 13.0 (StataCorp LP, College Station, TX, USA).

Results

Patient characteristics

The characteristics of recipients of DJ (SPK_{DJ}), SPK_{DD}, PTA_{DD} or DD (SPK_{DD} and PTA_{DD}) transplants are displayed in Table 1. In comparison with DD patients, DJ patients had more often coronary artery disease and peripheral artery disease (PAD) at the time of transplantation. PAD was

defined as intermittent claudication and/or need for percutaneous transluminal angioplasty in the lower extremity and/or amputation. Pancreas transplant ischemia time was also longer in the DJ group. Thirty-four of the 167 DJ patients (20%) used cyclosporine as a calcineurin inhibitor instead of tacrolimus, and only 110 of the 167 DJ recipients (66%) received induction therapy with ATG; otherwise the DJ and DD patients were similar in baseline characteristics.

Compared with the PTA_{DD} group, the SPK_{DD} group consisted of more male recipients, had a longer history of diabetes, and a higher incidence of coronary artery disease at the time of transplantation. Pancreas transplant ischemia time was also longer in the SPK_{DD} group. The median follow-up lengths in PTA_{DD} and SPK_{DD} recipients were similar: 2.1 years (interquartile range [IQR] 1.3, 3.2) and 2.2 years (IQR 1.1, 3.3), respectively (p=0.94).

Graft loss and postoperative complications with DD surgical technique compared with DJ surgical technique

There was no difference in pancreas graft loss at 3 months posttransplant when the DD and DJ groups were compared. In nine of 117 patients with DD (8%) and eight of 167 patients with DJ (5%), the cause of early pancreas graft loss was thrombosis; in one patient with DJ (1%), rejection; in two patients with DD (2%) and two patients with DJ (1%), infection; in one patient with DJ (1%), bleeding; and in one patient with DD (1%) and one with DJ (1%), death.

Early pancreas transplant-related complications with DD surgical technique compared with DJ surgical technique after transplantation are shown in Table 2. Pancreas transplant recipients with DD experienced bleeding complications leading to reoperation more often than SPK_{DD} recipients. One recipient with DD underwent a second surgery for severe bleeding after a percutaneous core needle biopsy of the pancreas transplant.

Pancreas graft rejection in PTA_{DD} versus SPK_{DD} transplants

Pancreas graft rejection episodes in PTA_{DD} and SPK_{DD} transplants are shown in Table 3. Biopsy-verified pancreas graft rejection was more common in recipients of PTA_{DD} transplants compared with recipients of SPK_{DD} transplants. Early (≤3 months posttransplant) pancreas graft rejection episodes were entirely T cell-mediated. Rejection episodes after three months posttransplant were still dominated by T cell-mediated rejections, but at that time vascular- and antibody-mediated and chronic rejections occurred more frequently. *De novo* donor-specific antibodies (DSAs) developed in 18% of the PTA_{DD} patients and 6% of the SPK_{DD} patients (p=0.051). Late (>3 months posttransplant) pancreas graft rejection episodes were preceeded in 8 of the 14 patients (57%) by leukopenia (primarly caused by drugs or cytomegalovirus [CMV]-related complications), and a subsequent period with reduced immunosuppression.

Kaplan-Meier plots for pancreas graft survival

Kaplan-Meier curves plotted by transplant type, PTA_{DD} versus SPK_{DD}, are shown in Figure 1. The Kaplan-Meier analysis showed a separation between the PTA_{DD} group and the SPK_{DD} group. In univariate Cox regression analysis, the only statistically significant risk factor for pancreas graft loss at the time of transplantation was transplant type, which yielded a hazard ratio for pancreas graft loss of 2.25 (95% CI 1.00, 5.05; p=0.049) in PTA_{DD} patients compared with SPK_{DD} patients (Table 4).

Patient and pancreas graft survival rates at 36 months posttransplant by transplant type

Similar patient survival rates were seen in PTA_{DD}, SPK_{DD}, and SPK_{DJ} at 36 months posttransplant (96% [95% CI 86%, 99%], 98% [95% CI 84%, 99%], and 93% [95% CI 88%, 96%], respectively). Pancreas graft survival rates were superior in SPK_{DD} and SPK_{DJ} transplants compared with PTA_{DD} (83% [95% CI 69%, 91%], 82% [95% CI 75%, 87%], and 64% [95% CI 48%, 77%], respectively).

There were no differences in pancreas graft survival rates at 3, 6, and 12 months posttransplant in PTA_{DD} patients when stratified into time periods: 2012-2013 (85% [95% CI 60%, 95%], 85% [95% CI 60%, 95%], and 70% [95% CI 45%, 85%] respectively), 2014 (100%, 86% [95% CI 54%, 96%], and 79% [95% CI 47%, 93%] respectively), and 2015-2016 (86% [95% CI 62%, 95%], 86% [95% CI 62%, 95%], and 73% [95% CI 45%, 88%] respectively). Pancreas graft survival rates in SPK_{DD} were also similar in the three time periods: 2012-2013 (91% [95% CI 69%, 98%], 91% [95% CI 69%, 98%], and 91% [95% CI 69%, 98%] respectively), 2014 (94% [95% CI 63%, 99%], 94% [95% CI 63%, 99%], and 94% [95% CI 63%, 99%] respectively), and 2015-2016 (87% [95% CI 65%, 96%], 87% [95% CI 65%, 96%], and 87% [95% CI 65%, 96%] respectively).

Causes of pancreas graft loss and patient death in PTA_{DD} and SPK_{DD} transplants

Data are shown in Table 5. Twenty (14 PTA_{DD} and 6 SPK_{DD} transplants) of a total of 26 (77%) pancreas graft losses during follow-up occurred during the first year after transplantation, including six pancreas graft losses in each group within three months posttransplant. Pancreas graft rejection was the single most commonly observed cause of graft loss, followed by pancreas graft vein thrombosis. However, graft loss by rejection was the only statistically different cause of graft loss between the two groups. There were no differences in deaths between the two groups. During follow-up two patients died in the PTA group. A 55-year-old female patient developed severe bone marrow depression due to CMV disease, and died of *Stenotrophomonas maltophilia* septicemia on day 83 posttransplant. A 57-year-old male patient died on day 198 posttransplant due to graft site bleeding subsequent to pancreas graftectomy because of rejection of the pancreaticoduodenal transplant. The rejection was complicated with invasive *Streptococcus anginosus* infection. In the SPK_{DD} group a 44-year-old male patient died for unknown reasons. He was found dead on day 588 posttransplant and no autopsy was performed.

Discussion

In comparison with a historical control group, the conversion of surgical technique from DJ to DD did not worsen the outcomes in terms of pancreas graft survival, although patients transplanted with the DD surgical technique required surgery intervention for bleeding complications more often than patients with the DJ technique. In this single-center study on patients with type 1 diabetes who received PTA_{DD} or SPK_{DD} transplants, we observed that pancreas graft survival rates were higher with SPK_{DD} transplantation than with PTA_{DD}. Pancreas transplant rejection was the single most commonly observed cause of pancreas graft loss during follow-up. Early pancreas graft loss was dominated by graft vein thrombosis.

Pancreas graft vein thrombosis is a feared postoperative complication and was the most frequent cause of early pancreas graft loss, but it did not differ in the DD and DJ groups. On the other hand, the frequency of postoperative complications in terms of bleeding requiring reoperation was higher with the DD technique compared with the DJ technique, although there was no difference in pancreas graft loss after three months posttransplant. Gunasekaran et al.[9] have reported pancreas transplant outcomes in 36 patients (10 PTA, 22 SPK, and 4 PAK transplants) with DJ, 14 patients (5 PTA, 7 SPK, and 2 PAK transplants) with stapled DD, and seven patients (1 PTA and 6 SPK transplants) with hand-sewn DD technique. They found that gastrointestinal bleeding occurred more frequently in those with stapled DD compared with DJ. One-year pancreas graft survival rates were 100% for hand-sewn DD, 79% for stapled DD, and 89% for DJ. Perosa et al.[10] reported on 53 (10 PTA and 43 PAK transplants) pancreas transplants with DD. Pancreas graft survival at 1 year was 83% (80% in PTA transplants). There were five cases (9%) of thrombosis. Khubutia et al.[11] compared 17 SPK_{DD} with 15 SPK_{DJ} and the two groups did not differ in early postoperative complications. Walter et al.[12] compared 125 DD recipients (3 PTA, 115 SPK, and 7 PAK transplants) with 116 DJ recipients (3 PTA, 104 SPK, and 9 PAK transplants), and reported that

graft vein thrombosis occurred more frequently in the DJ group (16% versus 4%), whereas enteric bleeding occurred more often in the DD group (11% versus 3%). The pancreas graft survival rates at 1 year were 82% and 78% in the DD and DJ groups respectively. Horneland et al.[5] compared 40 pancreas transplants using DD (17 PTA, 20 SPK, and 3 PAK) with 40 pancreas transplants using DJ (7 PTA, 30 SPK, and 3 PAK). The DD surgical procedure was associated with a higher rate of thrombosis (23% versus 5%) and reoperation (48% versus 30%). Overall, these studies report that exocrine drainage through a duodenoduodenostomy appears relatively safe, although there are some inconsistencies in the results.

Pancreas graft survival rates have been reported to be better after SPK transplantation compared with PTA. According to data from pancreas transplantation in US and non-US cases from 2005 to 2014, as reported to the United Network for Organ Sharing (UNOS) and the IPTR,[19] 1- and 3-year pancreas graft survival rates for SPK transplants using the DJ surgical technique were 85% and 79% respectively in the period 2005-2009 and 89% and 82% respectively in 2010-2014. The corresponding numbers for pancreas graft survival rates in PTA were 79% and 66% respectively, in 2005-2009, and 83% in 2010-2014 (only the 1-year survival rate was given for this period). UK Transplant Registry data (2006-2016)[20] reported SPK transplant pancreas graft survival of 87% and 75% at 1 and 5 years respectively. Gruessner et al.[21] reported single-center results at the University of Minnesota of 513 PTAs from 1966 to the end of 2006, in which the 1-year pancreas graft survival rate steadily increased from 31% in the pre-cyclosporine era to 75% in the tacrolimus era. Boggi et al.[22] reported in 2012 1- and 5-year PTA graft survival rates of 82% and 73%, respectively, in 71 consecutive PTA recipients who underwent the DJ surgical procedure at a single center in Pisa, Italy. In an International Pancreas Transplant Registry (IPTR) analysis,[23] 1,929 PTA recipients transplanted between December 1966 and December 2011 were reviewed. Pancreas graft survival rates with tacrolimus-based maintenance therapy were 86% at 1 year posttransplant and

69% at 3 years posttransplant, and 94% and 84% respectively when tacrolimus was combined with sirolimus. Based on these reports our SPK transplant pancreas graft survival rates are comparable to what others have reported, but pancreas graft survival rate with PTA is still inferior to SPK transplantation.

Early pancreas graft rejection episodes were entirely T cell-mediated, and were more frequent in the PTA_{DD} group. At 3 months posttransplant, there was no difference in pancreas graft loss between the PTA_{DD} and SPK_{DD} groups, but at the end of follow-up more pancreas graft losses had occurred in the PTA_{DD} group, primarily due to rejection. Rejection episodes after three months posttransplant were more frequently vascular- and antibody-mediated and with signs of chronicity. Additionally, more patients had developed *de novo* donor-specific antibodies (DSAs)[24, 25] in the PTA_{DD} group. Many patients with pancreas graft rejection and graft loss had previous episodes of leukopenia caused by drugs and/or CMV infection, with subsequent periods of reduced immunosuppression which tended to increase their risk of rejection.

Although pancreas graft loss was equal between PTA_{DD} and SPK_{DD} recipients 3 months after transplantation, already at 1 year posttransplant more grafts were lost in the PTA_{DD} group, predominantly due to rejection. There are several potential explanations for this: insufficient immunosuppression in more immune competent nonuremic patients, the pancreas graft being a more immunogenic organ when transplanted alone, limited monitoring of early signs of pancreas graft rejection, poorer patient compliance, poorer follow-up from the local nephrologist and/or endocrinologist due to less experience with this new and relatively small patient group, leukopenia due to immunosuppression, or CMV infections leading to reduced immunosuppression and enhanced risk of rejection.

The strength of our study is that it is a single-center study with complete history and with no patient lost to follow-up. Limitations of the study include its retrospective and non-randomized design, relatively small patient sample, and short follow-up time. Additionally, extrapolation of our data to non-white individuals may not be appropriate.

In conclusion, despite a theoretically better surveillance of pancreas transplant rejection with pancreaticoduodenal anastomosis, pancreas graft survival rates in PTA are still inferior compared with SPK transplantation at our center. Rejection is the major cause of graft loss. The change of surgical technique for exocrine drainage from DJ to DD has not altered pancreas transplant outcomes for SPK transplants.

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Duality of interest

The authors declare that there is no duality of interest associated with this manuscript.

Author contributions

The authors JPL and RH contributed equally to this work and are co-first authors.

JPL and RH contributed to each of the following: (1) substantial contribution to conception and design, acquisition of data, and analysis and interpretation of data; (2) drafting the article, and (3) final approval of the version to be published. EN, AH, EMA, KG, HH, GK, AÅ, and TJ contributed to each of the following: (1) substantial contribution to conception and design, acquisition of data and/or analysis and interpretation of data; (2) drafting the article and/or revising it critically for important intellectual content and (3) final approval of the version to be published.

Figure legends

Figure 1 Kaplan-Meier estimates of probability of pancreas graft survival (%) in PTA_{DD} and SPK_{DD} recipients. The apparent difference in plots by transplant type is statistically significant by logrank analysis (p=0.049).

Table 1 Characteristics of recipients of DD (SPK_{DJ}), SPK_{DD}, PTA_{DD} or DD (SPK_{DD} and PTA_{DD}) transplants

Variable	DJ (SPK_{DJ}, *n*=167)	SPK_{DD} (*n*=62)	PTA_{DD} (*n*=55)	DD (SPK_{DD} + PTA_{DD}) (*n*=117)	DD versus DJ	PTA_{DD} versus SPK_{DD}
Recipient age, years	41.8±7.9	42.4±6.4	40.2±9.6	41.4±8.1	*p*=0.70	*p*=0.15
Male sex, *n* (%)	119 (71%)	45 (73%)	28 (51%)	73 (62%)	*p*=0.12	*p*=0.016
Duration of diabetes, years	28.7±8.3	29.7±7.3	25.9±9.8	27.9±8.7	*p*=0.44	*p*=0.018
History of						
Coronary artery disease, *n* (%)	49 (29%)	12 (19%)	3 (5%)	15 (13%)	*p*=0.001	*p*=0.025
Cerebrovascular disease, *n* (%)	13 (8%)	1 (2%)	2 (4%)	3 (3%)	*p*=0.060	*p*=0.60
Peripheral artery disease, *n* (%)	12 (7%)	0 (0%)	0 (0%)	0 (0%)	*p*=0.002	*p*=1.00
Duration of dialysis, years	1.1 (0.6, 1.6)	1.2 (0.8, 2.0)				
Preemptive transplantation, *n* (%)	48 (29%)	22 (35%)				
Donor age, years	32.7 (20.4, 44.8)	32.1 (22.1, 44.2)	28.8 (19.3, 45.9)	30.5 (21.2, 44.6)	*p*=0.89	*p*=0.53
Ischemia time, hours						
Pancreas graft	9.5 (7.4, 12.3)	8.8 (7.6, 10.8)	7.4 (6.1, 9.7)	8.1 (6.6, 10.6)	*p*=0.002	*p*=0.023
Kidney graft	10.1 (7.8, 12.8)	10.4 (9.0, 12.7)				
HLA- A, B, DR mismatch, *n* (%)						
0 to 2	19 (12%)	6 (10%)	6 (11%)	12 (10%)	*p*=0.77	*p*=0.83
3 to 4	114 (68%)	34 (55%)	32 (58%)	66 (57%)	*p*=0.041	*p*=0.72
5 to 6	34 (20%)	22 (35%)	17 (31%)	39 (33%)	*p*=0.014	*p*=0.60
Immunosuppression, *n* (%)						
Induction therapy						
Anti-thymocyte globulin	110 (66%)	62 (100%)	55 (100%)	117 (100%)	*p*<0.001	*p*=1.00
Maintenance therapy						
Prednisolone	167 (100%)	62 (100%)	55 (100%)	117 (100%)	*p*=1.00	*p*=1.00
Cyclosporine	34 (20%)	0 (0%)	0 (0%)	0 (0%)	*p*<0.001	*p*=1.00
Tacrolimus	133 (80%)	62 (100%)	55 (100%)	117 (100%)	*p*<0.001	*p*=1.00
Mycophenolate mofetil	167 (100%)	62 (100%)	55 (100%)	117 (100%)	*p*=1.00	*p*=1.00

Data are presented as mean ± *SD*, median (interquartile range) or frequencies (percent).

Preemptive transplantation denotes patients receiving a transplant before starting dialysis.

p values denote differences between PTA and SPK groups.

Table 2 Pancreas graft-related complications in the first three months posttransplant with DD or DJ surgical technique

Variable	DD[a] technique (*n*=117)	DJ[b] technique (*n*=167)	DD technique vs DJ technique
Patients with reoperation[c], *n* (%)	39 (33%)	53 (32%)	*p*=0.78
Complications leading to reoperation:			
Bleeding	21 (18%)	16 (10%)	*p*=0.039
Graft vein thrombosis	11 (9%)	10 (6%)	*p*=0.28
Infection	6 (5%)	15 (9%)	*p*=0.22
Anastomotic leak	6 (5%)	7 (4%)	*p*=0.71
Other[d]	18 (15%)	25 (15%)	*p*=0.92
Patients with wound infection	36 (31%)	44 (26%)	*p*=0.42
Pancreas graft loss, *n* (%)	12 (10%)	13 (8%)	*p*=0.47

Data are presented as frequencies (percent).

[a]Patients who received transplants with DD (55 PTA and 62 SPK recipients) between September 2012 and July 2016.

[b]Patients who received transplants with DJ (167 SPK recipients) between September 2012 and July 2016.

[c]The total number of recipients requiring reoperation is less than the sum of the corresponding complications leading to reoperation because there were patients who underwent more than one reoperation.

[d]Other causes of reoperation included wound revision or rupture, exploratory laparotomy for acute abdomen, or ileus.

p values denote differences between PTA_{DD} and SPK_{DD} groups.

Table 3 Pancreas graft rejection episodes in PTA_{DD} and SPK_{DD} transplants

Variable	PTA_{DD} (*n*=55)	SPK_{DD} (*n*=62)	PTA_{DD} versus SPK_{DD}
Patients with biopsy-verified pancreas graft rejection			
In the 3 first months posttransplant, *n* (%)	19 (35%)	7 (11%)	*p*=0.003
T cell-mediated rejection	19 (35%)	7 (11%)	*p*=0.003
Subclinical rejection[a]	9 (16%)	2 (3%)	*p*=0.015
After 3 months posttransplant, *n* (%)	13 (24%)	1 (2%)	*p*<0.001
T cell-mediated, vascular, or chronic rejection	12 (22%)	1 (2%)	*p*=0.001
Antibody-mediated rejection	1 (2%)	0 (0%)	*p*=0.47
De novo donor-specific antibodies (DSA), *n* (%)	10 (18%)	4 (6%)	*p*=0.051

Data are presented as frequencies (percent).

[a]Protocol biopsies were performed on schedule at 3 and 6 weeks and 1 year posttransplant and revealed subclinical rejection according to the Banff classification scheme.

p values denote differences between PTA_{DD} and SPK_{DD} groups.

Table 4 Pancreas graft loss an associated risk factors in PTA_{DD} recipients compared with SPK_{DD} recipients

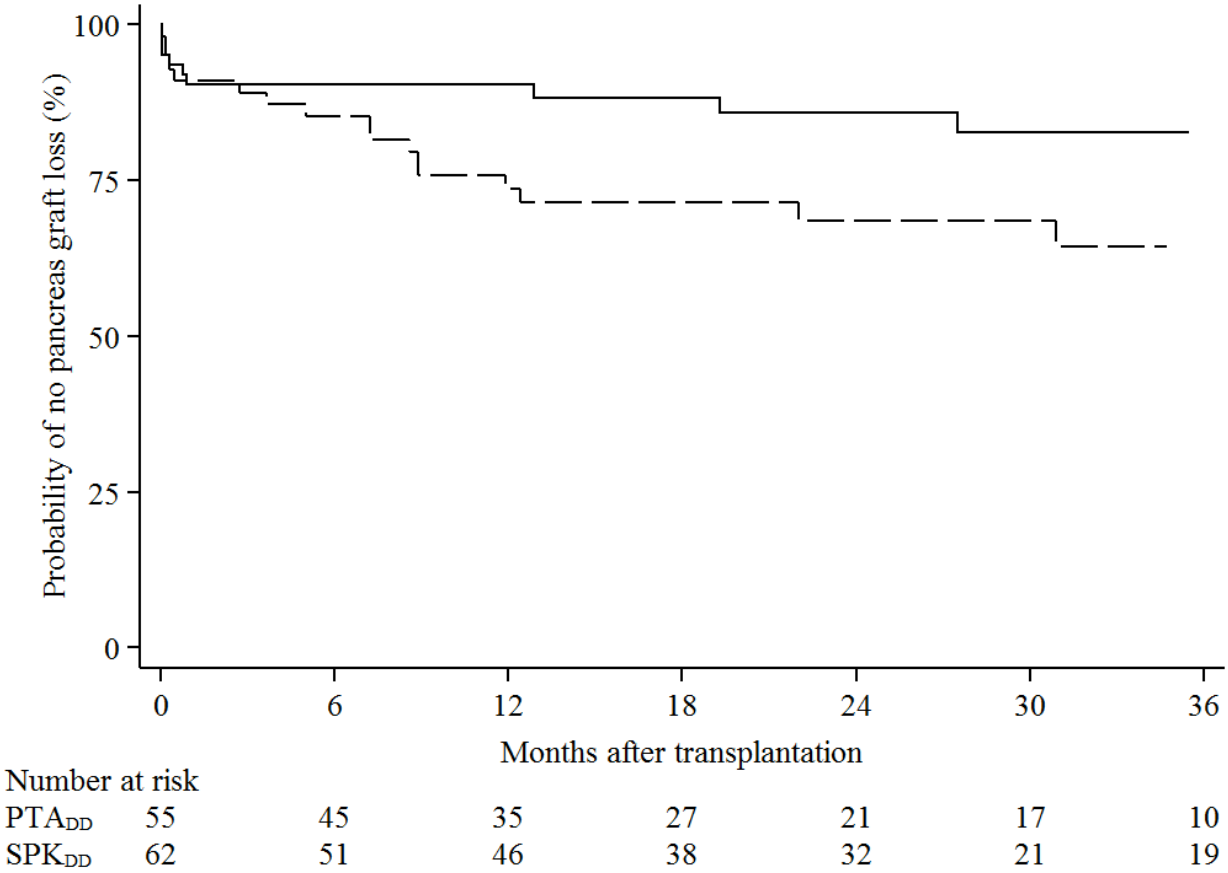
Variable	Unadjusted		
	HR	95% CI	*p* value
Transplant type			
PTA_{DD}	2.25	1.00, 5.05	0.049
SPK_{DD}		Reference	
Recipient age	0.97	0.92, 1.01	0.13
Male sex	0.57	0.26, 1.22	0.15
Diabetes duration	0.99	0.94, 1.03	0.59
Cardiovascular comorbidity	0.73	0.22, 2.45	0.61
Donor age	1.00	0.97, 1.02	0.85
Ischemia time	0.92	0.80, 1.07	0.29
HLA mismatch	1.22	0.86, 1.75	0.27

Table 5 Causes of pancreas graft loss and patient death according to transplant type: PTA_{DD} or SPK_{DD}

Variable	PTA_{DD} (*n*=55)	SPK_{DD} (*n*=62)	PTA_{DD} vs SPK_{DD}
Causes of pancreas graft loss			
Total pancreas graft losses, *n* (%)	17 (31%)	9 (15%)	*p*=0.033
Graft vein thrombosis	5 (9%)	4 (6%)	*p*=0.73
Rejection	11 (20%)	2 (3%)	*p*=0.004
Infection	0 (0%)	2 (3%)	*p*=0.50
Death	1 (2%)	1 (2%)	*p*=1.00
Causes of death			
Total deaths, *n* (%)	2 (4%)	1 (2%)	*p*=0.60
Infection	1 (2%)	0 (0%)	*p*=0.47
Bleeding	1 (2%)	0 (0%)	*p*=0.47
Cause of death uncertain/not determined	0 (0%)	1 (2%)	*p*=1.00

Data are presented as frequencies (percent).

Figure 1


100
75
50
25
0
Probability of no pancreas graft loss (%)
0
6
12
18
24
30
36
Months after transplantation
Number at risk
PTA$_{DD}$ 55 45 35 27 21 17 10
SPK$_{DD}$ 62 51 46 38 32 21 19

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