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Thirty Years of Pancreas Transplantation at Leiden University Medical Center: Long-Term Follow-Up in a Large Eurotransplant Center

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Background. An overview of 30 years of pancreas transplantation at a high volume center. Analysis of patient survival- and graft survival-associated risk factors. **Methods.** All pancreas transplantations performed in our center from January 1, 1984, till December 31, 2012, were evaluated. Covariates influencing pancreas graft survival were analyzed using both univariate and multivariate analysis and Kaplan-Meier analysis. **Results.** In the study period, 349 pancreas transplantations were performed. With the introduction of modern induction therapy in 1999, 5-year patient survival improved to 92.0% ($P = 0.003$). Five-year pancreas graft survival improved to 80.3% ($P = 0.026$). Pancreas graft survival was influenced by left or right donor kidney, transplant type, local origin of procurement team, pancreas cold ischemia time, recipient cerebrovascular disease. Pancreas donor risk index increased to 1.39 over the years and pancreas donor risk index 1.24 or higher is a risk factor for graft survival ($P = 0.007$). **Conclusions.** This study has shown excellent results in patient and pancreas graft survivals after 30 years of pancreas transplantation in a high volume center. Different donor, transplant, and recipient related risk factors influence pancreas graft survival. Even with higher risk pancreas donors, good results can be achieved.

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Simultaneous pancreas and kidney (SPK) transplantation is currently the first choice of treatment for patients with type 1 diabetes mellitus (T1DM) and related end-stage renal disease. Pancreas transplant alone (PTA) transplantation can be performed in case of T1DM with preserved kidney function in case of hypoglycemic unawareness.¹

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The first pancreas transplantation in the Netherlands was performed at the Leiden University Medical Center (LUMC) in 1984.² Over the past 30 years, LUMC has become one of the largest pancreas transplantation centers within the Eurotransplant region.³

In the current literature, there are several publications reporting on long-term results after pancreas transplantation. The first large series were described by Sutherland et al⁴ in 2001. More recently, Sollinger et al⁵ also reported on 22 years of follow-up of 1000 pancreas transplantations in Wisconsin, followed by more recent reports describing risk factors and long-term experiences.^{6–9} The largest European series is from Innsbruck, Austria, reporting on results of 509 consecutive pancreas transplantations with long-term follow-up.¹⁰

However, when comparing results from different transplant centers, it appears that no standard definition of pancreas graft survival is being used, making adequate comparison difficult. In 2008, the Pancreas Transplant Committee (PTC) of the Organ Procurement Transplantation Network (OPTN) pled for 1 definition of pancreas graft function and failure, pointing out the importance of a unified definition, which should be used worldwide.¹¹

In most studies, several donor-, transplant-, and recipient-related risk factors are believed to influence outcome after transplantation. The pancreas donor risk index (PDRI) was constructed by Axelrod and allowed for structural assessment of donor quality and prediction of 1 year graft survival after pancreas transplantation.⁸

TABLE 1.
Donor and transplant factors and their influence in univariate analyses on pancreas graft survival

Donor Factor	N (%)	P ^a	χ ²
Age category		0.006	12.391
<30 ^b	134 (38)		
30-39	78 (22)		
40-50	128 (37)		
>50	9 (3)		
Sex		0.48	0.507
Male	171 (49)		
Female	178 (51)		
Cause of death		0.37	3.143
Trauma	129 (37)		
CVA	199 (57)		
Anoxia	9 (3)		
Other	12 (3)		
Diabetes mellitus	0 (0)	n/a	
Hypertension (yes)	26 (7)	0.11	2.559
Malignancy (yes)	1 (0.3)	0.589	0.292
Drug use (yes)	8 (2)	0.51	0.426
Alcohol use (yes)	7 (2)	0.08	2.984
HCVAb pos	0 (0)	n/a	
HBcAb pos	2 (1)	0.342	2.143
HIVAb pos	0 (0)	n/a	
CMV IgM/IgG pos	130 (37)	0.76	0.092
Cardiac arrest (yes) ^b	40 (12)	0.019	5.508
Hypotensive period (yes) ^c	123 (35)	0.56	0.342
Use of vasopressors (yes)	277 (79)	0.52	0.405
DCDD (yes)	6 (2)	0.86	0.031
	Median (range)	P ^d	
Age, y	36 (10-57)	0.006	
BMI	23 (14-35)	0.81	
Serum sodium, mmol/L	144 (123-175)	0.58	
Serum creatinine, μmol/L	70 (25-190)	0.3	
Serum lipase, U/L	20 (7-332)	0.61	
Serum amylase, U/L	80 (7-1756)	0.029	
ICU stay, d	2 (1-33)	0.058	
Transplant factor	N (%)	P^a	χ²
Allocation		0.66	0.837
Local	48 (14)		
Regional	234 (67)		
Extra-regional	67 (19)		
Procurement team		<0.001	17.441
Local ^b	60 (17)		
Nonlocal	240 (69)		
Unknown	49 (14)		
Transplantation type		<0.001	15.355
SPK ^b	325 (93)		
PAK	21 (6)		
PTA	3 (1)		
Donor kidney		<0.001	32.951
No kidney	24 (7)		
Left ^b	276 (79)		
Right	49 (14)		
Perfusion fluid		<0.001	27.999
UW ^b	312 (89)		
HTK	25 (7)		
Other	12 (3)		

TABLE 1. (Continued)

Transplant Factor	N (%)	P ^a	χ ²
	Median (range)	P ^d	
Cold ischemia time, h	12 (3-20)	0.005	
PDRI	1.24 (0.68-2.31)	0.25	
P-PASS	16 (9-22)	0.74	

^a Univariate Kaplan-Meier analysis (log rank Mantel-Cox).^b Favorable factor in univariate analysis.^c Defined as: systolic pressure <80 mm Hg, for at least 10 minutes.^d Univariate Cox-regression analysis.

n/a, not applicable; HTK, histidine-tryptophan-ketoglutarate; ICU, intensive care unit; IgG, immunoglobulin G; IgM, immunoglobulin M.

Furthermore, center volume may also play a role in the outcome. In 2004, Mandal has shown that low volume pancreas transplantation centers (<10 transplantations/year) have poorer outcome in graft survival compared to medium (10–20 transplantations/year) or high (>21 transplantations/year) volume centers.¹²

The objective of this study is to describe the results, measured in patient and pancreas graft survivals, of 30 years of pancreas transplantation in recipients with T1DM and possible related complications at the LUMC and to analyze donor-, transplant-, and recipient-related risk factors influencing pancreas graft survival. Also, we hope to show that with relatively lower quality donors, indicated by high PDRI, we are able to achieve good outcome in our high volume center.

METHODS

This study is a retrospective database analysis of all consecutive pancreas transplantations performed at the LUMC, from the first pancreas transplantation on May 14, 1984, till December 31, 2012. For all 349 transplantations, follow-up was collected until October 31, 2013.

Data Collection

All donor, transplant (Table 1), and recipient (Table 2) characteristics were systematically registered. Follow-up data were recorded to analyze outcome after pancreas transplantation, including; Hba1c levels, insulin use, c-peptide, fasting plasma glucose, patient death date and cause, failure date, failure cause, number of treated rejection episodes, date of transplantectomy, date last patient contact.

Postoperative Care

From March 1999, patients received any form of modern induction therapy, either interleukin (IL)-II receptor antagonist or antithymocyte globulin (ATG). Currently, first started in December 2007, induction therapy consists of administration of anti-CD52 monoclonal antibody (alemtuzumab). Before 1999, patients received either anti-CD3 antibody (OKT3) or no induction therapy. As maintenance therapy, recipients are currently administered combination therapy, consisting of tacrolimus and mycophenolate mofetil. Until 1996, recipients received cyclosporine, azathioprine, and prednisone. From that time, until 2002, when cyclosporine was replaced with tacrolimus, patients received mycophenolate mofetil instead of azathioprine. Starting in 2008, routine administration of prednisone was ceased. Patients currently

TABLE 2.
Recipient factors and their influence in univariate analyses on pancreas graft survival

Recipient Factor	N (%)	<i>P</i> ^a	χ^2
Age category		0.59	1.915
<40	156 (45)		
40-49	142 (41)		
50-59	49 (14)		
≥60	2 (0.6)		
Sex		0.42	0.652
Male	210 (60)		
Female	139 (40)		
Type of dialysis		0.835	0.361
No dialysis (preemptive transplant)	144 (41)		
Haemodialysis	93 (27)		
Peritoneal dialysis	112 (32)		
Repeated transplantation		0.4	0.715
First transplant	330 (95)		
Retransplant	19 (5)		
Thromboembolic event	4 (1)	0.253	1.307
Cerebrovascular disease	21 (6)	0.011	6.418
Coronary artery disease	54 (16)	0.591	0.289
Coronary artery bypass grafting	11 (3)	0.557	0.345
Percutaneous transluminal coronary angioplasty	23 (7)	0.382	0.763
Cytomegalovirus mismatch		0.121	2.41
No mismatch (D-/R-)	269 (77)		
D+/R-	72 (21)		
Unknown	8 (2)		
Modern induction therapy		0.026	4.939
Yes ^b	237 (68)		
No	112 (32)		
Primary drainage		0.55	0.367
Bowel	91 (26)		
Bladder	256 (73)		
Unknown	2 (1)		
	Median (range)	<i>P</i> ^c	
Age	42 (23-64)	0.99	
BMI	24 (17-33)	0.2	
Time on waiting list	1.1 (0-10)	0.32	
Time since DM I, y	27 (12-48)	0.51	
Time since first dialysis treatment, y	0.69 (0-8)	0.3	
Total HLA mismatches	4 (0-6)	0.86	

^a Univariate Kaplan-Meier analysis (log rank Mantel-Cox).

^b Favorable factor in univariate analysis.

^c Univariate Cox-regression analysis.

receive low dose (2850 IE) low molecular weight heparin in a twice-daily regime as graft thrombosis prophylaxis. This regime was started in 2008. Before that, regular antithrombotic therapy consisted of the same dose, administered once daily. On discovery of partial graft thrombosis, patients are prescribed vitamin K antagonist for a duration of at least 3 months. Routine computed tomography imaging is performed between the 4th and 7th day after transplantation, depending on renal (graft) function.

Analysis

Outcome was characterized by patient survival and graft survival. Patient death with a functioning graft was not considered as graft failure (death-censored graft survival).

The moment of pancreas graft failure was determined using the “uniform definition of graft function/failure for whole pancreas and islet transplant” by the OPTN PTC as a guideline¹¹ (see Table S1, SDC, <http://links.lww.com/TP/B112>). Endocrine pancreatic function was subdivided in grades A to E, using HbA1c and use of insulin as markers for pancreatic graft function. In this study and in particular, when performing univariate analysis, the OPTN definition of graft failure was used as a guideline, in which allograft function classified as grade A and B were considered as functioning grafts, and grafts with grades C, D, and E were considered as failed allografts. According to this definition, persistent HbA1c greater than 6.3% and/or insulin was classified as grade C (insulin use less than 50% of pretransplant dose) or grade D (insulin use more than 50% of pretransplant dose), and persistent HbA1c 7.0% or higher was classified as grade E. Standard OGTT was not performed in analyzing graft function, for this was not required for classification of graft failure using the OPTN PTC definition. Graft thrombosis was defined as the presence of intravascular thrombus, proven after removal of the pancreas graft in case of complete thrombosis and, in case of partial thrombosis, presence of partial intravascular thrombus. Technical failure (TF) consists of pancreas graft thrombosis, infections, graft pancreatitis, leakage, and bleeding.¹³ Early graft failure was defined as graft failure within 90 days after transplantation.⁷

To compare groups based on outcome, we used the start of modern immunosuppressive induction therapy (ATG/IL-II receptor antagonist/alemtuzumab) in March 1999 as a dividing point in the analysis of graft survival. The start of immunosuppressive therapy as induction therapy was a landmark in transplantation medicine, with marked improvement of long-term results in pancreas transplantation.

Statistical Analysis

For statistical survival analysis, Kaplan-Meier and Cox regression models were performed using SPSS version 20.0. Significant factors in univariate analysis will be entered into a multivariate model. Other factors will be added to the model using stepwise forward selection. A *P* value less than 0.05 was considered significant for factors in both univariate and multivariate analyses.

RESULTS

Donor and transplant characteristics are shown in Table 1. In the study period, a total of 349 consecutive pancreas transplantations were performed at the LUMC, of which 325 (93.1%) were simultaneous pancreas kidney, 21 (6.0%) were pancreas after kidney, and 3 (0.9%) were PTA. Mean follow-up was 8.0 years (0–24.2 years). Recipient characteristics are shown in Table 2. Primary indication for transplantation was T1DM (99.7%) with (96.8%) or without (2.9%) renal complications. In total, 19 retransplantations (5.4%) were performed, all were included in the analysis.

In univariate analysis, death-censored pancreas graft survival was influenced by the following donor- and transplantation-related risk factors: donor age (*P* = 0.006), donor alcohol use (*P* = 0.08), serum amylase (*P* = 0.029), origin of procurement team (*P* < 0.001), transplantation type (*P* < 0.001), donor kidney side (*P* < 0.001), perfusion fluid (*P* < 0.001), and cold ischemia time (*P* = 0.005). Donor

cardiac arrest had a protective effect on pancreas graft survival ($P = 0.019$), not on kidney graft survival ($P = 0.823$). Retransplantation was found not to be a significant covariate for pancreas graft survival in univariate analysis ($P = 0.40$). Recipient-related risk factors influencing pancreas graft survival were: cerebrovascular disease ($P = 0.011$) and induction therapy ($P = 0.026$). Results of the univariate analyses of death-censored OPTN-defined graft survival of all donor, transplant, and recipient factors are also reported in Tables 1 and 2.

In 256 (73%) patients, bladder drainage was initial drainage method. Of these patients, 171 (66.7%) were converted to enteric drainage. Median (25th–75th percentile) interval between transplantation and conversion was 339 (173–772) days. Recipients who were bladder drained and not converted to bowel drainage had significantly worse pancreas graft survival ($P < 0.001$).

Overall patient survival at 1, 5, and 10 years was 95.7%, 86.9%, and 74.6%, respectively. One-, 5-, and 10-year overall pancreas graft survival was: 83.6%, 76.4%, and 70.8%, respectively, using the OPTN definition. Death-censored pancreas graft survival was 85.1%, 78.2%, and 72.8% at 1, 5 and 10 years in the SPK subgroup. For pancreas after kidney, this was 66.0% and 55.0%, longest follow-up before pancreas graft failure was 8.9 years. Longest death-censored graft survival was 3.2 years for PTA grafts, with 1 year graft survival at 33.0%.

When pancreas graft failure occurred ($n = 99$), in the majority of cases, this was caused by graft thrombosis (35.4%) or rejection (20.2%). Other causes of graft failure were atrophy or exhaustion of the graft (6.1%), infection (5.1%), and bleeding (4.0%). Early pancreas graft failure due to TF occurred in 33 cases, 29 of which were due to graft thrombosis. From January 1, 2001, 43 cases of partial graft thrombosis occurred in 213 patients (20.2%). From January 1, 2008, the incidence of graft failure due to complete thrombosis was 9.3%.

Kidney graft survival at 1, 5, and 10 years was 91.6%, 87.9%, and 81.6%. Kidney graft survival was significantly better when left kidney was donated, compared to when right kidney was donated: 94.4% versus 75.7% at 1 year follow-up ($P < 0.001$). Main reasons for right kidney graft loss were rejection (33.3%) or patient death (33.3%). Right kidney graft loss due to thrombosis occurred in 1 case.

Clinical Outcome in Different Periods of Induction Therapy

Long-term results of the transplantations performed in the LUMC are shown in Figure 1, divided by transplant period (using the start of modern induction therapy in March 1999 as a dividing point). Two hundred thirty-seven (67.9%) recipients received modern induction therapy. Recipients in the induction therapy group were older ($P < 0.001$), had higher body mass index ($P = 0.004$), had been on the waiting list longer ($P < 0.001$), and had longer duration of diabetes mellitus ($P < 0.001$). They received pancreas grafts from higher body mass index donors ($P = 0.025$) and higher Pancreas-Preprocurement Allocation Suitability Score donors ($P < 0.001$). Donors also had higher creatinine levels ($P = 0.013$), had had less hypotensive periods ($P = 0.003$), but had had more cardiac arrests ($P = 0.001$). They received more regionally allocated grafts ($P = 0.001$), but less local

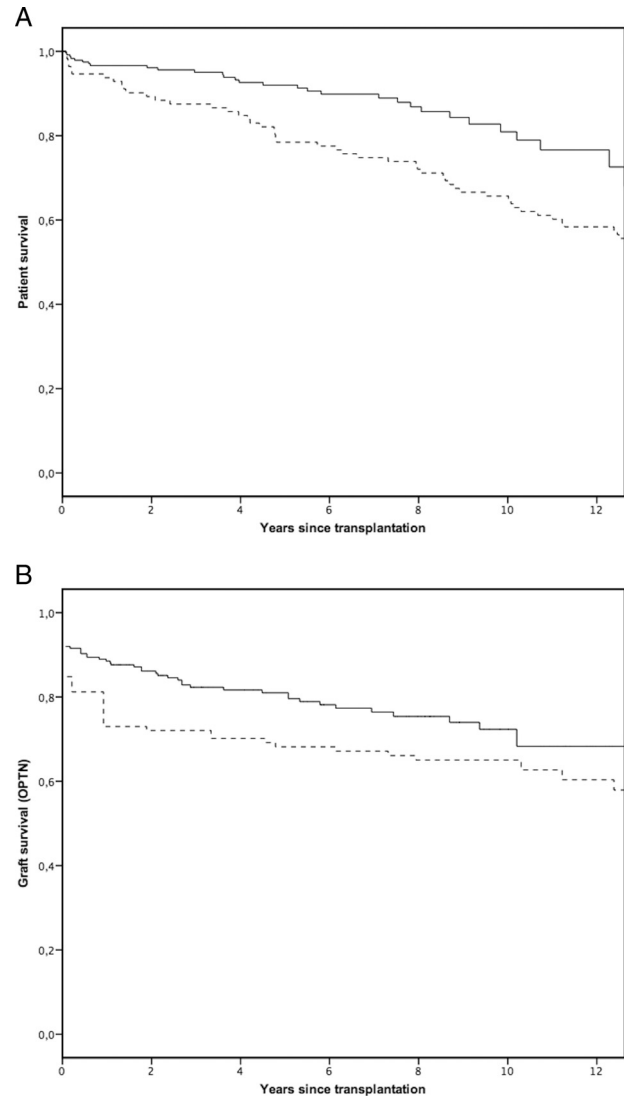


FIGURE 1. A, Kaplan-Meier survival curves of patient survival divided by use of induction therapy ($P = 0.003$). B, Kaplan-Meier survival curves of OPTN-defined death censored graft survival divided by use of induction therapy ($P = 0.026$).

and extraregional allocated grafts ($P = 0.001$). Also, they received more grafts procured by the local team ($P < 0.001$). In the modern era, more pancreas grafts were transplanted without kidney, but less with right kidney ($P < 0.001$). Additionally, 20 (8.4%) were PAK in the modern era versus 1 (0.9%) in the historic group ($P = 0.022$). All recipients in the historic group were bladder drained, whereas 91 (38.4%) in the modern group were primarily enteric drained ($P < 0.001$).

Patient survival (Figure 1A) at 1-year, 5-year, and 10-year follow-up was, respectively, 93.8%, 78.4%, and 65.7% for the historic group and 96.6%, 92.0%, and 80.9% for modern induction therapy group and was significantly better in the more recent period ($P = 0.003$). Death-censored pancreas graft survival (Figure 1B) at 1, 5, and 10 years was 73.0%, 68.2%, and 65.0%, respectively, in the historic group, and 88.5%, 80.3%, and 72.3%, respectively, in the modern induction therapy group. These results were also significantly better in the modern era ($P = 0.026$).

Different regimes of induction therapy led to following 1-year, 5-year, and 10-year pancreas graft survival rates: 75.6%, 69.5%, and 66.8% without induction therapy; 68.0%, 64.0%, and 64.0% for OKT3; 89.1%, 83.5%, and 77.4% for IL-II receptor antagonists; 85.1%, 78.2%, and 67.1% for ATG; and 91.2% for alemtuzumab. Long-term follow-up (5 years and 10 years) of alemtuzumab induction therapy is not yet available.

In the first 6 months after transplantation, kidney biopsy-proven acute rejection in SPK transplantation recipients occurred in 85.9% of recipients without induction therapy ($n = 91$), 82.6% with OKT3 ($n = 25$), 52.8% with IL-II receptor antagonists ($n = 37$), 42.6% with ATG ($n = 108$), and 11.4% with alemtuzumab ($n = 81$) ($P < 0.001$). Data on induction therapy were missing for 6 patients; 1 patient received both IL-II receptor antagonist and ATG.

Multivariate Analysis

Stratified by induction therapy, in a multivariate Cox-regression analysis, significant factors from univariate analysis were entered. Other factors were entered, and the model was fitted using forward selection. Significant factors of this multivariate analysis were: donor left versus right kidney: hazards ratio (HR), 3.18 (95% confidence interval [95% CI], 1.49–6.76, $P = 0.003$); SPK versus PAK/PTA: HR, 3.68 (95% CI, 1.65–8.19; $P = 0.001$); local origin of procurement center: HR, 2.72 (95% CI, 1.11–6.68, $P = 0.029$); pancreas cold ischemia time: HR, 0.9 (95% CI, 0.81–0.99; $P = 0.033$); recipient cerebrovascular disease: HR, 3.52 (1.41–8.78, $P = 0.002$) for OPTN-defined death-censored pancreas graft survival (Table 3). Primary enteric or bladder drainage was borderline associated with pancreas graft survival in favor of bladder drainage: HR, 3.81 ($P = 0.051$).

TABLE 3.

Multivariate analysis^a of risk factors influencing pancreas graft survival

Factor	HR	95% CI	P
Donor kidney side			
Left kidney	ref.		
Right kidney	3.18	1.49-6.76	0.003
No kidney ^b	n/a		n/a
Transplant type			
SPK	ref.		
PTA/PAK	3.68	1.65-8.19	0.001
Procurement center			
Local	ref.		
Nonlocal	2.72	1.11-6.68	0.029
Pancreas cold ischemia time	0.90	0.81-0.99	0.033
Recipient cerebrovascular disease			
No	ref.		
Yes	3.52	1.41-8.78	0.007

^a Forward selection stepwise multivariate analysis using OPTN definition for graft survival.

^b Unable to calculate HR due to stratum effect.

Donor Quality and Graft Survival

Median PDRI was 1.24. Quality of donors decreased since the start of the transplant program, indicated by an increase of median PDRI. The PDRI was calculated for each period: 1984 to 1991: PDRI, 1.14 (0.68–2.20); 1992 to 1998: PDRI, 1.20 (0.73–2.01); 1999 to 2005: PDRI, 1.25 (0.72–2.31); 2006 to 2012: PDRI, 1.39 (0.70–2.21). The PDRI of 5 recipients could not be calculated. The PDRI was not associated with pancreas graft survival in univariate analysis, when analyzed as a continuous variable ($P = 0.25$). However, PRDI 1.24 or higher donor grafts had significant poorer outcome compared to PDRI less than 1.24: 71.2% versus 83.8% graft survival at 5 years follow-up ($P = 0.007$). Starting in 2011, so far, 6 recipients were transplanted using grafts from donation after circulatory determination of death (DCDD) donors.¹⁴ With these numbers, DCDD did not influence graft survival ($P = 0.86$).

DISCUSSION

This article is an overview of 30 years of pancreas transplantation at our center.

Results, measured in patient and pancreas graft survival as defined by the OPTN, have improved over the last decade. As shown in this study, survival, especially 1-year graft survival, has significantly improved since the introduction of modern regimes of pre-transplantation induction therapy. Improvement in surgical technique and maintenance immunosuppression therapy, however, may also have contributed to improved outcome. Furthermore, clinical experience with pancreas transplantation has improved throughout the center over the course of these 30 years. Incidence of kidney biopsy-proven acute rejection has also declined with introduction of modern induction therapy.

Several limitations apply to the study. It concerns single-center results, albeit from one of the larger pancreas transplantation centers in Europe. Because of the retrospective nature of our study, some selected data are incomplete. Because routine follow-up in our center does not include measurement of plasma c-peptide, values were only used for the determination of graft failure when present.

We have shown satisfying results in concordance with other large transplant centers and databases: Ollinger et al¹⁰ report a 94.3% patient survival and 81.5% pancreas graft survival (exogenous insulin dependent) at 5-year follow up in the last decade in Innsbruck, Austria. The largest series of pancreas transplantations described is from Minnesota and reports 1-year patient survival rates between 93.8% and 96.2% and 1-year death censored pancreas graft survival between 78.6% and 80.7% for local or imported allografts between 1998 and 2008 ($P > 0.05$).⁶ Vinkers reported 1-year graft survival of 82% for recipients of P-PASS less than 17 donor allografts and 64% for recipients of P-PASS of 17 or higher donor allografts in a Eurotransplant cohort. Muthusamy et al¹⁵ compared DBD donors to DCDD donors in the United Kingdom and reported 88% versus 87% ($P = 0.9$) 1-year pancreas graft survival, defined as insulin administration dependency.

Discussion still remains about the value of predictive models. We have shown that median PDRI is not associated with pancreas graft survival in this series. The authors believe

that the increase of PDRI over time, together with simultaneous increase of pancreas graft survival over time, is responsible for this absent relationship. The continuous increase in PDRI over the years has not led to inferior outcome. On the contrary, outcome is still improving, whereas, from 2006 till 2012, median donor PDRI was 1.39, equally to an United Network for Organ Sharing donation after cardiac determination of death donor.⁸ In 2012, Leiden University Medical Center was the second largest whole organ pancreas transplantation center in the Eurotransplant region.¹⁶ Combining both findings might implicate that high-volume transplant centers might be able to compensate for inferior donor quality and that, currently, PDRI might not yet be reliable enough to predict outcome in the European cohort. As we have shown earlier, liver donor quality, measured in DRI, is inferior in the European region, as compared to the United States.¹⁷ Additional studies from own center show a relationship between pancreas graft survival and PDRI, when using median PDRI (1.24) as a cutoff value in multivariate analysis (unpublished data).

Multivariate analyses revealed left or right donor kidney, transplant type, local origin of procurement center, pancreas cold ischemia time, and recipient cerebrovascular disease as individual determinants of OPTN-defined death-censored pancreas graft survival. Interestingly, primary bladder drainage was borderline favorable for graft survival after multivariate analysis, even with nonconverted patients, which have inferior outcome, included in this group. This result is similar to results found by Finger et al⁷ when composing a risk model for predicting TF. The authors feel that the 2-step approach, initial bladder drainage followed by conversion to enteric drainage, is a suitable and feasible drainage method for high-risk recipients, for example, with repeated peritonitis or high-risk donors or grafts.^{18,19} However, risks of repeated surgery will have to be measured against graft survival benefit, as was stated earlier by Sollinger et al⁵ who reported no difference in outcome for both techniques. Even though the use of UW as perfusion fluid was a protective factor in univariate analysis, this effect did not remain significant after multivariate analysis. It has previously been shown that the use of histidine-tryptophan-ketoglutarate bears an increased risk of graft failure in pancreas transplantation.²⁰ The lack of relationship in this series might be due to the large amount of transplantations that were conducted using UW solution as perfusate. The use of DCDD pancreas did not influence graft survival in this series, and is, as we have shown earlier, a feasible option to expand the donor pool.¹⁴ After multivariate analysis, donor cardiac arrest was no longer a protective factor for pancreas graft survival. Also, donor cardiac arrest did not influence kidney graft survival. The authors believe that, in this study, the effect could be explained by small sample size, even though reports are published where ischemic preconditioning might have a beneficial effect on outcome.²¹ Pancreas graft thrombosis is still an important complication after pancreas transplantation, even with modern regimes of anticoagulation therapy.

All pancreas transplantations (SPK, PTA, and PAK) were analyzed together. It was previously shown that pooled results provide useful data for reporting on program-specific outcome.²² Results might even be better in patient and graft survivals if only SPK transplantations were analyzed because

it is known that both other categories are associated with poorer outcome.¹⁰

In our opinion, preemptive SPK transplantation is a feasible option in recipients suffering from preterminal renal disease. This is indicated by the high number of preemptive transplantations that was carried out at our center. Even though it did not influence graft survival, preventing recipients from becoming dialysis-dependent, provides improved quality of life in the pretransplantation phase. Interestingly, next to studies demonstrating superior outcome in kidney graft survival, depending on donation of left or right kidney,²³ this study demonstrates that a donated left or right kidney significantly influences pancreas graft survival. This could be explained, however, by the large difference in 1-year kidney graft survival of left and right donated kidneys. Early kidney graft loss results in a pancreas-alone state, probably with comparable results as initial PTA transplantations. Right renal vein length and possible fragility might bear an increased thrombosis risk; however, in this study, this does not appear to be the reason for inferior kidney graft survival of the right kidney. The authors do not have an explanation for high rejection rates with donated right kidneys.

Pancreas graft survival in this study was death censored and measured using the OPTN PTC definition as guideline, where death with functioning graft was not considered graft failure. Using this definition allows for objective measurement of graft failure, using HbA1c, fasting plasma glucose, and casual plasma glucose, rather than measuring graft failure using restart of insulin therapy definition, for this, is, in our opinion, a more subjective way and also, predominantly, physician dependent.

When using the restart of any exogenous insulin after the directly postoperative period as a measure for pancreas graft survival or graft failure, results are different. Insulin-defined graft survival is different than OPTN-defined graft survival, with a difference of almost 6% at 10 year follow-up. Comparing both definitions of graft survival and (re)initiating, the discussion on the definition of graft survival will be subject of further studies. Without a general consensus on the definition of graft survival, future studies comparing graft survival in different cohorts would be difficult. Future studies will also have to be evaluated for their definitions of pancreas graft survival.

Even though center size was not investigated in this study per se, this study still shows that in a large center, a good result can be achieved without the use of perfect donor grafts. It is our opinion that future studies will have to point out the value of center size on the outcome after transplantation, not only in the field of pancreas transplantation. This opinion was recently shared by Nijboer et al.²⁴ Also, this study has shown better result with grafts procured by the local team. This might be because our center performs pancreas transplantation itself, and this may lead to higher quality of the transplanted graft and thus improved graft survival.²⁵ In this perspective, the authors believe that early graft failure should be included in graft survival analysis, especially in pancreas transplantation because surgical complications are still an important risk factor in pancreas transplantation.

In conclusion, long-term patient and pancreas graft survival in this cohort was excellent and at least equal to results in other large centers. However, the exact nature and interpretation of the findings are highly dependent on which

definition for pancreas graft success or failure is used. Higher volume transplant centers might be able to achieve the same outcome in graft survival with higher-risk donors.

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