Transplant International

Transplant International ISSN 0934-0874

ORIGINAL ARTICLE

Long-term results of pancreas transplantation in patients older than 50 years

Peter Schenker,[1] Oliver Vonend,[2] Bernd Krüger,[3] Thomas Klein,[3] Stefan Michalski,[1] Andreas Wunsch,[1] Bernhard K. Krämer[4] and Richard Viebahn[1]

1 Department of Surgery, Knappschafts-Hospital, Ruhr-University Bochum, Bochum, Germany
2 Department of Nephrology, Heinrich-Heine-University, Düsseldorf, Germany
3 Department of Medicine I, Marienhospital Herne, Ruhr-University Bochum, Bochum, Germany
4 V. Department of Medicine, University Medical Center Mannheim, University of Heidelberg, Mannheim, Germany

Keywords
age, older recipients, outcome, pancreas transplantation, simultaneous pancreas–kidney transplantation.

Correspondence
Dr. med. Peter Schenker, Department of Surgery, Knappschafts-Hospital, Ruhr-University Bochum, In der Schornau 23-25, 44892 Bochum, Germany. Tel.: +49 234 299 3201; fax: +49 234 299 3209; e-mail: peter.schenker@rub.de

Received: 24 April 2010
Revision requested: 31 May 2010
Accepted: 13 September 2010
Published online: 13 October 2010

doi:10.1111/j.1432-2277.2010.01172.x

Summary

Aging of the population and improvements in diabetes therapy have led to an increased number of older pancreas transplant candidates. The aim of our retrospective study was to evaluate pancreas transplantation (PT) outcomes in patients ≥50 years, as limited data exist in these patients. We analyzed 398 consecutive pancreas transplant patients from June 1994 to June 2009 for different outcomes (patient/graft survival, rejection rate, and surgical complications) between the age groups ≥50 years ($n = 69$) and <50 years ($n = 329$). Donor and recipient characteristics were similar except for recipient age (54.0 vs. 38.8 years), BMI (24.6 vs. 22.9 kg/m^2), and duration of diabetes mellitus (36.0 vs. 27.7 years). One-, 5-, and 10-year patient and graft (kidney/pancreas) survival were not significantly different between the groups with patient survival rates reaching 84% and pancreas graft survival up to 67% after 10 years. Surgical complications such as relaparotomy rate (34% vs. 33%) or pancreas graft thrombosis (14% vs. 11%) as well as 1-year rejection rates (35% vs. 31%) were not significantly different. PT in selected patients aged ≥50 years resulted in survival comparable with that of younger patients. In conclusion, advanced age should no longer be considered as an exclusion criterion for PT. However, good medical assessment and careful patient selection are necessary.

Introduction

Simultaneous pancreas–kidney transplantation (SPK) is a well-established treatment for patients with insulin-dependent diabetes mellitus and end-stage renal disease. On the contrary, pancreas transplantation (PT) is associated with the highest surgical morbidity of all abdominal solid organ transplantations [1–3].

The aging of the general population has led to increased numbers of aged pancreas transplant recipients and more diabetic patients reach older age in better health than in previous generations [4–6]. Consequently, more elderly diabetic patients might be considered for PT.

Improved patient and allograft survival after PT reflects advances in surgical techniques, anesthesia, critical care, and infection control, as well as the development of targeted, potent immunosuppressants [1]. This success has expanded the pool of transplant recipients to include persons previously considered ineligible because of advanced age and comorbid conditions.

At our center, PT was initially restricted to patients younger than 50 years of age. In the Eurotransplant region, the previously accepted maximum recipient age ranged from 45 to 50 years and has been increased to 55 years in some centers in recent years. However, an international consensus is still missing.

The feasibility of kidney, liver, or heart transplantation in older recipients, with the use of potent immunosuppressive therapy, has been shown in several reports over the last decade, but only limited data are available for older pancreas transplant recipients [7–11]. The aim of this retrospective study was to determine whether pancreas transplant recipients aged 50 years and older achieve the same benefit after PT compared with those younger than 50 years.

Patients and methods

Between June 1994 and June 2009, 398 consecutive adult patients underwent PT at our center; 374 of them were SPK, 19 were pancreas after kidney transplants (PAK) and five were pancreas transplantation alone (PTA). All patients were C-peptide negative type 1 diabetics. Patients were divided into two groups according to the recipient's age at the time of transplantation. Sixty-nine (17% of total) patients were ≥50 years old (mean age 54.0 ± 3.4 years; range 50–65 years), and 329 patients were between 22 and 49 years (mean age 38.8 ± 5.9 years).

Outcome was analyzed for short- and long-term graft and patient survival as well as rejection rates and surgical complications (e.g. relaparotomy, vascular graft thrombosis) for both groups. Rejection episodes were diagnosed by renal biopsy (75%) or were defined by an increase in serum creatinine level by 30% or more from baseline, not attributable to other causes, with subsequent return to baseline after treatment. Treatment strategies were related to severity of acute rejection episodes, i.e. mild to moderate rejection episodes were treated with a steroid bolus for 3 days, whereas severe rejection episodes were treated with a 7- to 10-day course of OKT3 or antithymocyte globulin (ATG), rituximab and/or plasmapheresis. Pancreas graft biopsies were performed only in five cases.

Relaparotomy was defined as any operative procedure involving the intraperitoneal or retroperitoneal space during the first 3 months after transplantation or during the initial hospital stay, if it exceeded 3 months.

Preprocurement pancreas suitability score (P-PASS) was calculated when complete donor data were available. P-PASS is based on the following factors: age, body mass index, intensive care unit stay, pre-existing cardiac arrest, serum sodium level, serum amylase or lipase level, and the use of vasopressive agents [12].

Transplantation technique

Whole pancreas organs were used in 396 patients. Split PT was performed in two patients. A total of 349 pancreas grafts had exocrine enteric drainage, and bladder drainage was used in 49 patients. The venous outflow of the pancreas was systemic in the majority of cases (n = 335), while portal drainage was used in 63 patients. For organ preservation, University of Wisconsin (UW) solution (n = 329) or histidine–tryptophan–ketoglutarate solution (n = 69) was used. All patients received a 3-month antiviral prophylaxis with ganciclovir or valganciclovir, antibiotic and antifungal agents.

Patient selection

All patients referred to our center were interviewed by a transplant surgeon and a transplant coordinator. The pretransplant work-up includes a full medical assessment (e.g. electrocardiogram, chest X-ray, lung function test) with an emphasis on cardiovascular stress tests. All patients had to undergo a dobutamine stress echocardiography or a myocardial perfusion scintigraphy. In case of a positive stress test, coronary angiography was performed. In patients ≥50 years, all patients got a full cardiology review including cardiac catheterization. Exclusion criteria consist of, besides those commonly established for other solid organ transplants (active malignancy or infection, drug abuse, uncontrolled psychiatric disease or noncompliance to the medication), significant coronary disease not treatable by angioplasty, stenting or surgery, severe peripheral artery disease, body mass index >35 kg/m^2, or pronounced central obesity.

Immunosuppression

During the 15-year study period, immunosuppressive therapy changed as new agents became available. A quadruple immunosuppressive therapy was applied to all patients and included an induction with ATG (Thymoglobulin; Genzyme, Neu-Isenburg, Germany) or antilymphocyte globulin (ATG-Fresenius S; Fresenius Biotech, Graefelfing, Germany) as single-shot treatment in the majority of cases. Daclizumab (Zenapax; Roche Pharma, Grenzach-Wyhlen, Germany) induction was used in 13 patients. In a series of 25 SPK transplanted patients, daclizumab was administered in addition to ATG as described previously [13]. Initially, maintenance immunosuppression consisted of cyclosporine A (Sandimmun; Sandoz, Basel, Switzerland) in combination with azathioprine (Imurek; GlaxoSmithKline, München, Germany) and prednisolone (Solu Decortin H; Merck Pharma, Darmstadt, Germany). In 1995, azathioprine was replaced by mycophenolate mofetil (CellCept; Roche Pharma) and in 1996, cyclosporine A by tacrolimus (Prograf; Astellas, Munich, Germany). Our current regimen in SPK, PAK, and PTA recipients includes a thymoglobulin single-shot induction (1.5 mg/kg BW), tacrolimus, mycophenolate

mofetil and low-dose prednisolone. In the present study, maintenance immunosuppression included low-dose prednisolone, tacrolimus ($n = 313$; 79%) targeted to trough levels of 10–15 ng/ml during the first month or cyclosporine ($n = 85$; 21%) with trough levels of 150–250 ng/ml, mycophenolate mofetil (2–3 g/day) or azathioprine 100–150 mg/day and in six cases sirolimus. There were no differences in use of tacrolimus between both groups (58/69, 84% vs. 255/329, 78%).

Statistical analyses

For statistical analysis, the chi-square test and the Fisher's exact test were used to compare categorical variables, and the Mann–Whitney *U*-test to compare continuous variables. Patient and graft survivals were calculated using the Kaplan–Meier method including the log-rank test. A *P*-value below 0.05 was considered as statistically significant. Analysis was performed using SPSS (Chicago, IL, USA).

Results

From June 1994 through June 2009, 368 patients underwent 398 PT at the Department of Surgery, Knappschafts-Hospital, Ruhr-University of Bochum. Sixty-nine (17%) of them were performed in patients ≥50 years. Up to 2001, only 5% of patients were ≥50 years, but since then, the proportion of older patients increased steadily, comprising about 50% of all patients in 2009.

Donor characteristics are shown in Table 1. Mean donor age was slightly higher in the older recipients group. However, this difference did not reach statistical significance. Body mass index (BMI), donor sex, cause of death, use of perfusion solution, cold ischemic time, mean HLA-mismatches, and P-PASS were similar in both groups.

The recipient demographics are presented in Table 2. According to age group assignment, there was a significant difference in the mean age of the two groups (54.0 ± 3.4 years vs. 38.8 ± 5.9 years, $P < 0.001$). The oldest patient who underwent PT during the study period was 65 years old. The ratio of men to women was similar in both groups.

As expected, duration of diabetes mellitus before transplantation was approximately 8 years longer in the older patient group ($P < 0.001$). The number of CMV-positive recipients was significantly higher in patients aged 50 years and above ($P = 0.04$). Concerning preoperative time of dialysis, there was no difference between both groups. Recipients older than 50 years had a significantly higher BMI compared with the group younger than 50 years ($P < 0.001$).

The majority of pancreas grafts were transplanted simultaneously with a kidney. Sixty-four patients (93%) of the older group received a SPK compared with 310 patients (94%) in the group <50 years. PAKs were performed more often in the younger group, but this difference was not statistically significant. PTA ($n = 5$) was only performed in recipients younger than 50 years.

Patients and graft survival

The mean duration of follow-up was 7.7 ± 4.3 years. Patient survival rates at 1, 5, and 10 years were 100%, 89%, and 80% in the older group and 97%, 89%, and 84% in the younger group, respectively ($P > 0.05$; log-rank test, Fig. 1). One-, 5-, and 10-year kidney transplant survival was 95%, 81%, and 74% in patients older than 50 years and 97%, 91%, and 69% in younger recipients, respectively. Pancreas graft survival rates for 1, 5, and 10 years were 87%, 76%, and 67% in older recipients and 83%, 72%, and 67% in patients under 50 years, respectively. However, there was no significant difference in the 1-, 5-, and 10-year pancreas and kidney graft survival between both groups ($P > 0.05$; log-rank test, Fig. 1). The overall rate of acute rejection episodes within the first

Table 1. Donor characteristics.

Donor characteristics	Older ($n = 69$)	Younger ($n = 329$)	*P*-value
Age (years)	34.7 ± 12.7	31.9 ± 12.4	0.087
BMI (kg/m^2)	22.9 ± 2.9	22.8 ± 3.0	NS
Gender (male/female)	36/33	154/174	NS
P-PASS	18.2 ± 1.6 ($n = 62$)	17.0 ± 3.7 ($n = 266$)	NS
Traumatic cause of death	17 (25)	119 (36)	NS
Preservation solution UW	50 (72)	273 (83)	NS
Cold ischemic time (h)			
Pancreas	12.3 ± 3.0	12.9 ± 5.0	NS
Kidney	13.2 ± 2.2	13.5 ± 5.6	NS
HLA mismatch	4.3 ± 1.1	4.1 ± 1.3	NS

Values are given as mean ± SD or *n* (% of group).
UW, University of Wisconsin solution; P-PASS, preprocurement pancreas suitability score.

Table 2. Recipient characteristics.

Recipient characteristics	Older (n = 69)	Younger (n = 329)	P-value
Age (years)	54.0 ± 3.4	38.8 ± 5.9	<0.001
Gender (male/female)	40/29	187/142	NS
BMI (kg/m^2)	24.6 ± 3.1	22.9 ± 3.0	<0.001
Time of diabetes mellitus (years)	36.0 ± 8.9	27.7 ± 7.0	<0.001
Time of dialysis (months)	26.7 ± 28.2	26.2 ± 27.4	NS
Previous transplantation	7 (10)	27(8)	NS
SPK	64 (93)	310 (94)	NS
PAK	5 (7)	14 (4)	NS
PTA	0	5 (2)	NS
Enteric drainage	66 (96)	283 (86)	0.02
CMV recipient positive	40 (58)	147 (45)	0.04
CMV (R–/D+)	15 (22)	86 (26)	NS
CMV (R–/D–)	14 (20)	96 (29)	NS
CMV (R+/D+)	15 (22)	70 (21)	NS
CMV (R+/D–)	25 (36)	77 (23)	0.03
ATG	66 (96)	319 (97)	NS
IL-2 RA	7 (10)	31 (9)	NS
Tacrolimus	58 (84)	255 (78)	NS
Cyclosporine A	11 (16)	74 (22)	NS
Mycophenolate mofetil	67 (97)	299 (90)	NS
Azathioprine	2 (3)	24 (7)	NS
1-year acute rejection rate	24 (35)	103 (31)	NS

Values are given as mean ± SD or n (% of group).
BMI, body mass index; SPK, simultaneous pancreas kidney transplantation; PAK, pancreas after kidney transplantation; PTA, pancreas transplantation alone; CMV, cytomegalovirus; R, recipient; D, donor; IL2-RA, interleukin 2-receptor antibody; ATG, antithymocyte globulin.

year was 31.6%; 34.8% in patients ≥50 years, and 31.3% in patients <50 years (P = 0.57).

The main reason for early pancreas graft loss was venous graft thrombosis (11.5%, 46/398), with nine (14%) cases in the older group and 37 (11%) cases in the younger group. Cause of death for both groups is listed in Table 3. Complications, requiring repeated laparotomy in the first 3 months (older vs. younger: 34% vs. 33%) as well as length of hospital stay were also similar in both groups (mean 36.0 ± 22 vs. 36.6 ± 19 days). The rather long hospital stay includes also the rehabilitation process during the initial admission.

Table 3. Cause of death (n = 48) in 398 consecutive adult patients undergoing pancreas transplantation in the older and younger recipient group during the study period.

	Older (n = 69)	Younger (n = 329)
Cause of death	N (%)	n (%)
Infection	2 (28.5)	15 (36.5)
Cardiovascular	3 (43)	9 (22)
Cerebrovascular	0 (0)	2 (5)
Malignancy	2 (28.5)	5 (12)
Suicide	0 (0)	2 (5)
Other	0 (0)	8 (19.5)
Total	7 (100)	41 (100)

Discussion

This is the first large single-center study showing the feasibility of PT in patients older than 50 years with comparable risks for death or graft loss than in younger recipients. PT is currently the only treatment of type 1 diabetes mellitus that restores normoglycemia and returns hemoglobin A_{1c} (HbA1c) levels to normal. Additionally, SPK has become a therapy of choice in type 1 diabetics with end-stage renal disease. Over the past 20 years, the outcome of SPK transplants has been improved substantially in terms of long-term survival and protection from secondary diabetes complications [14–16]. Nevertheless, PT has the highest surgical complication rate of all routinely performed solid organ transplantations, resulting in relaparotomy in 30–40% of patients [1–3]. The long-term advantages of this surgical procedure have to be balanced to the associated morbidity and mortality, as well as the side effects of the long-term immunosuppression.

In the present study, the patient survival rates were not different at 1, 5, and 10 years between both groups. Increasing recipient age was not associated with higher risk for early or late death. A potential concern in the elderly patients is the risk of death as a result of post-transplant cardiovascular complications and infections, which were observed in 43% and 28.5% of our patients aged 50 years or older compared with 22% and 36.5% in

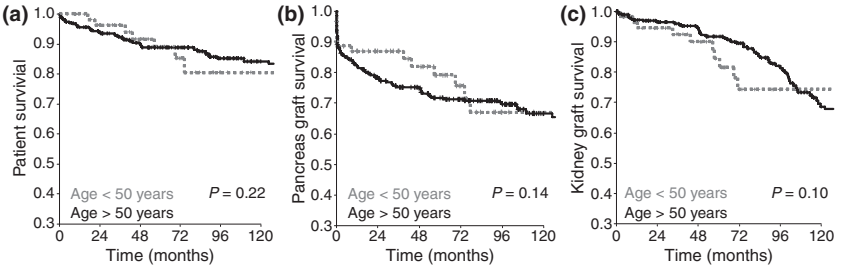

Figure 1(a–c) Kaplan–Meier survival estimates after simultaneous pancreas kidney transplantation, by patient age at time of transplantation. There was no significant difference between the two survival curves (P > 0.05; log-rank test).

the younger group respectively. This difference was not statistically significant.

The duration of diabetes mellitus was more than 8 years longer in the older patients group. However, looking at end-organ failures such as renal insufficiency, there were no apparent differences. Improved diabetes therapy, early aggressive antihypertensive treatment, and progress in prevention and treatment of diabetic nephropathy have led to a type 1 diabetic population that increasingly suffers from end-stage renal disease at an age older than 50 years.

Pancreas graft survival rates for 1, 5, and 10 years were 87%, 76%, and 67% in older recipients and 83%, 72%, and 67% in patients below 50 years, respectively. These survival rates are comparable with results from enteric drained pancreas recipients in the United States [17,18] and elsewhere [19,20].

Elderly patients are by far the fastest growing population requiring renal replacement therapy both in Europe and in the USA [21,22]. Only two decades ago, elderly people had limited access to dialysis therapy, whereas nowadays patients older than 65 years of age constitute 69% of all German patients starting therapy for end-stage renal failure [22,23].

Because of the critical shortage of donor organs, selection of candidates for transplantation is based on the potential for maximal benefit in terms of functional recovery and long-term survival. The upper age limit used to select potential candidates for PT has significantly changed over the last 15 years, and it is still a matter of debate. Several studies have shown an increased morbidity and mortality in elderly pancreas transplant patients, and some concluded that PT should be reserved for young patients [24–27]. Ojo and coworkers [28] reported an evident survival advantage of SPK across different demographic subgroups except in patients who were ≥50 years old at the time of transplantation. However, these studies have in common a small number of elderly patients studied.

Initially, PT was restricted to patients younger than 50 years. As short- and long-term survival after transplantation improved, selection criteria, including age, were progressively liberalized at our center. Evidence for such a change in the upper age limit came from our own experience regarding kidney transplantation in older patients (Eurotransplant Senior Program) and from several studies reporting that morbidity and mortality after kidney, liver and heart transplantation were not significantly increased in selected older patients [8–11].

To the best of our knowledge, only limited data are available reporting outcome of PT in patients aged 50 years and above. Ablorsu *et al.* [7] reported about their single center experiences with similar outcomes in significantly less patients. Sutherland *et al.* [29] had quite similar results in their experiences, which were also confirmed by US registry data [30,31]. However, the definition of 'old recipients' was >45 years of age in most of these studies, with similar results to our group of 'old recipients' ≥50 years of age.

With a mean follow-up of 7.7 years, this is the first study that demonstrates comparable long-term patient and graft survival in selected pancreas transplant recipients older than 50 years. The careful selection of pancreas transplant candidates is a likely explanation for the good outcomes in the older group. In this regard, coronary angiography was performed in the majority (94%) of older patients prior to acceptance on the waiting list. Half of these patients had to undergo coronary stent angioplasty or coronary artery bypass surgery. We have not used coronary disease as exclusion criteria for PT. As long as the coronary lesions are correctable by stent angioplasty or bypass, we will perform a PT.

Improvements in PT are another explanation for the good results and the increase in upper age limit for potential pancreas transplant recipients. Likely reasons for improved patient survival rates and decreased surgical complications after PT include better surgical techniques and critical care, better antimicrobial therapy, and a more sophisticated immunosuppressive therapy (e.g. tacrolimus, mycophenolate mofetil).

Center experience and surgeon-related factors may influence the outcome of PT. It has been shown that pancreas transplant center volume did not affect patient survival in the United States [32]. Other reports have demonstrated an inverse relationship between center volume and mortality for a number of surgical procedures [33–37]. In 2009, approximately one quarter (24%) of all SPK in Germany was performed at our institution [38]. As a high volume center for PT, we did accept a higher number of elderly patients.

In summary, despite the limitations of a retrospective study, our experience with selected patients aged 50 years and older is favorable and indicates that PT can be successfully performed in these patients, with long-term survival comparable with that seen in younger patients.

We conclude that advanced age alone should no longer be considered a contraindication to PT. However, good medical assessment and careful patient selection are necessary.

Authorship

PS: designed study, collected and analyzed data, wrote the paper. OV, BK, SM, AW and TK: analyzed data and

wrote the paper. BKK and RV: analyzed results, wrote and edited the paper.

References

1. Humar A, Kandaswamy R, Granger D, Gruessner RW, Gruessner AC, Sutherland DE. Decreased surgical risks of pancreas transplantation in the modern era. *Ann Surg* 2000; **231**: 269.
2. Schenker P, Vonend O, Ertas N, *et al.* Incidence of pancreas graft thrombosis using low-molecular-weight heparin. *Clin Transplant* 2009; **23**: 407.
3. Steurer W, Malaise J, Mark W, Koenigsrainer A, Margreiter R. Spectrum of surgical complications after simultaneous pancreas-kidney transplantation in a prospectively randomized study of two immunosuppressive protocols. *Nephrol Dial Transplant* 2005; **20**(Suppl. 2): ii54.
4. Hovind P, Tarnow L, Rossing K, *et al.* Decreasing incidence of severe diabetic microangiopathy in type 1 diabetes. *Diabetes Care* 2003; **26**: 1258.
5. Ravera M, Ratto E, Vettoretti S, Parodi D, Deferrari G. Prevention and treatment of diabetic nephropathy: the program for irbesartan mortality and morbidity evaluation. *J Am Soc Nephrol* 2005; **16**(Suppl. 1): S48.
6. Rossing P. The changing epidemiology of diabetic microangiopathy in type 1 diabetes. *Diabetologia* 2005; **48**: 1439.
7. Ablorsu E, Ghazanfar A, Mehra S, *et al.* Outcome of pancreas transplantation in recipients older than 50 years: a single-centre experience. *Transplantation* 2008; **86**: 1511.
8. Aduen JF, Sujay B, Dickson RC, *et al.* Outcomes after liver transplant in patients aged 70 years or older compared with those younger than 60 years. *Mayo Clin Proc* 2009; **84**: 973.
9. Demers P, Moffatt S, Oyer PE, Hunt SA, Reitz BA, Robbins RC. Long-term results of heart transplantation in patients older than 60 years. *J Thorac Cardiovasc Surg* 2003; **126**: 224.
10. Heldal K, Hartmann A, Grootendorst DC, *et al.* Benefit of kidney transplantation beyond 70 years of age. *Nephrol Dial Transplant* 2009; **25**: 1680.
11. Schmitt TM, Kumer SC, Pruett TL, Argo CK, Northup PG. Advanced recipient age (>60 years) alone should not be a contraindication to liver retransplantation. *Transpl Int* 2009; **22**: 601.
12. Vinkers MT, Rahmel AO, Slot MC, Smits JM, Schareck WD. How to recognize a suitable pancreas donor: a Eurotransplant study of preprocurement factors. *Transplant Proc* 2008; **40**: 1275.
13. Schulz T, Flecken M, Kapischke M, Busing M. Single-shot antithymocyte globuline and daclizumab induction in simultaneous pancreas and kidney transplant recipient: three-year results. *Transplant Proc* 2005; **37**: 1818.
14. Dean PG, Kudva YC, Stegall MD. Long-term benefits of pancreas transplantation. *Curr Opin Organ Transplant* 2008; **13**: 85.
15. Schenker P, Viebahn R. [Pancreas and islet transplantation. The role in the treatment of diabetes mellitus]. *Chirurg* 2009; **80**: 422.
16. White SA, Shaw JA, Sutherland DE. Pancreas transplantation. *Lancet* 2009; **373**: 1808.
17. Gruessner AC, Sutherland DE, Gruessner RW. Pancreas transplantation in the United States: a review. *Curr Opin Organ Transplant* 2010; **15**: 93.
18. Sollinger HW, Odorico JS, Becker YT, D'Alessandro AM, Pirsch JD. One thousand simultaneous pancreas-kidney transplants at a single center with 22-year follow-up. *Ann Surg* 2009; **250**: 618.
19. Bechstein WO, Malaise J, Saudek F, *et al.* Efficacy and safety of tacrolimus compared with cyclosporine microemulsion in primary simultaneous pancreas-kidney transplantation: 1-year results of a large multicenter trial. *Transplantation* 2004; **77**: 1221.
20. Boggi U, Vistoli F, Signori S, *et al.* Outcome of 118 pancreas transplants with retroperitoneal portal-enteric drainage. *Transplant Proc* 2005; **37**: 2648.
21. US Renal Data System. *Annual Report 2009*. Available from http://www.usrds.org, 2009 edn. 2009 (accessed March 2010).
22. Jager KJ, van Dijk PC, Dekker FW, Stengel B, Simpson K, Briggs JD. The epidemic of aging in renal replacement therapy: an update on elderly patients and their outcomes. *Clin Nephrol* 2003; **60**: 352.
23. Frei U, Schober-Halstenberg H-J. *Renal Replacement Therapy in Germany. Annual Report 2006/2007*. Available from http://bundesverband-niere.de, 2008 (accessed March 2010).
24. Bunnapradist S, Cho YW, Cecka JM, Wilkinson A, Danovitch GM. Kidney allograft and patient survival in type I diabetic recipients of cadaveric kidney alone versus simultaneous pancreas kidney transplants: a multivariate analysis of the UNOS database. *J Am Soc Nephrol* 2003; **14**: 208.
25. Cheung AH, Sutherland DE, Gillingham KJ, *et al.* Simultaneous pancreas-kidney transplant versus kidney transplant alone in diabetic patients. *Kidney Int* 1992; **41**: 924.
26. Freise CE, Stock PG, Melzer JS. Increased morbidity and mortality of simultaneous pancreas-renal transplantation in patients over 49 years of age. *Transplant Proc* 1998; **30**: 292.
27. Manske CL, Wang Y, Thomas W. Mortality of cadaveric kidney transplantation versus combined kidney-pancreas transplantation in diabetic patients. *Lancet* 1995; **346**: 1658.
28. Ojo AO, Meier-Kriesche HU, Hanson JA, *et al.* The impact of simultaneous pancreas-kidney transplantation on long-term patient survival. *Transplantation* 2001; **71**: 82.
29. Sutherland DE, Gruessner RW, Dunn DL, *et al.* Lessons learned from more than 1,000 pancreas transplants at a single institution. *Ann Surg* 2001; **233**: 463.

30. Gruessner AC, Sutherland DE. Pancreas transplant outcomes for United States (US) and non-US cases as reported to the United Network for Organ Sharing (UNOS) and the International Pancreas Transplant Registry (IPTR) as of June 2004. *Clin Transplant* 2005; **19**: 433.
31. Gruessner AC, Sutherland DE. Pancreas transplant outcomes for United States (US) cases as reported to the United Network for Organ Sharing (UNOS) and the International Pancreas Transplant Registry (IPTR). *Clin Transpl* 2008; 45.
32. Mandal AK, Drew N, Lapidus JA. The effect of center volume on pancreas transplant outcomes. *Surgery* 2004; **136**: 225.
33. Begg CB, Cramer LD, Hoskins WJ, Brennan MF. Impact of hospital volume on operative mortality for major cancer surgery. *JAMA* 1998; **280**: 1747.
34. Birkmeyer JD, Stukel TA, Siewers AE, Goodney PP, Wennberg DE, Lucas FL. Surgeon volume and operative mortality in the United States. *N Engl J Med* 2003; **349**: 2117.
35. Holscher AH, Metzger R, Brabender J, Vallbohmer D, Bollschweiler E. High-volume centers – effect of case load on outcome in cancer surgery. *Onkologie* 2004; **27**: 412.
36. Sosa JA, Bowman HM, Gordon TA, *et al.* Importance of hospital volume in the overall management of pancreatic cancer. *Ann Surg* 1998; **228**: 429.
37. Tracy ET, Bennett KM, Danko ME, *et al.* Low volume is associated with worse patient outcomes for pediatric liver transplant centers. *J Pediatr Surg* 2010; **45**: 108.
38. Eurotransplant International Foundation. *Pancreas and Kidney Balance 2009*. Available from http://www.eurotransplant.org/files/balance/pancreaskidney_dec09.pdf, 2010. (accessed March 2010).