Outcomes of pancreas retransplantation in patients with pancreas graft failure

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Background: Pancreas retransplantation is still a controversial option after loss of a pancreatic graft. This article describes the experience of pancreas retransplantation at a high-volume centre.

Methods: This was a retrospective observational study of all pancreas retransplantations performed in a single centre between 1997 and 2013. Pancreatic graft loss was defined by the return to insulin dependence. Risk factors for graft loss as well as patient and graft survival were analysed using logistic and time-to-event regression models.

Results: Of 409 pancreas transplantations undertaken, 52 (12.7 per cent) were identified as pancreas retransplantations. After a median follow-up of 65.0 (range 0.8–174.3) months, 1- and 5-year graft survival rates were 79 and 69 per cent respectively, and 1- and 5-year patient survival rates were 96 and 89 per cent. During the entire follow-up, 22 grafts (42 per cent) were lost. Patient survival was not associated with any of the donor- or recipient-related factors investigated. Five-year graft survival was better after simultaneous kidney–pancreas retransplantation than pancreas retransplantation alone: 80 per cent (16 of 20) versus 63 per cent (20 of 32) (P = 0.226). Acute rejection (odds ratio 4.49, 95 per cent c.i. 1.59 to 12.68; P = 0.005) and early surgical complications (OR 3.29, 1.09 to 9.99, P = 0.035) were identified as factors with an independent negative effect on graft survival.

Conclusion: Pancreas retransplantation may be considered for patients whose previous graft has failed.

Introduction

With improvements in immunosuppression, surgical technique and perioperative management, simultaneous kidney–pancreas transplantation represents the therapy of choice nowadays for patients with insulin-dependent diabetes mellitus and end-stage renal disease3–5. Single pancreas transplantation, either as pancreas after kidney transplantation or as pancreas transplantation alone, is performed less frequently and harbours a greater immunological and surgical risk, resulting in less favourable outcomes6–8. According to data published by the International Pancreas Transplantation Registry9, the 5-year graft survival rate is 73 per cent for simultaneous kidney–pancreas transplantation, 53 per cent for pancreas transplantation alone and 64 per cent for pancreas after kidney transplantation.

The question of whether pancreas retransplantation offers a valuable option for patients who have experienced pancreatic graft loss cannot be answered fully at this time. This is because of a paucity of data, with the few existing studies reporting estimates for 1-year graft survival following pancreas retransplantation ranging from 37 to 80 per cent, and rates in some studies differing significantly from results following first pancreas transplantation10,11. The highly controversial results form the basis of the ongoing debate regarding indications and recommendations for pancreas retransplantation. On the one hand, some consider the high morbidity associated with pancreas retransplantation to be unacceptable; on the other hand,
Table 1  Baseline data for recipients

| No. of patients* (n = 52) |
|--------------------------|
| **Age (years)**†        |
| 47 (23–59)              |
| **Sex (M : F)**         |
| 31 : 21                 |
| **BMI (kg/m²)**†        |
| 23.4 (16.9–33.2)        |
| **CMV status**          |
| Positive                |
| 36 (69)                 |
| Negative                |
| 16 (31)                 |
| **Type of DM**          |
| Type 1                  |
| 50 (96)                 |
| Type 2                  |
| 2 (4)                   |
| **Pretransplant C-peptide** |
| Positive                |
| 7 (13)                  |
| Negative                |
| 29 (56)                 |
| Unknown                 |
| 16 (31)                 |
| **Waiting time (months)**† |
| 11.1 (0.2–88.4)         |

*With percentages in parentheses unless indicated otherwise; †values are median (range). CMV, cytomegalovirus; DM, diabetes mellitus.

Table 2  Baseline data for donors

| No. of patients* (n = 52) |
|--------------------------|
| **Age (years)**†        |
| 31 (12–51)              |
| **Sex (M : F)**         |
| 31 : 21                 |
| **BMI (kg/m²)**†        |
| 22.9 (17.4–30.3)        |
| **CMV status**          |
| Positive                |
| 30 (58)                 |
| Negative                |
| 22 (42)                 |
| **Serum sodium (mmol/l)**† |
| 147.2 (8.3)             |
| **Serum amylase (units/l)**† |
| 148.3 (184.8)           |
| **Serum lipase (units/l)**† |
| 60.5 (70.8)             |
| **Leucocytes (× 10⁹/μl)** |
| 12.9 (4.7)              |

*With percentages in parentheses unless indicated otherwise; †values are median (range). CMV, cytomegalovirus.

the progression of serious long-term complications of insulin-dependent diabetes mellitus may justify pancreas retransplantation in selected patients8,10,11.

The aim of this study was to review patients undergoing pancreas retransplantation after loss of a pancreatic graft, and to use multivariable analyses to identify risk factors associated with worse graft and patient survival.

Methods

Following approval from the ethics committee of the Medical University of Innsbruck (study number AN 2014-0334), the authors undertook a retrospective analysis of prospectively collected and auditable medical records of all pancreas transplantations performed between January 1997 and December 2013 at the Medical University of Innsbruck. Patients considered for this study had undergone either a simultaneous kidney–pancreas retransplantation or a single pancreas retransplantation. Multivisceral transplantations were excluded. This study was conducted and the results reported in accordance with the STROBE checklist12.

Definitions

Pancreatic graft loss was defined by return to insulin dependence. Technical graft loss was defined as graft loss owing to early surgical complications (within 90 days after transplantation), including vascular thrombosis, severe necrotizing pancreatitis, anastomotic leakage, bleeding or intra-abdominal infections13. Immunological graft
Table 4  Patient and graft survival, and complications after kidney–pancreas and single pancreas retransplantation

|                          | All patients (n = 52) | Kidney–pancreas (n = 20) | Single pancreas (n = 32) | P* |
|--------------------------|-----------------------|--------------------------|--------------------------|----|
| 1-year survival          |                       |                          |                          |    |
| Patients                 | 50 (96)               | 19 (95)                  | 31 (97)                  | 0.783† |
| Grafts                   | 41 (79)               | 18 (90)                  | 23 (72)                  | 0.136† |
| Graft loss               | 22 (42)               |                          |                          |    |
| Surgical                 | 8 (15)                |                          |                          |    |
| Immunological            | 10 (19)               |                          |                          |    |
| Other                    | 4 (8)                 |                          |                          |    |
| Early surgical complication| 21 (40)              | 9 (45)                   | 12 (38)                  | 0.402 |
| Bleeding                 | 13 (25)               | 7 (35)                   | 6 (19)                   | 0.371 |
| Thrombosis               | 8 (15)                | 3 (15)                   | 5 (16)                   | 0.840 |
| Pancreatitis             | 3 (6)                 | 1 (5)                    | 2 (6)                    | 0.825 |
| Wound dehiscence         | 1 (2)                 |                          | 0 (0)                    | 0.604 |
| Clavien–Dindo ≥ IIIa complications | 20 (38)     |                          |                          |    |
| Infection                | 25 (48)               |                          |                          |    |
| Pneumonia                | 4 (8)                 |                          |                          |    |
| CMV                      | 2 (4)                 |                          |                          |    |
| HCV                      | 2 (4)                 |                          |                          |    |
| Herpes simplex           | 7 (13)                |                          |                          |    |
| Clostridium              | 1 (2)                 |                          |                          |    |
| Sepsis                   | 7 (13)                |                          |                          |    |
| Wound infection          | 8 (15)                |                          |                          |    |
| Acute rejection          | 10 (19)               | 1 (5)                    | 9 (28)                   | 0.040 |

*Values in parentheses are percentages. CMV, cytomegalovirus; HCV, hepatitis C virus. *χ² test, except †log rank test.

loss included chronic and acute rejections resulting in graft loss.

Patient selection

As described previously14, all patients considered for pancreas (re)transplantation must undergo a thorough prelisting cardiac evaluation, which includes echocardiography, exercise stress test, myocardial perfusion test and coronary angiography.

At the time of listing, solid-phase assays (enzyme-linked immunosorbent assay or Luminex® (Luminex, Austin, Texas, USA)) were used to detect HLA antigens to which the recipient had preformed antibodies. So-called unacceptable HLA antigens are HLA antigen specificities that must not occur in donor HLA antigens. Matches of unacceptable HLA antigens between donor and recipient (positive allocation cross-matches) precluded allocation and transplantation of grafts into a recipient. Pretransplant solid-phase assays were implemented in August 2004. Before then, immunological compatibility was based on cross-matching immediately before transplantation.

Surgical procedure and surgical complications

Donor and recipient surgical procedures were performed as described previously15. On recovery, abdominal organs were perfused via the aorta with histidine–tryptophan–ketoglutarate solution (Dr Franz Koehler Chemie, Bensheim, Germany) or University of Wisconsin solution (Bridge to Life, London, UK). The superior mesenteric and splenic arteries were reconstructed using a donor-derived Y-graft consisting of the iliac arterial bifurcation. If still present, the decision whether or not to remove the failed graft was made during surgery. If possible, the Y-graft was anastomosed to the recipient’s right common iliac artery and the graft’s portal vein to the recipient’s inferior vena cava. Grafts were drained enterically via a direct duodenojejunoanastomosis approximately 40 cm distal to the duodenojejunal flexure without a Roux-en-Y enteric limb.

Surgical complications were graded according to the Clavien–Dindo classification16, which is based on the therapy needed to treat the complication. Complications with a Clavien–Dindo grade of IIIa or more require general anaesthesia and are generally rated as major surgical complications.

Immunosuppression and postoperative care

Standard immunosuppression included induction therapy with a single dose of 8 mg per kg bodyweight antithymocyte globulin (ATG) (ATG-Fresenius®; Fresenius Biotech, Gräfelfing, Germany); tacrolimus (Prograf®;
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Astellas Pharma, Vienna, Austria) with trough levels of 12–15 ng/ml for the first 3 months, aiming at 3–5 ng/ml at 2 years after transplantation; mycophenolate mofetil (CellCept®; Roche Austria, Vienna, Austria) at a dose of 1 g twice daily, or enteric coated mycophenolic acid (Myfortic®; Novartis Austria, Vienna, Austria) at a dose of 720 mg twice daily; and a steroid taper with an attempt to wean steroids at 1 year.

Perioperative antimicrobial prophylaxis consisted of tazobactam/piperacillin (Tazocin®; Pfizer Austria, Vienna, Austria) and ciprofloxacin (Ciproxin®; Bayer Austria, Vienna, Austria) for 3 days. Fluconazole (Diflucan®; Pfizer Austria) was given for 7 days. In the event of a CMV mismatch (D+/R–), antiviral prophylaxis consisted of valganciclovir (Valcyte®; Roche Austria) for 3 months. Octreotide acetate (Sandostatin®; Novartis Austria) was administered for 7 days. Blood glucose levels were kept below 120 mg/dl in the ICU. In the general ward, levels exceeding 150 mg/dl were treated with subcutaneous insulin. Grafts were monitored closely by daily ultrasound examination

Assessment and treatment of acute rejection

Acute rejection episodes were suspected if there was an abrupt increase in serum amylase (exceeding 160 units/l) and/or serum glucose levels, together with a significant drop in serum C-peptide level and/or abdominal pain associated with sonographic swelling of the graft. If possible, the diagnosis was confirmed from endoscopic biopsies of the duodenal segment of the graft. Pancreatic biopsies were not undertaken. A renal biopsy was performed if rejection was suspected after simultaneous kidney–pancreas retransplantation. Treatment of acute cellular rejection consisted of pulsed steroids (500 mg methylprednisolone on 3 consecutive days) or administration of 8 mg per kg bodyweight ATG in parallel with increased baseline immunosuppression.

Follow-up and endpoints

Graft survival was followed prospectively in all patients. Follow-up time was calculated from the date of transplantation and censored at the date of last clinical follow-up or patient death, which ever came first. Death with a functioning graft was not counted as graft loss (death-censored graft survival) for calculation of graft survival.

Statistical analysis

Data are reported as mean(s.d.), median (range) or numbers with percentages. Donor and recipient factors described as potential risk factors for diminished graft survival in the scientific literature were entered into a stepwise Cox regression model for multivariable analysis of risk factors.

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Risk analyses to identify factors associated with graft loss after pancreas transplantation

| Cause of previous graft loss                  | Graft loss (n = 22) | No graft loss (n = 30) | Univariable analysis | Multivariable analysis |
|----------------------------------------------|---------------------|------------------------|----------------------|------------------------|
| Immunological                                | 11                  | 19                     | 0.79 (0.34, 1.85)    | 0.587                  |
| Technical failure                            | 10                  | 9                      |                      |                        |
| Other                                        | 1                   | 2                      |                      |                        |
| Previous retransplantations                  |                     |                        | 1.16 (0.76, 1.76)    | 0.500                  |
| 0                                            | 18                  | 27                     |                      |                        |
| 1 or 2                                       | 4                   | 3                      |                      |                        |
| CMV mismatch                                 | 12                  | 18                     | 0.19 (0.25, 1.41)    | 0.104                  |
| Recipient age                                | 44.2 (7.4)          | 47.5 (8.8)             | 1.03 (0.97, 1.09)    | 0.428                  |
| Recipient BMI (kg/m²)                        | 23.2 (2.9)          | 24.0 (3.4)             | 0.94 (0.79, 1.11)    | 0.444                  |
| Surgical retransplantation procedure         |                     |                        | 1.99 (0.64, 6.18)    | 0.235                  |
| Kidney–pancreas                               | 5                   | 15                     |                      |                        |
| Single pancreas                              | 17                  | 15                     |                      |                        |
| Duration of cold ischaemia >14 h             | 12                  | 15                     | 1.03 (0.38, 2.78)    | 0.947                  |
| Perfusion solution                           |                     |                        | 1.03 (0.29, 3.62)    | 0.969                  |
| UW                                           | 18                  | 23                     |                      |                        |
| HTK                                          | 4                   | 7                      |                      |                        |
| Donor age (years)*                           | 30.0 (11.3)         | 32.2 (10.6)            | 0.99 (0.95, 1.04)    | 0.693                  |
| Donor BMI (kg/m²)*                           | 23.2 (2.9)          | 23.2 (2.9)             | 0.96 (0.80, 1.15)    | 0.651                  |
| Anastomosis time > 30 min                    | 10                  | 19                     | 0.44 (0.16, 1.20)    | 0.107                  |
| Acute rejection                              | 8                   | 2                      | 6.42 (2.35, 17.56)   | <0.001                 |
| Early surgical complications                 | 13                  | 8                      | 4.71 (1.62, 13.68)   | 0.004                  |

Values in parentheses are 95 per cent confidence intervals unless indicated otherwise; *values are mean(s.d.). CMV, cytomegalovirus; UW, University of Wisconsin; HTK, histidine–tryptophan–ketoglutarate.

Results

A total of 409 consecutive pancreas transplantations were performed in the study period. Of these, 52 (12.7 per cent) were pancreas retransplantations, including 45 first pancreas retransplantations (87 per cent), six second (12 per cent) and one third pancreas retransplantation (2 per cent). Baseline data for recipients and donors are summarized in Tables 1 and 2. Pretransplant solid-phase assays were reported for 28 patients (54 per cent). Unacceptable HLA antigens were detected in 12 and polyspecific antibodies in two patients; no antibodies were detected in 14 patients.

Surgical data and immunosuppression

Twenty patients (38 per cent) underwent simultaneous kidney–pancreas retransplantation and 32 (62 per cent) had single pancreas retransplantation; the latter included two pancreas-alone transplantations in preuremic patients and 30 pancreas after kidney transplantations in previous simultaneous kidney–pancreas transplantation recipients who still had functioning kidney grafts. Standard induction immunosuppression consisted of a depleting antibody; in four patients this was combined with a non-depleting IL-2 receptor antagonist. Three patients received a non-depleting IL-2 receptor antagonist alone as induction agent (Table 3).

Postoperative complications

Twenty patients (38 per cent) had to undergo relaparotomy, with bleeding (13) and thrombosis (8) being the leading causes. Median length of hospital stay was 23 (range 16–110) days. The rate of relaparotomy and length of hospital stay did not differ from those among patients undergoing primary pancreas transplantation (39.7 per cent and 26 (9–189) days respectively).

In one patient, a short dissection and subsequent complete thrombosis of the femoral artery led to amputation of the lower limb. Acute rejection occurred in ten patients (19 per cent), half whom lost the graft (Table 4).

Graft survival

Graft loss occurred in a total of 22 patients, in six this was more than 5 years following transplantation.
After a median follow-up of 65.0 (range 0.8–174.3) months, the 5-year overall graft survival rate was 69 per cent. Recipients undergoing simultaneous kidney–pancreas retransplantation had a 5-year graft survival rate of 80 per cent (16 of 20), compared with 63 per cent (20 of 32) among recipients undergoing single pancreas retransplantation (Fig. 1).

The 1- and 5-year graft survival rates in patients receiving their first pancreas retransplantation were 80 per cent (36 of 45) and 71 per cent (32 of 45) respectively; corresponding rates among those who had received more than one pancreas retransplantation were 71 per cent (5 of 7) and 57 per cent (4 of 7).

Multivariable analysis revealed that only two of the factors analysed were significantly associated with long-term graft survival: early surgical complications (odds ratio 3.29, 95 per cent c.i. 1.09 to 9.99; \( P = 0.035 \)) and acute rejection (odds ratio 4.49, 1.59 to 12.68; \( P = 0.005 \)) (Table 5).

**Patient survival**

Seven patients died during follow-up: three from septic complications (2 with a functioning graft), two from stroke and in three patients the cause of death could not be determined. The 5-year overall patient survival rate was 89 per cent overall, 90 per cent (18 of 20) for simultaneous kidney–pancreas retransplantation and 88 per cent (28 of 32) for single pancreas retransplantation (Fig. 2).

Forty-five patients who underwent their first pancreas retransplantation had 1- and 5-year survival rates of 96 per cent (43 of 45) and 87 per cent (39 of 45) respectively. Seven recipients who had undergone more than one pancreas retransplantation achieved 1- and 5-year survival rates of 100 per cent.

**Discussion**

The 5-year graft survival rate was almost 70 per cent following pancreas retransplantation in this study, and 80 per cent in the simultaneous kidney–pancreas retransplantation subgroup. Acute rejection episodes and early surgical complications were the two independent risk factors for graft loss.

Successful pancreas transplantation slows or even stops progression of diabetic retinopathy and nephropathy, with the potential to increase quality of life as well as patient survival. However, the choice between pancreas retransplantation or continuous insulin therapy treatment after loss of a pancreatic graft remains a matter of debate. Given that pancreas transplantation is not a life-saving operation, the benefits must be balanced carefully against the risks of the procedure. Furthermore, inferior outcomes in patients undergoing retransplantation of several solid organs have prompted discussion in the transplant community because every organ used for retransplantation can be regarded as a missed opportunity for a patient listed for a...
first transplantation. Therefore, after retransplantation, it would be desirable to achieve outcomes similar to those for a first transplantation.

In the present study, 1- and 5-year graft survival rates were comparable to those in patients undergoing their first pancreas transplantation in the same centre\textsuperscript{22}. Not surprisingly, graft survival was better after simultaneous kidney–pancreas retransplantation compared with single pancreas retransplantation (80\% versus 63\% per cent after 5 years). The less favourable outcome following single pancreas retransplantation has also been described by other groups, and is already known for primary single pancreas transplantation\textsuperscript{8,9,11}. One suggested reason for this is that a pancreatic graft is more immunogenic than, for example, a combined kidney graft. Non-uraemic patients are considered more immune competent than patients with end-stage renal disease, which is reflected in the dependence on higher levels of immunosuppression, and in patients receiving a combined simultaneous kidney–pancreas transplantation the kidney graft acts as a surrogate marker for ongoing rejection of the pancreatic graft\textsuperscript{23}. The Oxford group\textsuperscript{24} recently tried to address the problem of ‘silent’ rejection by performing bladder exocrine drainage in patients undergoing pancreas transplantation alone or pancreas after kidney transplantation. This type of drainage allows closer monitoring of the transplanted graft by regularly measuring urinary amylase. However, this advantage has to be weighed against the need for a second surgical procedure as, historically, up to 38\% of the grafts required conversion to enteric drainage within a few years after transplantation\textsuperscript{24}. So far, there are no data comparing enteric- and bladder-drained grafts in patients undergoing pancreas retransplantation.

A number of demographic donor variables, such as age, BMI and length of ICU stay, have been suggested to have a negative impact on graft success\textsuperscript{25–27}. In the present analysis, no single demographic variable was able to predict a significantly adverse outcome. This might be a result of the strict selection of both recipients and donors for pancreas retransplantation.

The high graft survival rate in the present series is also backed by excellent overall patient survival, with 1- and 5-year rates in line with recent results from the group in Minneapolis\textsuperscript{11}. Of note, these patient survival rates were similar to those after primary pancreas transplantation\textsuperscript{4,22,28}. Interestingly, recipients of multiple pancreas retransplantations achieved even better survival. Although this result should be accepted with some reservation owing to the small number of patients in this subgroup, it presumably reflects strict patient selection. All patients undergo thorough cardiac evaluation, including invasive evaluation by coronary angiography, which has been shown to reduce the risk of post-transplant cardiac events in patients who often have multiple co-morbidities\textsuperscript{14}. Such evaluation has also been highlighted by others as a prerequisite for immunologically and surgically high-risk patients\textsuperscript{29–33}. Excellent compliance after the first pancreas transplantation is a further selection criterion. Non-adherence to medication has been repeatedly shown to jeopardize favourable outcomes\textsuperscript{14}.

From an immunological point of view, solid-phase assays are used at the time of listing to detect HLA antigens against which the recipient has preformed antibodies. Matches of these preformed antibodies preclude allocation and transplantation of grafts into the recipient. The Euro-SPK 001 study\textsuperscript{35} has shown that HLA mismatches do not influence pancreatic graft survival. In line with these data, the number of HLA mismatches was not decisive when allocating the organ to pancreas retransplantation recipients. In the present authors’ centre, crucial components of donor–recipient matching are unacceptable HLA antigens and pretransplant cross-match.

Although data from islet transplantation show that residual C-peptide production protects against deterioration of cardiovascular pathologies and serious hypoglycaemic episodes\textsuperscript{36}, positive C-peptide was not a contraindication to pancreas retransplantation. Long-term data regarding insulin-dependent patients with initial positive C-peptide levels following islet transplantation are still lacking, and prevention of deterioration of the native kidney is crucial in pre-uraemic patients experiencing pancreatic graft loss. The same applies to functioning kidney grafts in previous recipients of a simultaneous kidney–pancreas transplantation who have lost the pancreatic graft. Of note, the occurrence of end-stage renal disease has been shown to increase the risk of death dramatically while on the waiting list; the risk of death is over 40\% per cent for patients awaiting simultaneous kidney–pancreas transplantation compared with 10\% per cent for non-uraemic candidates awaiting pancreas transplantation alone\textsuperscript{37}. Therefore, C-peptide levels might not be decisive in the absence of any contraindication to pancreas retransplantation.

Finally, primary pancreas transplantation has been shown to improve quality of life\textsuperscript{5}. Impairment of quality of life as a result of return to insulin therapy is also considered in candidates for pancreas retransplantation.

From the donor point of view, the authors avoid using organs from donors with multiple risk factors, which has been shown to be to be associated with early surgical complications following pancreas transplantation\textsuperscript{38}. For
example, higher amylase and lipase levels were accepted only in very young donors.

Multivariable analysis in this study identified early complications as an independent risk factor for graft loss. Complications were associated with a decline in overall graft survival from 71 per cent (22 of 31) to 38 per cent (8 of 21). This finding is consistent with a previous report\textsuperscript{39} that even recipients of a first pancreas transplantation undergoing relaparotomy following transplantation had a significantly lower graft survival rate than those without relaparotomy. Even though single pancreas transplantation is known to be associated with increased surgical risk\textsuperscript{6}, the incidence of early surgical complications among the transplantation types did not differ significantly in the present study.

The second independent risk factor identified here was the occurrence of acute allograft rejections. Overall graft survival following pancreas retransplantation declined from 67 per cent (28 of 42) to 20 per cent (2 of 10) with the occurrence of an acute rejection episode. Acute rejection occurred significantly more frequently in single pancreas retransplantation recipients. Accordingly, depending on the proportion of recipients undergoing pancreas retransplantation in the form of a pancreas transplantation alone in a cohort, acute rejection may affect overall graft survival. These findings are in line with the those of Rudolph and colleagues\textsuperscript{11}, who attributed the lower graft survival rate in their pancreas retransplantation recipients to the much higher number of solitary pancreas retransplantations compared with the number of simultaneous kidney–pancreas retransplantations and, therefore, did not regard retransplantation itself as an independent risk factor for acute rejection\textsuperscript{11}.

Recently, an analysis of the United Network for Organ Sharing (UNOS) database in the USA of all single pancreas transplantsations or simultaneous kidney–pancreas transplantations found that graft survival was much poorer among recipients undergoing pancreas retransplantation than among those having primary pancreas transplantation\textsuperscript{10}. Even though these data have to be taken into consideration, the discrepancy between the UNOS data and the favourable outcomes published by selected high-volume centres highlights the importance of referring patients to experienced centres\textsuperscript{8,11,31}. Surgical experience and meticulous immunological monitoring are crucial in patients selected for retransplantation.

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S.G. and B.C. contributed equally to this study.

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**References**

1. Kelly WD, Lillehei RC, Merkel FK, Idezuki Y, Goetz FC. Allotransplantation of the pancreas and duodenum along with the kidney in diabetic nephropathy. Surgery 1967; 61: 827–837.
2. Sutherland DE, Gruessner RW, Dunn DL, Matas AJ, Humar A, Kandaswamy R et al. Lessons learned from more than 1000 pancreas transplants at a single institution. *Ann Surg* 2001; 233: 463–501.
3. Gruessner AC, Sutherland DE. Analysis of United States (US) and non-US pancreas transplants as reported to the International Pancreas Transplant Registry (IPTR) and to the United Network for Organ Sharing (UNOS). *Clin Transpl* 1998; 53–73.
4. 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: 618–630.
5. White SA, Shaw JA, Sutherland DE. Pancreas transplantation. *Lancet* 2009; 373: 1808–1817.
6. Ozaki CF, Stratta RJ, Taylor RJ, Langnas AN, Bynon JS, Shaw BW Jr. Surgical complications in solitary pancreas and combined pancreas–kidney transplantations. *Am J Surg* 1992; 164: 546–551.
7. Venstrom JM, McBride MA, Rother KI, Hirshberg B, Orchard TJ, Harlan DM. Survival after pancreas transplantation in patients with diabetes and preserved kidney function. *JAMA* 2003; 290: 2817–2823.
8. Buron F, Thaunat O, Demuylder-Mischler S, Badet L, Brunet M, Ber CE et al. Pancreas retransplantation: a second chance for diabetic patients? *Transplantation* 2013; 95: 347–352.
9. Gruessner AC, Gruessner RW. Long-term outcome after pancreas transplantation: a registry analysis. *Curr Opin Organ Transplant* 2016; 21: 377–385.
10. Siskind E, Maloney C, Jayaschandaran V, Kressel A, Akerman M, Shen A et al. Pancreatic retransplantation is associated with poor allograft survival: an update of the United Network for Organ Sharing database. *Pancreas* 2015; 44: 769–772.
11. Rudolph EN, Finger EB, Chondalas N, Kandaswamy R, Sutherland DE, Dunn TB. Outcomes of pancreas retransplantation. *Transplantation* 2015; 99: 367–374.
12. von Elm E, Altman DG, Egger M, Pocock SJ, Gotzsche PC, Vandenhoute JP, STROBE Initiative. The Strengthening the Reporting of Observational Studies in Epidemiology (STROBE) statement: guidelines for reporting observational studies. *Lancet* 2007; 370: 1453–1457.
13. Troppmann C, Gruessner AC, Dunn DL, Sutherland DE, Gruessner RW. Surgical complications requiring early relaparotomy after pancreas transplantation: a multivariate risk factor and economic impact analysis of the cyclosporine era. *Ann Surg* 1998; 227: 255–268.
14. Escherthuber S, Hohlrieder M, Boesmuller C, Pomaroli A, Steurer W, Junker T et al. Incidence of coronary heart disease and cardiac events in patients undergoing kidney and
pancreatic transplantation. Transplant Proc 2005; 37: 1297–1300.

15 Gruessner R. Recipient procedures. In Transplantation of the Pancreas, Gruessner RWG, Sutherland DER (eds). Springer: New York, 2004; 150–178.

16 Clavien PA, Barkun J, de Oliveira ML, Vauthey JN, Dindo D, Schulick RD et al. The Clavien–Dindo classification of surgical complications: five-year experience. Ann Surg 2009; 250: 187–196.

17 Schwarz C, Mühlbacher J, Böhmig GA, Purtic M, Pabliz E, Unger L et al. Impact of ultrasound examination shortly after kidney transplantation. Eur Surg 2017; 49: 140–144.

18 Margreiter C, Aigner F, Resch T, Berenji AK, Oberhuber R, Sucher R et al. Enteroscopic biopsies in the management of pancreas transplants: a proof of concept study for a novel monitoring tool. Transplantation 2012; 93: 207–213.

19 Giannarelli R, Coppelli A, Sartini MS, Del Chiario M, Vistoli F, Rizzo G et al. Pancreas transplant alone has beneficial effects on retinopathy in type 1 diabetic patients. Diabetologia 2006; 49: 2977–2982.

20 Fioretto P, Mauer M. Reversal of diabetic nephropathy: lessons from pancreas transplantation. J Nephrol 2012; 25: 13–18.

21 Martins LS, Outerelo C, Malheiro J, Fonseca IM, Henriques AC, Dias LS et al. Health-related quality of life may improve after transplantation in pancreas–kidney recipients. Clin Transplant 2015; 29: 242–251.

22 Ollinger R, Margreiter C, Bösmüller C, Weissenbacher A, Frank F, Schneeberger S et al. Evolution of pancreas transplantation: long-term results and perspectives from a high-volume center. Ann Surg 2012; 256: 780–786.

23 Gruessner RW. Immunosuppression after pancreas transplantation. Transplant Proc 2005; 37: 1663–1666.

24 Voskuil MD, Mittal S, Sharples EF, Vaidya A, Gilbert J, Friend PJ et al. Improving monitoring after pancreas transplantation alone: fine-tuning of an old technique. Clin Transplant 2014; 28: 1047–1053.

25 Douzdjian V, Guigliuzza KG, Fish JC. Multivariate analysis of donor risk factors for pancreas allograft failure after simultaneous pancreas–kidney transplantation. Surgery 1995; 118: 73–81.

26 Odorico JS, Heisey DM, Voss BJ, Steiner DS, Knechtle SJ, D’Alessandro AM et al. Donor factors affecting outcome after pancreas transplantation. Transplant Proc 1998; 30: 276–277.

27 Humar A, Ramcharan T, Kandaswamy R, Gruessner RW, Gruessner AG, Sutherland DE. The impact of donor obesity on outcomes after cadaver pancreas transplants. Am J Transplant 2004; 4: 605–610.

28 Gruessner AC, Sutherland DE, Gruessner RW. Pancreas transplantation in the United States: a review. Curr Opin Organ Transplant 2010; 15: 93–101.

29 Sansalone CV, Maione G, Rossetti O, Aseni P, Soldano S, De Roberto A et al. Pancreas retransplantation: ideal timing and early and late results. Transplant Proc 2006; 38: 1153–1155.

30 Fellmer P, Lanzenberger K, Ulrich F, Pascher A, Langrehr J, Jonas S et al. Complication rate of pancreas retransplantation after simultaneous pancreas–kidney transplantation compared with pancreas after kidney transplantation. Transplant Proc 2007; 39: 563–564.

31 LaMattina JC, Sollinger HW, Becker YT, Mezrich JD, Firsch JD, Odorico JS. Simultaneous pancreas and kidney (SPK) retransplantation in prior SPK recipients. Clin Transplant 2012; 26: 495–501.

32 Morel P, Schumpf R, Dunn DL, Moudry-Munns K, Najarian JS, Sutherland DE. Pancreas retransplants compared with primary transplants. Transplantation 1991; 51: 825–833.

33 Bösmüller C, Maglione M, Margreiter C, Dziodzio T, Biel M, Pratschke J et al. Successful combined pancreas fourth–kidney third and pancreas third–kidney second transplantation: a case report. Transplant Direct 2015; 1: e22.

34 Fine RN, Becker Y, De Geest S, Eisen H, Ettenger R, Evans R et al. Nonadherence consensus conference summary report. Am J Transplant 2009; 9: 35–41.

35 Berney T, Malaise J, Morel P, Toso C, Demuylder-Mischler S, Majno P et al.; Euro-SPK Study Group. Impact of HLA matching on the outcome of simultaneous pancreas–kidney transplantation. Nephrol Dial Transplant 2005; 20(Suppl 2): ii48–ii53, ii62.

36 Holmes-Walker DJ, Kay TW. Long-term effects of islet transplantation. Curr Opin Organ Transplant 2016; 21: 497–502.

37 Gruessner RW, Gruessner AC. Pancreas transplant alone: a procedure coming of age. Diabetes Care 2013; 36: 2440–2447.

38 Finger EB, Radosevich DM, Dunn TB, Chinnakotla S, Sutherland DE, Matas AJ et al. A composite risk model for predicting technical failure in pancreas transplantation. Am J Transplant 2013; 13: 1840–1849.

39 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: 269–275.