Improved surgical outcomes following simultaneous pancreas-kidney transplantation in the contemporary era

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Abstract

Background: Complications leading to early technical failure have been the Achilles’ heel of simultaneous pancreas-kidney transplantation (SPKT). The study purpose was to analyze longitudinally our experience with early surgical complications following SPKT with an emphasis on changes in practice that improved outcomes in the most recent era.

Study design: Single center retrospective review of all SPKTs from 11/1/01 to 8/12/20 with enteric drainage. Early relaparotomy was defined as occurring within 3 months of SPKT. Patients were stratified into two sequential eras: Era 1 (E1): 11/1/01–5/30/13; Era 2 (E2) 6/1/13–8/12/20 based on changes in practice that occurred pursuant to donor age and pancreas cold ischemia time (CIT).

Results: 255 consecutive SPKTs were analyzed (E1, n = 165; E2, n = 90). E1 patients received organs from older donors (mean E1 27.3 vs. E2 23.1 years) with longer pancreas cold CITs) (mean E1 16.1 vs. E2 13.3 h, both p < .05). E1 patients had a higher early relaparotomy rate (E1 43.0% vs. E2 14.4%) and were more likely to require allograft pancreatectomy (E1 9.1% vs. E2 2.2%, both p < .05). E2 patients underwent systemic venous drainage more frequently (E1 8% vs. E2 29%) but pancreas venous drainage did not influence either relaparotomy or allograft pancreatectomy rates. The most common indications for early relaparotomy in E1 were allograft thrombosis (11.5%) and peri-pancreatic phlegmon/abscess (8.5%) whereas in E2 were thrombosis, pancreatitis/infection, and bowel obstruction (each 3%).

Conclusion: Maximizing donor quality (younger donors) and minimizing pancreas CIT are paramount for reducing early surgical complications following SPKT.

KEYWORDS
allograft pancreatectomy, cold ischemia time, donor age, early relaparotomy, era, pancreas thrombosis, simultaneous pancreas-kidney transplant
Vascularized pancreas transplantation (PTx) entails a major surgical procedure and the necessity for long-term immunosuppression. Therefore, the history of PTx largely parallels advances in surgical techniques and clinical immunosuppression, which have led to steadily improving outcomes over time. According to the International Pancreas Transplant Registry (IPTR), as of 2022, >36 000 PTxs have been performed in the United States (US) in the past 50+ years.1–3 Success rates for PTx have progressively improved secondary to refinements in diagnostic and therapeutic technologies and surgical techniques, advancements in immunosuppression and anti-infective prophylaxies, new and more effective techniques in organ retrieval and preservation technology, and increased experience in the selection of donors and recipients.1–3

In the 1980s, the introduction of bladder drainage of the exocrine secretions revolutionized the safety and improved the success of PTx.4 However, starting in 1995, a seismic shift from bladder to enteric exocrine drainage occurred coincident with improvements in immunosuppression, preservation techniques, diagnostic monitoring, general medical care, and the success and frequency of enteric conversion.5 At present, most PTxs are performed as whole organ pancreaticoduodenal grafts with systemic venous delivery of insulin and enteric exocrine drainage (systemic-enteric [S-E] technique).3–5 To improve the physiology of PTx, an innovative surgical technique of intraperitoneal portal venous drainage using an anterior approach to the superior mesenteric vein (SMV) was developed by Gaber et al.6 and subsequently refined to a “retroperitoneal” or lateral approach by Boggi et al.7 combining portal venous delivery of insulin with enteric drainage of the exocrine secretions (portal-enteric [P-E] technique). However, the potential of P-E drainage has never been fully realized as it is currently performed in only 12% of SPKTs in the US.1–3

Although nearly all PTxs are performed with one of the above techniques, contemporary philosophy dictates that the most appropriate technique is the one with which the surgical team has the most experience and confidence.4,8 At our center, we have extensive experience with each technique but currently perform P-E drainage preferentially using the anterior approach to the SMV.4,8,9 Entering the new millennium, surgical complication rates following PTx ranged from 25% to 50% including allograft pancreatectomy for thrombosis in 5%–10% of cases.10–12 Although rates of surgical complications have decreased over time, some centers still report early relaparotomy rates of 20%–40%.13–17 The purpose of this study was to examine outcomes in SPKT recipients with either P-E or S-E drainage at our center in the new millennium with an emphasis on risk factors and changes in decision-making that have led to a reduction in surgical complications in the most recent era.

2 | METHODS

2.1 | Study design

We retrospectively reviewed 255 consecutive SPKTs performed at our center from November 2001 (inception of our PTx program) to August 2020 (minimum 16 month follow-up) including 216 with P-E drainage and 39 with S-E drainage. A total of 23/39 (59%) of SPKTs with S-E drainage were performed from July 2018 to August 2020, which coincided with the addition of a new surgeon. S-E drainage accounted for half of the SPKTs performed during the last 2 years of the study period. For study purposes, SPKT recipients were stratified into 2 sequential study eras: Era 1(E1): 11/1/01–5/30/13; and Era 2(E2): 6/1/13–8/12/20. These eras were not arbitrary but corresponded to a change in center-specific policies when we stopped using deceased pancreas donors ≥40 years of age and aimed to target pancreas cold ischemic times (CIT) of ≤16 h.20–22

Primary outcomes were patient survival, pancreas and kidney overall allograft survival, death-censored pancreas and kidney allograft survival, and the incidences of early relaparotomy and allograft pancreatectomy according to Era. Early relaparotomy was defined as occurring with 3 months of SPKT. Renal allograft loss was defined as death with a functioning graft (DWFG), transplant nephrectomy, return to dialysis, or kidney retransplantation. Pancreas graft loss was defined as DWFG, allograft pancreatectomy, pancreas retransplantation, or resumption of daily insulin therapy.

2.2 | Donor and recipient selection

General indications for PTx at our center were selecting patients with insulin-requiring diabetes with complications and the predicted ability to tolerate the operative procedure, manage the requisite immunosuppression, and deal with the need for close follow-up post-SPKT irrespective of C-peptide production.23–26 Specific indications for SPKT included stage 4/5 chronic kidney disease or end stage renal disease and the absence of any contraindications. Contraindications included age >65 years; insufficient cardiovascular reserve; current substance abuse; active infection or recent malignancy; major ongoing psychiatric illness, recent noncompliance or lack of adequate social support; significant obesity (body mass index [BMI] >32 kg/m²); severe vascular disease; inadequate health literacy with inability to either understand or commit to the more intense follow-up associated with SPKT compared to kidney alone transplantation; and severe frailty or sarcopenia.23–26 A history of multiple prior laparotomies was a relative contraindication to SPKT. Selection criteria for SPKT in “type 2” diabetes included patients <60 years of age, insulin-requiring for a minimum of 3 years with a total daily insulin requirement <1 U/kg/day, a fasting C-peptide level <12 ng/mL, absence of severe vascular disease or tobacco abuse, adequate cardiac function (ejection fraction >45%), and presence of “complicated” or hyperlabeile diabetes.26 For purposes
of this study, “type 2” diabetes was defined as having a pretransplant C-peptide level $\geq 2.0$ ng/ml.

### 2.3 Technical aspects

All patients were blood type ABO compatible and T- and B-cell negative by flow cytometry crossmatch. Nearly all SPKTs were initially approached as intent-to-treat with P-E drainage ($n = 216$) using an anterior approach to the SMV (pancreas positioned above the small bowel mesentery) and enteric exocrine drainage to the proximal ileum in the recipient (side-to-side duodeno-enterostomy without a diverting Roux limb). Arterial inflow was based on the recipient’s right common iliac artery through a window in the distal ileal mesentery after the pancreas dual artery blood supply was reconstructed with a donor common iliac bifurcation “Y” graft. In patients with unsuitable anatomy for P-E drainage, S-E drainage ($n = 39$) was performed with the pancreas positioned below the small bowel mesentery with vascular anastomoses to the right common iliac artery and vein. Of the first 121 SPKTs (from 11/01 to 8/10), all but two were performed by transplanting the kidney to the left iliac vessels and the pancreas to the right common or external iliac artery through a midline intraperitoneal approach. However, since 8/10, most SPKTs were performed with ipsilateral placement of the kidney and pancreas to the right iliac vessels in order to reduce operating time and to preserve the left iliac vessels for future transplantation. Most SPKTs were performed by two attending surgeons who were experienced in PTx. Two active sump drains were placed adjacent to the pancreas and kidney allografts, respectively, and removed prior to hospital discharge.

### 2.4 Anti-coagulation

In selected SPKT recipients, 2000–3000 units of intravenous heparin (30–50 u/kg) were administered as a single dose during surgery prior to implantation of the pancreas and a heparin infusion was continued post-transplant (continuous infusion of 300 u/h for 24 h, then 400 u/hour for 24 h, and then 500 u/h until post-operative day 5) in the absence of bleeding. Indications for intravenous heparin included preemptive SPKT, history of thrombophilia or clotting disorder in the recipient, small or diseased donor or recipient vessels, prolonged pancreas CIT ($>16$ h), extended donor criteria (older donor age, higher BMI, cerebrovascular cause of death), or history of prior pancreas graft thrombosis. Anti-platelet therapy, consisting of oral aspirin (81 mg/day), was administered to all patients.

### 2.5 Immunosuppression and post-transplant management

Patients received depleting antibody induction with either single dose alemtuzumab or multi-dose alternate day rabbit anti-thymocyte globulin (RATG, 1.5 mg/kg/dose, total three to five doses) in combination with tacrolimus, mycophenolate mofetil or mycophenolic acid, and tapered steroids. RATG was the primary induction agent from 2001 to 2004. From 2005 through 2008, 46 SPKT patients were prospectively randomized to receive either alemtuzumab or RATG. Since 2009, alemtuzumab has been the primary induction agent. The majority of SPKT recipients ($n = 192$) received single dose alemtuzumab induction (30 mg intravenous administered intraoperatively) in combination with tacrolimus (target 12 h trough levels 8–10 ng/ml), full dose mycophenolate (720 mg bid), and rapid prednisone taper (dose reduction to 5 mg/day by 1 month following SPKT). The remaining 63 patients received RATG induction in combination with triple maintenance immunosuppression and rapid prednisone taper as above. All patients received anti-infective prophylaxis with peri-operative cefazolin for surgical site prophylaxis, fluconazole for 1 month, valganciclovir for 3–6 months (6 months in patients for primary cytomegalovirus [CMV] exposure, 3 months for all other patients), and trimethoprim-sulfamethoxazole long-term. Most patients were discharged from the hospital after placement of a tunneled central venous catheter and received intravenous fluid and electrolyte supplementation at home for a variable period. Treatment of hypertension, hyperlipidemia, anemia, and other medical conditions was initiated as indicated, aiming to maintain the blood pressure $<160/90$ mm Hg, fasting serum cholesterol $<200$ mg/dl, and hemoglobin $>7–8$ gm/dl.

### 2.6 Statistical analysis

Data were compiled from institutional prospective and retrospective databases along with manual electronic medical record review in accordance with local Institutional Review Board guidelines and approval. Categorical data were summarized as proportions with percentages, and continuous data were summarized as means and standard deviations. Student’s t-test and one-way ANOVA tests were utilized to compare continuous variables, respectively, according to whether the data was normally distributed. For categorical variables, the chi-square test and Fisher’s exact test were utilized as appropriate to determine significance. Patient and graft survival rates (GSRs) were compared using Kaplan-Meier curves and log-rank tests. Cox multivariate regression was used to compare survival adjusting for donor and recipient characteristics. Univariate analysis was performed for each of the following variables: donor and recipient age and weight at transplant, donor cause of death, pancreas CIT, recipient race, recipient dialysis duration and type (hemodialysis, peritoneal dialysis, preemptive), organ import, method of antibody induction (alemtuzumab versus RATG), technique of transplant (P-E vs. S-E drainage), and pretransplant C-peptide level $\geq 2$ ng/ml.

Factors included in survival models were chosen a priori based on clinical significance and secondarily according to significant differences between treatment groups defined by a p-value $< .05$. Final
multivariate models included variables identified as significant in univariate analysis or if covariate was significantly different between eras. All variables used in regression models had a level of missingness <5%. Schoenfeld residuals tests were utilized to evaluate proportional hazards assumptions. Additionally, a graphical assessment of proportional hazards was performed according to log-log survival curves. Goodness of fit was assessed according to chi-squared statistics for survival models. A two-sided p-value of <.05 was considered to be significant. All analyses were performed using STATA/IC 15.1 for Windows (College Station, TX).

3 | Results

We studied retrospectively 255 consecutive SPKTs performed at our center from November 2001 to August 2020 (minimum 16 month follow-up) including 216 with P-E drainage and 39 with S-E drainage. A total of 84 patients (32.9%) underwent early relaparotomy in the first 3 months post-SPKT. From November 2001 through May 2013 (E1), we performed 165 SPKTs including 152 (92.1%) with P-E and 13 (7.9%) with S-E drainage. From June 2013 to August 2020 (E2), we performed 90 SPKTs including 64 (71.1%) with P-E and 26 with S-E drainage (28.9%, p < .0001 compared to E1). Table 1 compares donor/preservation/immunological characteristics between the two sequential eras. In E1, 24 deceased pancreas donors (14.5%) were ≥40 years of age compared to none (p < .0001) in E2. The corresponding values for deceased pancreas donors ≥35 years of age were 28% in E1 versus 8% in E2 (p < .0001). Pancreas CITs ≥20 h occurred in 34 cases (20.6%) in E1 compared to one case (1%, p < .0001) in E2. The corresponding values for pancreas CITs > 16 h were 46% in E1 versus 23% (p = .0004) in E2. Cerebrovascular cause of death was twice as common in E1 (17%) compared to E2 (7.8%, p = .056) whereas brain death secondary to anoxia (usually from drug overdose) was twice as common in E2 (32%) compared to E1 (15%, p = .002). Increased (behavioral) risk donors were nearly 3 times more frequent in p-E (p = .001). Organ import was also more common in E2 (27%) compared to E1 (14.5%, p = .03).

Table 2 shows recipient and transplant characteristics according to era. In addition to more transplants performed with S-E drainage in E2, more patients received alemtuzumab induction (97%) in E2 compared to E1 (61%, p < .0001). E2 was also characterized by more non-Caucasian recipients (38%) compared to E1 (24%, p = .03). Time on the waiting list was on average 3.4 months shorter in E2 (p < .0001). However, in univariate analyses, none of these variables were associated with a higher risk of early relaparotomy. There were also trends towards more pretransplant peritoneal dialysis and less hemodialysis in E2 compared to E1. However, preemptive SPKT was similar (21% of cases) in both eras. There were no differences in recipient age, gender, weight, BMI, dialysis duration, or pretransplant C-peptide status according to era.

Indications for early relaparotomy according to era are displayed in Table 3. The most notable reductions in early relaparotomy occurred for thrombosis (19 vs. 3), bleeding (8 vs. 0), peri-pancreatic phlegmon/abscess (14 vs. 1), and enteric/duodenal segment leak (7 vs. 0) in E1 versus E2, respectively (all p ≤ .05).

Table 4 compares outcomes between the two sequential eras. Because follow-up was much longer in E1, only 1- and 3-year actual survival rates are displayed for direct comparative analyses. More than 86% of patients had at least 3-year follow-up. One- and 3-year patient and kidney GSRs were not significantly different in the two eras. However, 1- and 3-year pancreas GSRs were significantly higher in E2, even when censoring for early allograft pancreatectomy. In Kaplan-Meier analysis, patient survival was comparable between eras (log rank: p = .18) (see Figure 1). There were also no significant differences in overall or death-censored kidney GSRs according to era, but there was a trend towards an improved overall kidney GSR in E2 (log rank: p = .06; see Figure 2), not seen once limited to death-censored graft survival (log rank: p = .1; see Figure 3). Overall and death-censored pancreas GSRs were significantly higher in E2 compared to E1 (log rank: p = .002 and p = .0007, respectively; see Figures 4 and 5). Importantly, the incidence of early relaparotomy was reduced threefold in

### Table 1: Comparison of donor, preservation, and immunological characteristics according to era

|                | Era 1 | Era 2 | p-Value |
|----------------|-------|-------|---------|
| **Mean ± SD**  |       |       |         |
| Donor age (years) | 27.3±11.2 | 23.1±7.2 | .002    |
| Donor age ≥35 years | 46 (27.9%) | 7 (7.8%) | <.0001  |
| Donor gender: Female | 58 (35.2%) | 27 (30%) | .4      |
| Donor Race: Caucasian | 117 (70.9%) | 59 (65.6%) | .06    |
| African American | 36 (21.8%) | 18 (20%) |         |
| Other | 12 (7.3%) | 13 (14.4%) |         |
| Donor weight (kg) | 71.6±15.9 | 70.1±17.4 | .5      |
| Donor weight ≥85 kg | 31 (18.8%) | 18 (20%) | .81     |
| Donor BMI (kg/m²) | 23.9±4.1 | 24.2±6.0 | .62     |
| Donor BMI ≥28 kg/m² | 26 (15.8%) | 19 (21.1%) | .28     |
| Donor cause of death |         |       |         |
| Head trauma | 112 (67.9%) | 54 (60%) | .22     |
| Cerebrovascular event | 28 (17%) | 7 (7.8%) | .056    |
| Anoxia | 25 (15.1%) | 29 (32.2%) | .002    |
| Increased risk donor | 12 (7.3%) | 18 (20%) | .001    |
| Pancreas cold ischemia (hours) | 16.1±4.2 | 13±3.4 | <.0001  |
| Pancreas CIT ≥20 h | 34 (20.6%) | 1 (1.1%) | <.0001  |
| Five to six HLA-mismatch | 93 (56.4%) | 45 (50%) | .36     |
| HLA-mismatch | 4.5±1.2 | 4.4±1.4 | .28     |
| cPRA ≥20% | 19 (11.5%) | 10 (11.1%) | 1.0     |
| CMV donor+/Recipient- | 48 (29.1%) | 25 (27.8%) | .88     |
| Retransplant | 6 (3.6%) | 2 (2.2%) | .72     |
| Organ import | 24 (14.5%) | 24 (26.7%) | .028    |
| KDPI (%) | 20±18 | 20±15 | .86     |

Bold value indicates p < 0.05.

Abbreviations: BMI, body mass index; HLA, human leukocyte antigen; KDPI, kidney donor profile index.

Table 4 shows recipient and transplant characteristics according to era. In addition to more transplants performed with S-E drainage in E2, more patients received alemtuzumab induction (97%) in E2 compared to E1 (61%, p < .0001). E2 was also characterized by more non-Caucasian recipients (38%) compared to E1 (24%, p = .03). Time on the waiting list was on average 3.4 months shorter in E2 (p < .0001). However, in univariate analyses, none of these variables were associated with a higher risk of early relaparotomy. There were also trends towards more pretransplant peritoneal dialysis and less hemodialysis in E2 compared to E1. However, preemptive SPKT was similar (21% of cases) in both eras. There were no differences in recipient age, gender, weight, BMI, dialysis duration, or pretransplant C-peptide status according to era.
TABLE 2  Comparison of recipient and transplant characteristics according to era

|                          | Era 1 | Era 2 | p-Value |
|--------------------------|-------|-------|---------|
| **Mean ± SD**            |       |       |         |
| **N**                    | 165   | 90    |         |
| Recipient age            | 42.7 ± 9.4 | 42.1 ± 9.7 | .63     |
| Recipient age ≥ 45 years | 67 (40.6%) | 36 (40%) | .93     |
| Recipient gender: Female | 70 (42.2%) | 42 (46.7%) | .51     |
| Recipient race: Caucasian | 125 (75.8%) | 56 (62.2%) | .03     |
| African American         | 38 (23.0%) | 28 (31.1%) |         |
| Other                    | 2 (1.2%) | 6 (6.7%) |          |
| Recipient weight         | 71.3 ± 13.9 | 71.1 ± 12.9 | .91     |
| Recipient weight ≥ 85 kg | 29 (17.6%) | 15 (16.7%) | .85     |
| Recipient BMI (kg/m²)    | 24.5 ± 3.1 | 24.5 ± 3.5 | .95     |
| Dialysis history: Hemodialysis | 90 (54.6%) | 40 (44.5%) | .15     |
| Peritoneal dialysis      | 39 (23.6%) | 31 (34.4%) | .08     |
| None (preemptive)        | 36 (21.8%) | 19 (21.1%) | .10     |
| Duration of dialysis (months) | 25.0 ± 21.2 | 23.5 ± 22.4 | .63     |
| Dialysis duration ≥ 24 months | 48 (29.1%) | 20 (22.2%) | .30     |
| Pretransplant C-peptide ng/ml | 31 (18.8%) | 19 (21.1%) | .66     |
| Time on waiting list (months) | 10.3 ± 7.4 | 6.9 ± 8.2 | <.0009 |
| Alemtuzumab induction    | 101 (61.2%) | 87 (96.7%) | <.0001 |
| Systemic-enteric technique | 13 (7.9%) | 26 (28.9%) | <.0001 |

Bold value indicates \( p < 0.05 \).
Abbreviation: BMI, body mass index.

E2 (14.4%) compared to E1 (43%, \( p < .0001 \)). Similarly, the incidence of early allograft pancreactectomy decreased from 9% in E1 to 2% in E2 (\( p = .04 \)). The incidences of pancreas thrombosis (8% E1 vs. 2% E2, \( p = .09 \)) and multiple laparotomies (10% E1 vs. 1% E2, \( p = .0075 \)) were each diminished in E2 compared to E1, which was reflected by a significantly reduced length of hospital stay in E2 (Table 4).

In Cox multivariate regression (Table 5), E1 and E2 had comparable patient survival rates after adjusting for multiple donor and recipient variables (HR = .44, 95% CI = .14–1.35). Recipient age was the only significant predictor of mortality with a 3% increased mortality hazard per year (HR = 1.03, 95% CI = 1.002–1.06). E2 was not associated with a difference in death-censored kidney graft survival after adjustment according to the multivariate model (HR = .43, 95% CI = .16–1.15, \( p = .09 \)). Older recipient age was associated with a reduced hazard of death-censored kidney graft failure of 3% per year of age (HR = .97, 95% CI = .94–.99). African-American recipients had an almost double hazard of death-censored kidney graft failure compared with other races in the cohort (HR = 1.88, 95% CI 1.02–3.46, \( p = .04 \)). However, race was no longer a significant predictor of graft failure once recipient weight ≥ 85 kg and P-E drainage were removed from the final model (HR = 1.55, 95% CI 85–2.82, \( p = .15 \), Table 5).

E2 was associated with 71% decreased odds of early relaparotomy compared to E1 (OR = 29, 95% CI = 14.59) after adjusting for differences in donor age, pancreas CIT, portal vs systemic drainage, and recipient weight (Table 5). Pancreas CIT was a significant predictor of increased odds of early relaparotomy with a 9% increased odds per hour (OR = 1.09, 95% CI = 1.02–1.18). E2 was also associated with a 58% decreased hazard of pancreas graft failure compared to E1 (HR = .42, 95% CI = .18–.98).

### 4 DISCUSSION

One of the purported reasons for the lack of growth and universal acceptance of PTx is the perception amongst diabetes care professionals that it is a “radical” therapy requiring major surgery and lifelong immunosuppression for a “benign” yet life-shortening disease. Other available treatment options are less invasive and, for that reason alone, are more appealing to diabetologists, endocrinologists, and primary care physicians. Prior to the new millennium, the “developmental” phase of PTx was characterized by refinements in surgical techniques in response to a myriad of surgical complications.4,5,10–13 The goal of PTx is to safely transplant functioning islet cells, which represent about 2% of the total human pancreas mass. Ironically, surgical complications arise from the remaining 98% of the non-endocrine portions of the gland (i.e., leaks, pancreatitis, infection, and vascular issues) and remain important because they can lead to graft loss, morbidity, mortality and increased health care costs.5,13,18,29 With improved surgical
TABLE 4  Outcomes according to era

|                              | Era 1                      | Era 2                      | p-Value |
|------------------------------|---------------------------|----------------------------|---------|
| **Mean ± SD**                |                           |                            |         |
| One year patient survival    | 159 (96.4%)               | 90 (100%)                  | .093    |
| One year kidney graft survival| 157 (95.2%)               | 89 (98.9%)                 | .166    |
| One year pancreas graft survival| 142 (86.1%)               | 88 (97.8%)                 | .0018   |
| 1-year pancreas survival censored for early allograft pancreatectomy | 142/150 (94.7%)           | 88/88 (100%)               | .028    |
| Actual 3-year patient survival| 154/165 (93.3%)           | 54/55 (98.2%)              | .30     |
| Actual 3-year kidney survival  | 141/165 (85.5%)           | 52/55 (94.5%)              | .0965   |
| Actual 3-year pancreas survival| 128/165 (77.6%)           | 51/55 (92.7%)              | .015    |
| Three-year pancreas survival censored for early allograft pancreatectomy | 128/150 (85.3%)           | 51/53 (96.2%)              | .045    |
| DWFGs                        | 31                         | 3                          | *       |
| DWFG - Kidney                | 10                         | 1                          | *       |
| DWFG - Pancreas              | 14                         | 0                          | *       |
| DCGS** - Kidney             | 74/124 (59.7%)            | 81/86 (94.2%)              | *       |
| DCGS** - Pancreas            | 59/120 (49.2%)            | 80/87 (92%)                | *       |
| Pancreas graft survival censored for death + early pancreatectomy | 59/105 (56.2%)            | 80/85 (94.2%)              | *       |
| Follow-up (months)           | 137 ± 56                   | 48 ± 25                    | <.001   |
| Early relaparotomy           | 71 (43.0%)                 | 13 (14.4%)                 | <.0001  |
| Kidney thrombosis            | 1 (.6%)                    | 1 (1.1%)                   | 1.0     |
| Pancreas thrombosis          | 13 (7.9%)                  | 2 (2.2%)                   | .09     |
| Allograft pancreatectomy     | 15 (9.1%)                  | 2 (2.2%)                   | .037    |
| Multiple laparotomies        | 16 (9.7%)                  | 1 (1.1%)                   | .0075   |
| Initial length of stay (days)| 11.3 ± 6.7                 | 8.6 ± 4.6                  | .0012   |

Bold value indicates $p < 0.05$.
*Follow-up much longer in Era 1.
**DCGS – Death-censored graft survival.

FIGURE 1  Patient survival following SPKT according to Era

outcomes over time, however, exocrine drainage is no longer the ‘Achilles’ heel’ of PTx and vascular complications have become the most relevant surgical complication with respect to early relaparotomy and graft loss.4,13–19

At present, 5%–7% of all PTxs in the US are still lost secondary to early technical failure (depending on transplant category) with reoperative rates ranging from 12% to 44%.1–3,13–19 Graft thrombosis continues to be the leading cause of technical failure in the current era, accounting for 80% of early technical pancreas graft losses.2,28,30

Other reasons for early technical failure include anastomotic leaks, pancreatitis, bleeding, infection, and primary nonfunction. In addition, gastrointestinal, urologic, and wound complications may contribute to poor early outcomes and surgical morbidity. Potential risk factors for surgical complications following PTx include donor factors (donor age $>$40–45 years, stroke as a cause of brain death, donation after cardiocirculatory death, donor BMI $>$ 30 kg/m²), procurement and
preservation factors (procurement injury, over-flushing of the pancreas during the donor procedure, prolonged cold ischemia [>14-16 h]), recipient factors, and technical considerations.\textsuperscript{5,13-22,31-34} Consequently, it is worth re-emphasizing that the keys to minimizing surgical complications following SPKT include selecting appropriate donors and recipients, performing meticulous bench and intraoperative sur-

![Figure 3](image1)

**Figure 3** Death-censored kidney graft survival following SPKT according to Era

![Figure 4](image2)

**Figure 4** Pancreas graft survival following SPKT according to Era

![Figure 5](image3)

**Figure 5** Death-censored pancreas graft survival following SPKT according to Era

gical work, minimizing warm and cold ischemia, providing appropriate medical management including selective anti-coagulation and evidence-based immunosuppression, and maintaining close follow-up post-operatively to address issues in a timely fashion.

Recognizing that our early surgical complication rate following SPKT was excessive in the first and early second decade of the new millennium, in May 2013 we made intentional changes in our practice that included using younger donors (preferably <35 years of age) and attempting to keep pancreas CITs \(\leq 16\) h. Historically, we have always been reluctant to use donors with a BMI \(\geq 30\) kg/m\(^2\), which has remained consistent in our practice during the period of study. As shown in Table 1, these changes in practice were associated with a marked reduction in donor age and pancreas CIT when comparing E1 to E2. Paradoxically, organ import was nearly doubled in E2 but was associated with greater use of charter aircraft in order to minimize CIT. A consequence of younger donor selection was a reduction in using organs from donors with a cerebrovascular cause of brain death coupled with an increase in donors with anoxic encephalopathy (usually secondary to drug overdose). Parenthetically, changes in causes of donor death coincided with the opioid epidemic and our increasing comfort level with using organs from increased behavioral risk donors for SPKT (which nearly tripled from E1 to E2).

When analyzing the “era effect,” it is important to note that the majority of SPKTs were performed by three experienced PTx surgeons in E1, usually with two attending surgeons performing the transplant together. Our transplant surgery fellowship program did not start until 2007 and expanded from one to two fellows in 2012. We added a fourth attending surgeon in 2011 and a fifth surgeon in 2018. Although one might attribute improved outcomes over time to a “learning curve,” we do not believe that this played a major role because less experienced staff performed some of the SPKTs in E2. As shown in Tables 3 and 4, outcomes were clearly superior in the most recent era, which we attribute predominantly to better donor selection and minimizing pancreas CIT. In both eras, vascular complications (particularly thrombosis) were the most common cause for early relaparotomy (Table 3). A number of studies have demonstrated that early vascular thrombosis can be minimized if not eliminated by keeping pancreas cold ischemia times to 12 h or less.\textsuperscript{5,12,21,22} In most cases, early graft thrombosis is not due to anastomotic or other technical problems but is venous in origin and related to the relatively low-flow state of the pancreas. In addition, the development of local and systemic hypercoagulability and pancreatic edema following reperfusion may further impair microcirculatory flow in the pancreas that may lead to thrombosis. Other donor and preservation factors have been implicated as well.\textsuperscript{28,30,35-40} Specific risk factor analysis is rendered difficult by the wide array of variables implicated in the pathogenesis of pancreas graft thrombosis.

A major limitation of this study is its retrospective nature spanning nearly 19 years. Changes in practice and personnel have occurred over time and one might fully expect improved outcomes with increasing experience. However, it was extremely discouraging for us to have an early relaparotomy rate in excess of 40% spanning >12 years in the hands of three experienced PTx surgeons (all former directors of PTx
at other centers) in E1. A major change in practice (and philosophy) was required in order to achieve better outcomes in E2. In recent years (E2), we have performed SPKT in a higher proportion of non-Caucasian recipients (Table 2) without any apparent detrimental effect on early surgical outcomes. When censoring for early allograft pancreatectomy, the pancreas GSR in E1 was still significantly lower compared to E2 (Table 4).

It is important to note that method of antibody induction and technique of transplant did not influence the rate of surgical complications in this study. Operating times were similar in the two eras even though junior personnel were more involved in the cases over time. Our use of selective anti-coagulation, maintenance immunosuppression, anti-infective prophylaxes, and discharging patients on supplemental intravenous fluids were consistent throughout the study period. Consequently, we do not believe that these factors contributed significantly to the improvement in surgical outcomes in the most recent era. At our center, all of the kidney and kidney-pancreas offers come directly to the attending surgeon on call, who then makes the decisions regarding organ acceptance, recipient selection, transportation arrangements, and timing of the transplant surgery.

One might assert that implementing more stringent donor selection (younger donor age, low BMI) and reducing CIT may further aggravate stagnation in the field of pancreas transplantation, which has occurred over the past several years. With broader geographic sharing based upon concentric circle distribution, logistical issues have become an increasingly critical component of the decision-making algorithm whether to accept or refuse an organ offer. However, we were able to lower CIT in era 2 in the setting of importing more organs by “treating” an SPKT similar to a lung, liver, or heart transplant with more liberal use of charter aircraft. It is our contention that by keeping pancreas CIT to a minimum, this actually permits the use of non-ideal donors but may increase transportation costs. In some instances, the local organ procurement organization may be willing to split transportation costs with the transplant center. Otherwise, most of these costs can be recaptured on the Medicare Cost Report as a pretransplant expense. In any event, increasing upfront costs are offset by lower costs following transplant related to fewer surgical complications. Moreover, there exists a relative surplus of pancreas grafts available, as the pancreas is the most underutilized solid organ other than intestine. For example, circa 2000, SPKTs represented 11% of all deceased donor kidney transplant activity in the US. Since 2020, less than 5% of deceased donor kidneys in the US have been utilized for SPK transplantation in spite of liberalization of recipient selection criteria to include older patients, minorities, and patients with a type 2 diabetes phenotype. Finally, if rates of early relaparotomy of 10%–15% and early thrombosis rates of <3% becomes the “standard of care” in SPKT, there likely will be greater interest (in the transplant, nephrology, and diabetes communities) in offering this procedure to more patients with diabetes and chronic kidney disease.

Another limitation in this study is that having 11 covariates and 80 graft losses might result in a regression model that is overfit. However, we have reasonably sized cohorts with granular data who received standardized management, which are weaknesses of large registry studies. Moreover, we performed a multivariate analysis that adjusted for differences between eras at the risk of overfitting the model by including many different variables that were significantly different. We attempted to address this limitation by also examining univariate models and by performing sensitivity analyses with pared down models, which documented stability of our key findings included herein. Furthermore, the differences in surgical outcomes are dramatic and the
regression analysis failed to identify any other significant factors to explain this finding.

5 | CONCLUSIONS

Entering the new millennium, early surgical complication rates following PTx ranged from 25% to 50%.10-12 Although surgical complications following PTx remain problematic, the frequency has decreased over time to 10%–20% in some reports.5,12 Aside from graft losses, surgical complications increase morbidity, mortality, costs, and may affect the kidney allograft as well. The best strategy to limit complications is prevention and we have experienced a marked reduction in early relaparotomy and the need for allograft pancreatectomy in the past 7 years by selecting younger donors who are not obese and minimizing pancreas CITs. Our data suggest that donor and preservation factors eclipse recipient factors with respect to early surgical complications in patients who are not obese. Perhaps the “learning curve” takeaway from this study is related more to decision-making regarding donor selection and logistics to minimize pancreas CIT rather than any perceived improvement in surgical technique related to surgeon experience. In spite of using more import organs at donors at a greater distance from our transplant center in era 2, surgical outcomes were superior provided that arrangements were made (often with charter aircraft) to minimize CIT. Given the current allocation system based on concentric circle distribution and broader geographic sharing and the prospect of continuous distribution, it is important to note that minimizing pancreas CIT is paramount, attainable, and has the potential to expand pancreas transplant activity because of a more acceptable benefit to risk ratio.

CONFLICT OF INTERESTS

None of the others authors have any conflicts of interest to disclose pursuant to this study.

DATA AVAILABILITY STATEMENT

The data that support the findings of this study are available on request from the corresponding author. The data are not publicly available due to privacy or ethical restrictions.

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