Exocrine drainage in vascularized pancreas transplantation in the new millennium

Hany El-Hennawy, Robert J Stratta, Fowler Smith

Abstract

The history of vascularized pancreas transplantation largely parallels developments in immunosuppression and technical refinements in transplant surgery. From the late-1980s to 1995, most pancreas transplants were whole organ pancreatic grafts with insulin delivery to the iliac vein and diversion of the pancreatic ductal secretions to the urinary bladder (systemic-bladder technique). The advent of bladder drainage revolutionized the safety and improved the success of pancreas transplantation. However, starting in 1995, a seismic change occurred from bladder to bowel exocrine drainage coincident with improvements in immunosuppression, preservation techniques, diagnostic monitoring, general medical care, and the success and frequency of enteric conversion. In the new millennium, pancreas transplants are performed predominantly as pancreatico-duodenal grafts with enteric diversion of the pancreatic ductal secretions coupled with iliac vein provision of insulin (systemic-enteric technique). The portal-enteric technique has spawned a number of newer and revisited techniques of enteric exocrine drainage including duodenal or gastric diversion. Reports in the literature suggest no differences in pancreas transplant outcomes irrespective of type of either venous or exocrine diversion. The purpose of this review is to examine the
In the United States, solitary pancreas transplants has been captured in the ensuing 13 cases performed between 1966 and 1973, however, Lillehei et al.6 transplanted a pancratico-duodenal graft with either an external ostomy/cutaneous fistula or connection between the recipient bowel and graft duodenum for exocrine drainage. Consequently, optimal management of the pancreatic ductal secretions was identified as a controversy very early in the development of pancreas transplantation. In the late 1970s and early 1980s, partial or segmental pancreatic grafts (based on the body and tail of the pancreas) with pancreatic ductal ligation or occlusion were the preferred methods of controlling the pancreatic secretions5,9. During this developmental phase, exocrine drainage techniques were considered to be the “Achilles’ heel” of pancreas transplantation. The introduction of bladder diversion of the exocrine secretions into clinical transplantation in the mid-1980s revolutionized the safety and improved the success of pancreas transplantation10. From this point in time onward, whole organ pancreaticoduodenal largely replaced segmental pancreas grafts as the preferred method of transplantation. However, segmental pancreas grafts remain the only surgical option in pancreas transplantation from living donors5,11. From 1988 to 1995, > 90% of pancreas transplants in the United States were whole organ pancreatic grafts with iliac vein and bladder exocrine diversion (systemic-bladder technique), usually using a trimmed segment of donor duodenum inclusive of the ampulla of Vater as a channel for drainage of the exocrine pancreas12.

In uremic patients with type 1 diabetes mellitus, SPK transplantation is a highly regarded treatment alternative because it addresses both kidney failure and diabetes3. The number of United States annual pancreas transplants reached a high of 1484 in 2004 and had dropped to < 1000 by 20141,3. The number of annual pancreas transplants reported to the Eurotransplant Network has similarly declined in the past decade whereas annual activity in the United Kingdom has remained relatively stable and activity elsewhere in the world has increased1-3. In spite of declining numbers, outcomes have continued to improve and include higher risk groups such as African-Americans, patients with a phenotype suggesting “type 2 diabetes” and solitary pancreas transplant recipients1,9. Five year patient survival rates are now nearly 90% across all three transplant types and 10-year patient survival is > 70% in all three groups. Moreover, insulin independence is sustained at 5 years in 73% of SPK, 64% of PAK, and 53% of PTA recipients. The pancreas graft half-life is currently 10-15 years, which is amongst the lengthiest for extra-renal transplants2.

Evolution in surgical techniques has characterized and paralleled the growth and development of pancreas transplantation. In late 1966 at the University of Minnesota, Kelly et al.6 reported the first human pancreas transplant. The initial case was an SPK transplant with a segmental pancreas graft implanted in the iliac fossa with ligation of the pancreatic duct. In the ensuing 13 cases performed between 1966 and 1973, however, Lillehei et al.6 transplanted a pancratico-duodenal graft with either an external ostomy/cutaneous fistula or connection between the recipient bowel and graft duodenum for exocrine drainage. Consequently, optimal management of the pancreatic ductal secretions was identified as a controversy very early in the development of pancreas transplantation. In the late 1970s and early 1980s, partial or segmental pancreatic grafts (based on the body and tail of the pancreas) with pancreatic ductal ligation or occlusion were the preferred methods of controlling the pancreatic secretions5,9. During this developmental phase, exocrine drainage techniques were considered to be the “Achilles’ heel” of pancreas transplantation. The introduction of bladder diversion of the exocrine secretions into clinical transplantation in the mid-1980s revolutionized the safety and improved the success of pancreas transplantation10. From this point in time onward, whole organ pancreaticoduodenal largely replaced segmental pancreas grafts as the preferred method of transplantation. However, segmental pancreas grafts remain the only surgical option in pancreas transplantation from living donors5,11. From 1988 to 1995, > 90% of pancreas transplants in the United States were whole organ pancreatic grafts with iliac vein and bladder exocrine diversion (systemic-bladder technique), usually using a trimmed segment of donor duodenum inclusive of the ampulla of Vater as a channel for drainage of the exocrine pancreas12.

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INTRODUCTION

Since the inception of the International Pancreas Transplant Registry (IPTR) in 1984, data on > 48000 pancreas transplants has been captured in the ensuing 30 years1. There exist 3 major types of vascularized pancreas transplantation; simultaneous pancreas-kidney (SPK), sequential pancreas after kidney (PAK), and pancreas transplantation alone (PTA). Solitary pancreas transplants refer to the PAK and PTA types. They are usually analyzed together because of similar outcomes coupled with the fact that these procedures are performed in the absence of uremia. However, the state of kidney function is quite different; post-uremic in PAK compared to non-uremic in PTA. In the past 3 decades, the results of SPK transplantation have been superior to solitary pancreas transplantation although the disparity in outcomes has decreased over time. In the United States, solitary pancreas transplants (PAK-17%, PTA-9%) represent the minority of activity while 74% are characterized as SPK transplants1-3.
Figure 1 Technique of systemic-bladder drainage with creation of an anastomosis between the allograft duodenal segment and vesical dome of the recipient bladder.

To this day, there remains controversy regarding the optimal method for managing the pancreatic exocrine secretions. By review of data provided by the IPTR, it is evident that the overwhelming majority of pancreas transplants involve whole organ pancreateo-duodenal grafts with either bowel (systemic-enteric) or bladder diversion of the pancreatic ductal secretions coupled with systemic venous delivery of insulin[1,2]. However, starting in 1995, a seismic change from bladder to bowel exocrine diversion transpired coincident with improvements in immunosuppression, preservation techniques, diagnostic monitoring, general medical care, and the success and frequency of enteric conversion[13,14]. Enteric drainage usually refers to jejunal or ileal diversion of the exocrine secretions either as a direct anastomosis or in the presence of a defunctionalized Roux en y limb. By 1998, > 50% of SPK transplants were accomplished with bowel diversion and by 2003 this figure had risen to > 80% of cases in the United States although the systemic-bladder technique was still deployed in 50% of solitary pancreas transplants[13,15]. At present, pancreas transplantation with primary enteric exocrine drainage is performed in 90% of cases in the United States from 2010-2014 although the systemic-bladder technique is a reasonable alternative in selected cases and a preferred option at specific centers[11]. Roux limb diversion is performed in a minority of cases including 21% of SPK and 15% of solitary pancreas transplants[1].

To mimic the natural physiology of the endocrine pancreas, an innovative method of portal vein delivery of insulin (by anastomosing the donor portal vein to the recipient superior mesenteric vein for venous outflow) and bowel diversion of the exocrine secretions (portal-enteric technique) was pioneered in the early 1990s and refined over the past ≥ 20 years[16,17]. At present, the proportions of enteric-drained cases with portal venous delivery of insulin are 22% in SPK, 11% in PAK, and 13% in PTA cases. Consequently, > 80% of bowel drained pancreas transplants in the United States are performed without a decompressing Roux limb of small bowel and with systemic (iliac or vena cava) venous delivery of insulin[1]. Although the promise of the portal-enteric technique has not been achieved, it has spawned a number of newer and revisited techniques of enteric exocrine drainage including duodenal or gastric diversion[18-32]. Previous reports have not shown any main variances in outcomes for bladder- or enteric-diverted pancreas transplants regardless of method of venous drainage[33-55]. Although one of the three described techniques is deployed in nearly all pancreas transplants at present, the prevailing viewpoint is that the most appropriate procedure to be used is best determined both by recipient and donor anatomy as well as the practicing surgeon’s comfort level and experience. A number of previous excellent reviews have emphasized technical aspects of pancreas transplantation but few have been published in the past 6 years[52,56-64]. The purpose of this review is to examine the prevailing literature on exocrine drainage in the past 20 years (the purported “enteric drainage” era) with special attention to surgical techniques that have been introduced over time and with experience in pancreas transplantation.

Bladder drainage of the exocrine secretions (systemic-bladder technique)

Following the groundbreaking studies of Sollinger et al[65] and Nghiem et al[66] in the 1980s, bladder drainage with a donor duodenal segment became the preferred method of handling the pancreatic ductal secretions in pancreas transplantation until the mid- to late-1990s (Table 1)[67-74]. With this technique, the donor duodenum functions as an exocrine conduit and is anastomosed to the vesical dome either using a 2-layer hand sewn technique or a circular stapled anastomosis[75] (Figure 1). Bladder diversion gained wide acceptance owing to its safety, sterility, convenience, and ease of performance. In addition, bladder drainage enabled direct monitoring of the pancreatic secretions in the urine, permitted a direct approach for trans-cystoscopic biopsy of either the allograft duodenum or pancreatic parenchyma, and provided easy diagnosis and management of anastomotic problems with cystography and urethral catheter drainage[76]. Similar to the use of low pressure cystography to diagnose urine leaks following kidney transplantation, cystography facilitated the detection of anastomotic or duodenal segment leaks following pancreas transplantation with bladder drainage. Prolonged urethral catheter drainage in effect decompressed the anastomosis and enabled control of the exocrine leakage while promoting healing.

Bladder diversion of the pancreatic ductal secretions avoided the inherent bacterial contamination (e.g., peritonitis) that occurred with bowel diversion leaks, contamination that lead to substantial morbidity and even mortality[77]. Consequently, it was associated with a lower risk of intra-abdominal infections and sepsis (because of the sterility of the lower urinary tract) compared to previous techniques of either segmental or whole organ pancreas transplantation with enteric
to anastomotic bleeding, however, administration of octreotide, bladder clot removal by cystoscopy with direct fulguration of bleeding sites, or enteric conversion might be indicated. Rates of hematuria are noted in Table 3.

In addition, bladder drainage resulted in obligatory fluid (up to 1-2 L/d of pancreatic exocrine secretions) losses and urinary bicarbonate wasting with consequent changes in the acid-base balance and enzyme-free environment of the lower genitourinary tract. Many patients were prone to dehydration, metabolic acidosis, erythrocytosis, and orthostasis, particularly in the setting of severe autonomic neuropathy secondary to diabetes. For these reasons, the length of donor duodenum transplanted with the pancreas was progressively shortened over time in an attempt to minimize protein diversion. In addition, bladder drainage also provided a means to monitor for pancreas allograft rejection by measuring urinary parameters such as amylase, insulin or cytology. However, bladder diversion created an abnormal linkage between the allograft pancreas with intervening donor duodenal conduit and the urinary bladder, which resulted in a number of unique metabolic, urologic, infectious, and miscellaneous complications. Disadvantages and advantages of bladder diversion are specified in Table 2.

With bladder drainage, anastomotic bleeding could be easily diagnosed by the presence of hematuria and usually managed non-operatively with urethral catheter drainage, alkalization of the urine, administration of blood products, and correction of coagulation parameters. In refractory or persistent cases of hematuria secondary to anastomatic bleeding, however, administration of octreotide, bladder clot removal by cystoscopy with direct fulguration of bleeding sites, or enteric conversion might be indicated. Rates of hematuria are noted in Table 3.

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**Table 1  Bladder drainage: Literature review**

| Center, authors, year, ref., study design, and follow-up | Number and type of transplant | Complications | Enteric conversion | 1 yr patient survival | 1 yr pancreas graft survival |
|----------------------------------------------------------|--------------------------------|---------------|-------------------|----------------------|-----------------------------|
| University of Minnesota, Hakim et al[67], Retrospective, mean follow-up 55 mo | n = 425 with bladder drainage, SPK - 53%; PAK - 23%; PTA - 24% | Duodenal stump complications - 20%; Duodenal leak - 10%; Recurrent UTI - 9%; Hematuria - 6% (19% required surgery); Bladder stone - 0.5%; CMV duodenitis - 1.5%; Graft loss - 9% | 16% | ND | ND |
| University of Nebraska, Stratta et al[68], Retrospective, mean follow-up 44 mo | n = 201 with bladder drainage | Duodenal stump complications - 19%; Duodenal leak - 6% (all required surgery); Hematuria - 13% (30% required surgery); CMV duodenitis - 3% | 13% | 94% | 80% |
| University of Wisconsin, Sollinger et al[69], Retrospective | n = 500; 338 with bladder drainage, 112 with enteric drainage | Duodenal leak - 15.4%; Graft Thrombosis - 0.7%; Hematuria - 3%; UTI - 52.5%; Graft loss - 13%; Death with a functioning graft - 8% CMV - 2%; Intra-abdominal infection - 15%; Wound infection - 8%; Rejection - 55%; Hematuria - 14%; Bladder leak - 10% | 24% | 96.4% | 87.5% |
| The Ohio State University, Henry et al[70], Retrospective, mean follow-up 16 mo | n = 300 with bladder drainage | Bladder tumor - 2%; Allograft pancreatitis - 19%; Duodenal leaks 17%, (all required surgery); Ureteral lesions - 9% | 4% | 92% | 82% |
| University of Maryland, Del Pizzo et al[71], Retrospective, mean follow-up 35 mo | n = 140; SPK - 68%, PAK - 25%, PTA - 7% | Urological complication - 50%; Bladder stone - 10%; Duodenitis - 11%; Retained foreign bodies - 12% | 21% | ND | ND |
| Mayo Clinic Rochester, Gettman et al[72], Retrospective, mean follow-up 44 mo | n = 65 | Bladder tumor - 2%; Hematuria - 26%; Ureteral lesions - 9%; Allograft pancreatitis - 19% | ND | 92% | 86% |
| Hospital Universitario Spain, Medina Polo et al[73], Retrospective, mean follow-up 52 mo | n = 107, all SPK, bladder drainage in 58, enteric drainage in 49 | UTI - 72%; Hematuria - 20%; Bladder stone - 8%; Reflux pancreatitis - 48% | 10% | 92.7% | 78.1% |
| University of Nebraska, Sudan et al[74], Retrospective, mean follow-up 60 mo | n = 57, all with bladder drainage | UTI - 15%; Dehydration - 20%; Rejection - 1% | ND | 95% | 88% |

SPK: Simultaneous pancreas-kidney; PAK: Pancreas after kidney; PTA: Pancreas transplantation alone; UTI: Urinary tract infection; CMV: Cytomegalovirus; ND: Not determined/no data.
and bicarbonate loss from the allograft duodenal mucosa. In some patients, intractable, recurrent, or refractory complications would occur, which were then treated with open conversion from bladder to bowel diversion (enteric conversion) (Figure 2). Paradoxically, the success of “enteric conversion” paved the way for renewed enthusiasm in primary enteric drainage. Enteric conversion frequency ranged from 10% to 40% (Table 3)\(^{[79-86]}\). Several authors reported that enteric conversion resulted in superb long-term graft function coupled with marked symptom improvement even when performed several years following SPK transplant\(^{[84,87,88]}\). Despite urological morbidity and the finite risk of enteric conversion, 5-year actuarial patient and graft survival rates with bladder drainage were excellent and most complications could be managed with conservative (non-operative) therapy.

For diabetic patients with neurogenic bladders, episodes of reflux pancreatitis (managed with urethral catheter drainage) and recurrent urinary tract infections were not uncommon. In the setting of urinary tract infection, the pH of urine would become more acidic, which led to pancreatic enzyme activation and a variety of complications including hematuria, duodenitis, cystitis, urethritis, urethral stricture or disruption, and balanitis. In severe cases, some investigators even reported reduction cystoplasty and bladder re-anastomosis in an attempt to control persistent urologic problems.

Most patients required daily oral sodium bicarbonate supplementation and some received chronic suppressive antibiotics to limit the morbidity attributable to the abnormal physiology. Alternative treatments to reduce exocrine drainage side effects included the use of oral pancreatic enzymes or long-acting somatostatin analogues. Other late complications comprised duodenal leaks, stone formation, and the risk of urothelial dysplasia.

At present, bladder drainage remains an important option in selected cases, such as those in which pancreas graft quality in general or viability of the allograft duodenum in particular is suspect. In cases of duodenal ischemia or severe reperfusion injury, the bladder anastomosis can be performed by invaginating the duodenum into the bladder in order to minimize leaks (Figure 1). In addition, if the recipient has severe adhesions from multiple previous intra-abdominal procedures or sclerosing peritonitis, then a bowel anastomosis may be risky. Moreover, until recently, bladder drainage was preferred by many centers in solitary pancreas transplantation (PAK, PTA) because of the increased incidence of acute rejection (early and late) in this setting coupled with the established difficulty in the timely detection of pancreas rejection in the absence of either a urinary marker (with bladder drainage) or serum creatinine monitoring (with an SPK transplant).

A number of centers have reported excellent long-term outcomes in pancreas transplantation with the systemic-bladder technique\(^{[9,52,69,70,74,80,89]}\). For a period of time, the bladder drainage technique was also associated with lower incidences of thrombosis, early technical complications, and graft loss in IPTR reports compared to enteric drainage\(^{[12,13,15]}\). Consequently, many new centers (including those in developing countries) elected to embark on their experience in pancreas transplantation with systemic-bladder drainage owing to its technical simplicity and purported lower technical complication rate. In some instances, centers have adopted a 2-stage approach in which primary bladder diversion is followed by planned enteric conversion in order to avoid the immediate complications of primary enteric diversion.
Table 3  Enteric conversion: Literature review

| Center, authors, year, ref., and study design | Overall rate (%) | Urologic indications # (%) | Metabolic indications # (%) | Pancreatitis/other indications # (%) | Operative complications # (%) |
|-----------------------------------------------|------------------|----------------------------|-----------------------------|--------------------------------------|-------------------------------|
| University of Wisconsin, Van der Werf et al.[86], Retrospective | 95/449 (21%) | 90 (95) | 1 (1) | 4 (4) | 21 (22) |
| Sollinger et al.[84], Retrospective | 160/390 (41%) | 93 (58) | 1 (0.6) | 47 (29) | ND |
| University of Minnesota, West et al.[85], Retrospective | 79/500 (16%) | 43 (54) | 26 (33) | 15 (19) | 12 (15) |
| University of Nebraska, Sindi et al.[84], Retrospective | 25/195 (13%) | 7 (28) | 18 (72) | 0 | 3 (12) |
| University of Barcelona, Spain, Fernandez-Cruz et al[80], Retrospective | 16/74 (22%) | 0 | 0 | 16 (100) | Death 1 (6); Wound infection 2 (12); Anastomotic leak 3 (18) |
| Leiden University Medical Center, Netherlands, van de Linde et al[84], Retrospective | 51/ND | 39 (76) | 23 (45) | Pancreatitis 2 (3); Fistula 1 (1) | UTI 7 (13); Minor bleeding 1 (0.5); Phlebitis 1 (0.3); Paralytic ileus 1 (0.3); Relaparotomy 2 (3) |
| University of Cincinnati, Kaplan et al[85], Retrospective | 26 (32%) | 13 (50) | 13 (50) | 0 | Death 1 (3); Anastomotic bleeding 1 (3) |
| Beaumont Hospital, Ireland, Connolly et al[84], Retrospective | 6/ND | 3 (50); 2 hematuria; 1 UTI | 3 (50) | ND | Pulmonary edema 1 (6) |

UTI: Urinary tract infection; ND: Not determined/no data.

(intra-abdominal infections, early graft loss) and the long-term metabolic and urologic problems related to bladder diversion[84,87]. For example, Marang-van de Mheen et al.[87] routinely used a two-step approach in SPK transplant; primary bladder diversion followed by planned enteric conversion (Figure 2). They found that this approach resulted in urological complication rates similar to bowel-drained grafts with subsequent excellent survival rates. Conversions were performed by separating the graft duodeno-cystostomy, then re-establishing continuity and diversion by a side-to-side recipient jejunal-graft duodenal-anastomosis either without (most commonly) or with a diverting Roux limb.

The drawback to planned conversion is loss of urinary amylase as an immunological biomarker, especially in PAK and PTA recipients. In SPK transplant recipients, however, the renal allograft and serum creatinine can still be monitored as a biomarker for allograft rejection. Contrary to previous IPTR reports, however, there is no longer a survival, technical complication, or immunological monitoring advantage associated with bladder drainage, so the practice of “intentional” enteric conversion has been largely supplanted by primary bowel diversion[1-3].

**Bowel diversion of the pancreatic ductal secretions (systemic-enteric technique)**

Initial attempts at bowel exocrine diversion in the 1970-80s were fraught with complications including intra-abdominal sepsis and mortality because of limitations in preservation techniques, immunosuppression, diagnostic monitoring, and general medical care. However, the introduction of University of Wisconsin solution (that was initially developed as a pancreas preservation solution), tacrolimus, mycophenolate mofetil, ganciclovir, newer monoclonal and polyclonal antibody agents, biopsy-directed surveillance, and improvements in general medical and critical care (including higher resolution computerized tomographic scanning, more effective antibiotics, and the development of safe and more sophisticated percutaneous interventions) were pivotal in the re-emergence of primary bowel drainage as an alternative to bladder drainage. During the transitional phase from primary bladder to enteric drainage in the late 1990s to early 2000s, several studies (both prospective and retrospective) reported comparable outcomes with either technique although primary enteric drainage was not associated with the requisite long-term metabolic and urologic complications unique to bladder drainage (Table 4)[80]. In addition, the success of enteric conversion corroborated the safety and feasibility of primary enteric drainage following pancreas transplantation, which in essence eliminated the need for re-operation in 10%-40% patients with urinary bladder diversion. Moreover, bowel diversion of the pancreatic ductal secretions was much more acceptable to the medical community at large because it was more “physiologic” and logical to drain the pancreatico-duodenal secretions into the small bowel. Disadvantages and advantages of primary bowel diversion are noted in Table 5.

Potential risk variables for early bowel leaks include poor characteristics of the allograft duodenum (related to donor hemodynamic instability or trauma), ischemia-reperfusion and preservation injury (related to preservation solution as well as warm and cold ischemia), complications with either the vascular or bowel anastomosis because of adhesions or other technical issues, higher donor or recipient age or body mass index, peritoneal dialysis, and deconditioning in the recipient. In
| Center, authors, year, ref., and study design | Number and type of transplant | Complication/enteric conversion | Acute rejection/graft loss | Reoperation and readmissions | 1 yr patient survival | 1 yr pancreas (and kidney) graft survival |
|-----------------------------------------------|--------------------------------|--------------------------------|---------------------------|----------------------------|---------------------|------------------------------------------|
| University of Maryland, Kuo et al<sup>[35]</sup>, Retrospective | 23 SPK ED | ED: Fewer UTIs and urologic complications | ND | ND | ED 100%; BD 96% | ED 88%; BD 91% |
| University of Chicago, Newell et al<sup>[33]</sup>, Retrospective | SPK; ED 12; BD 12 | Acidityosis and dehydration less with ED (P < 0.005); Hematuria; BD 25%; ED 0%; No anastomotic leaks in either group; No intra-abdominal infection in either group; Enteric conversion: 33% | ND | BD: 4 patients underwent enteric conversion | BD 100%; ED 83.3% | BD 91.7%; ED 83.3% |
| University of Wisconsin, Sollinger et al<sup>[80]</sup>; Retrospective | 1000 SPK; BD 390; ED 610 | Kidney rejection; Pancreas graft thrombosis; BD 2.3% ED 3.6%; Infection; BD 1.8% ED 0.8%; Pancreatitis; BD 1.3% ED 0.3%; Pancreatic leak BD: 12% ED: 5% (P = 0.06) | Similar in both groups | Similar kidney, and pancreas graft survival in both groups |
| Pirsch et al<sup>[37]</sup>, Retrospective | 48 BD; 78 ED | Kidney rejection; Acidosis and dehydration less with ED (P = 0.002); CMV; BD 21% ED 4% (P = 0.04); Fungal infection; BD 17% ED 4%; UTI BD 63% ED 20% (P = 0.001) | ND | Similar in both groups |
| University of Washington, Friedrich et al<sup>[34]</sup>, Retrospective | 34; ED 17; BD 17 | Kidney rejection; Enteric conversion: 5% | ED 41%; BD 53% | Readmissions: ED 29%; BD 24% | ED 41%; BD 47% | |
| University of Tennessee-Memphis, Stratta et al<sup>[41]</sup>, Prospective | BD 16; ED 16 | Kidney rejection; UTI BD 50% ED 19%; Urologic complications; BD 25% ED 12.3%; Dehydration BD 100% ED 44% | BD 25%; ED 25% | Readmissions: BD 2.6 ± 1.8; ED 1.75 ± 1.2 | BD 88%; ED 94% | Kidney survival; BD 92%; ED 93% |
| Albert Einstein Medical Center, Bloom et al<sup>[36]</sup>, Retrospective | 71 SPK; BD 37; ED 34 | Dehydration BD 34% ED 3.4%; Acidosis BD 41% ED 0% Pancreatitis BD 40% ED 3.4% UTI BD 71% ED 27% (P < 0.005) Enteric conversion: 19% | BD: 13.5%; ED: 14.7% | Similar between groups | |
| Emory University, Pearson et al<sup>[36]</sup>, Retrospective | SPK; BD 55; ED 11 | BD; UTI 78%; Hematuria 27%; Dehydration 38%; ED no complication | BD 24%; ED 16% | Similar between groups | |
| University of Pittsburgh Corry et al<sup>[36]</sup>, Retrospective | BD 44; ED 199 | BD 1 patient to ligate an arteriovenous fistula in the pancreas graft; BD 4 patients; (bleeding in one, partial wound dehiscence in one, negative laparotomy in two) | BD 95%; ED 100% | Kidney graft survival; BD 95%; ED 100% | |
| Toronto General Hospital, Cattral et al<sup>[40]</sup>, Retrospective | SPK; BD 20; ED 20 | BD 37%; ED 15% (P = 0.20) | BD 1 patient to ligate an arteriovenous fistula in the pancreas graft; BD 4 patients; (bleeding in one, partial wound dehiscence in one, negative laparotomy in two) | BD 95%; ED 100% | Kidney graft survival; BD 95%; ED 100% |

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| Technique (Donor) | SPK | SE | PE | BD |
|-------------------|-----|----|----|----|
| No differences were seen in surgical complications including pancreas thrombosis; Infections: SE 49%; PE 85%; BD 63% | SE 19%; PE 26%; BD 30% | SE 61%; PE 63.5%; BD 63% | SE 97%; PE 99%; BD 97% | Kidney: SE 94%; PE 98%; BD 93%; Pancreas: SE 87%; PE 92%; BD 87% |

Table 5 Advantages and disadvantages of enteric drainage of the exocrine secretions

**Advantages**

- Safety
  - Lower rates of urinary tract infections and urologic complications
  - More “physiologic”; fewer metabolic and volume problems
  - Fewer readmissions

- Technical considerations
  - Treats exocrine insufficiency (in patients following total pancreatoduodenectomy or in patients with cystic fibrosis)
  - Avoidance of need for enteric conversion; lower relaparotomy rate
  - Can be used with either systemic or portal venous outflow

- Disadvantages
  - Safety
    - Higher incidence of leakage of pancreatic enzymes, pancreatitis, per-pancreatic fluid collections
    - Higher incidence of intra-abdominal abscess, peritonitis, sepsis
    - Anastomotic leaks, GI bleeding
    - Increased risk of wound infections, wound healing problems (contaminated case with GI tract breach)
  - Technical considerations
    - Selective need for enterolysis or diverting Roux en y limb
    - Loss of direct access to anastomosis and allograft for diagnosis and treatment
  - Miscellaneous problems
    - Inability to directly monitor exocrine secretions

**Figure 3** Technique of systemic-enteric drainage with side-to-side anastomosis between allograft duodenum and recipient small bowel.

Techniques that incorporated diverting Roux limbs with temporary external ostomies were also described in an attempt to permit direct endoscopic access and provide decompression of the enteric anastomosis and allograft duodenum. However, with time and experience, most pancreas transplant surgeons evolved to directing the head and duodenum of the pancreas allograft away from the pelvis to simplify the enteric anastomosis, which was typically performed side-to-side between the allograft duodenum and either the recipient proximal jejunum or ileum without a Roux limb (Table 6).

Table 6
d|SPK| SE| PE| BD |
|---|---|---|----|
|Readmissions: SE 97%; PE 99%; BD 97% | Kidney: SE 94%; PE 98%; BD 93%; Pancreas: SE 87%; PE 92%; BD 87% |

Inability to directly monitor exocrine secretions.

Additional, late intra-peritoneal infectious complications may occur in bowel-drained transplants. In more recent series, however, the incidence of and outcomes associated with surgical complications following enteric diversion are similar to those following bladder drainage and the rates of early graft loss with either technique are comparable. The incidence of surgical complications is also similar by type of transplant (SPK compared to solitary pancreas transplantation). Leaks from the allograft duodenum have been reported to occur in 5%-20% of bladder-drained and 5%-8% of bowel-drained pancreas transplants. Increasing experience with enteric exocrine drainage is likewise associated with a decreased rate of technical complications.

Because of lingering concerns regarding the safety of enteric drainage based on historical precedent, the use of diverting Roux limbs was not uncommon in the late 1990s and many centers continued to direct the head and duodenum of the pancreas allograft toward the pelvis in case “bladder conversion” was required.
Table 6  Systemic-enteric drainage: Literature review

| Center, authors, year, ref., and study design | Number and type of transplant | Complications | Readmission/reoperation/length of stay | 1 yr patient survival | 1 yr kidney/pancreas survival |
|---------------------------------------------|-----------------------------|---------------|-------------------------------------|----------------------|-----------------------------|
| Medical University of South Carolina, Douzdjian et al[94], Retrospective | ED 16; BD 26 | Recurrent/persistent urinary complications BD 46% ED 6% (P = 0.01); Dehydration BD 27% ED 6% (P = 0.05); Pancreatitis BD 8% ED 6% (P = NS); Wound infection BD 12% ED 19% (P = 0.5) | Readmissions BD: 1.7 ± 1.5; ED 1.2 ± 1.2 (P = 0.2) Reoperations BD 23% ED 0 (P = 0.04); Length of stay BD: 12.9 ± 5.6; ED: 20.4 ± 9.6, (P = 0.007) | BD 96%; Kidney BD 94%; ED 94% P = 0.6 | BD 85%; Kidney BD 87%; Pancreas BD 80%; ED 85%; (P = 0.6) |
| Institut de Maladies Digestives, Spain, Heredia et al[92], Retrospective | 205 SPK; BD 97 | Duodenal leaks: (n = 11); Acute rejection (n = 6); CMV infection (n = 3); Technical failure (n = 2); Death: (n = 2) as a consequence of sepsis | Reoperation for duodenal leak; Roux-en-Y technique: (n = 3) DJ technique: (n = 2) Transplantectomy: (n = 6) | ND | ND |
| Toronto General Hospital, Spetzler et al[90], Retrospective | Total 284; 191 SPK (67.3%); 93 PAK (32.7%) | Duodenal leak (incidence 6.3%); 12 (67%) occurred within the first 100 d after transplantation | Six grafts (33%) were rescued by duodenal segment resection; Reoperation for intra-abdominal infection Pancreatectomy: 5 Necrosectomy and drainage: 5 Percutaneous drainage: 1 | ND | ND |
| Innsbruck University Hospital, Austria, Steurer et al[90], Retrospective | 40 ED | Intra-abdominal infection - 11 (27.5%) | Reoperation for intra-abdominal infection Pancreatectomy: 5 | ND | ND |
| Ruhr-University Bochum, Germany, Ziaja et al[95], Retrospective | 30 SPK | Perioperative mortality 3.3% | Early relaparotomy was required in 20%; pancreatectomy in 10% | ND | ND |
| Indiana University, Fridell et al[90], Retrospective | 49; SPK; 49; All ED | Death: (n = 2) (1 patient died from multi-system organ failure and a second from graft vs host disease); Pancreatic graft failures: (2); renal graft failure: (1) | Reapproratomies: (n = 5) bowel obstructions: (2) anastomotic leak: (1) ureteral stenosis: (1) | 96% | Kidney 94%; Pancreas |
| University of Pittsburgh, Corry et al[90], Retrospective | 104 SPK | Graft loss in 6 patients, Death in one patient | Splenic artery hemorrhage: (1) | 98% | 92%; Kidney 95%; Pancreas 83% |
| University of Maryland, Bartlett et al[90], Prospective | 27; Solitary pancreas transplants | One graft lost to acute rejection in the tacrolimus group because of patient noncompliance | ND | ND | 90% in patients receiving tacrolimus, 53% in patients receiving cyclosporine (P = 0.002) |

BD: Bladder drainage; ED: Enteric drainage; CMV: Cytomegalovirus; ND: Not determined/no data; DJ: Duodeno-jejunosotmy.

placement to perform the enteric anastomosis[109,110].

Bowel drainage of the pancreatic ductal secretions (portal-enteric technique)

To address the unusual anatomy of pancreas transplantation, Gaber et al[109] introduced a new technique in which an anterior intraperitoneal approach to the recipient superior mesenteric vein (SMV) was deployed for venous drainage. This procedure was later modified to a "retroperitoneal" approach to the SMV by Boggi et al's group in Pisa. Both of these techniques combined bowel drainage of the pancreatic ductal secretions with portal venous delivery of insulin (portal-enteric technique)[106,107,108]. Alternative methods to achieve portal venous delivery of insulin have been reported using either the recipient portal vein directly, the inferior mesenteric vein, or splenic vein. However, in most cases, "portal venous" drainage usually infers that the allograft has a vertical orientation with the body and tail directed towards the pelvis, the head and duodenum directed cephalad, and the recipient SMV as the site for the venous anastomosis[18-22] (Figure 4). The bowel anastomosis is most commonly performed to a bowel loop that is not excluded from the transit of intestinal contents[4,16,17,33-42,44-46,49-53,112-121]. Alternatively, the allograft duodenum can be connected directly into the native stomach or duodenum, to a diverting Roux limb without or with a venting jejunosotmy, or to an omega loop[23-32,122] (Table 7). Utilizing the native stomach or duodenum affords straightforward access to the allograft duodenum and pancreas for biopsy and surveillance by endoscopic techniques and also expands the possibilities for exocrine drainage sites, particularly in cases of pancreas retransplantation (Table 8)[28-32,123]. However, because up to 5%-10% of transplanted pancreatic are at risk for early technical failure that may lead to leaks,
many centers are reluctant to perform enteric diversion either to the native stomach or duodenum. Following reperfusion of the transplanted pancreas, if the allograft duodenum does not appear well vascularized, bowel drainage with creation of a diverting Roux limb may be preferred to bypass the enteric stream and promote healing even though this procedure mandates an additional bowel anastomosis.

Although the rate of bleeding at the may be higher, some surgeons prefer to use either a circular or linear stapling device to create the bowel anastomosis. However, most commonly, the connection between the allograft duodenum and recipient small bowel is performed using a 2-layer hand sewn technique that comprises a running continuous inner layer of interlocking absorbable suture coupled with an interrupted seromuscular outer layer of simple interrupted non-absorbable sutures to create a "watertight" and hemostatic closure. The bowel anastomosis can be located anywhere between the distal ileum and native stomach although most commonly is performed as a primary side-to-side connection to the proximal jejunum (Figure 4). Other methods of reconstruction may include either an end-to-side or end-to-end anastomosis between the allograft duodenum and recipient gastrointestinal tract. When using portal-enteric drain-
age, the recipient ileum can be anastomosed to the distal graft duodenum whereas the recipient jejunal can be anastomosed to the proximal graft duodenum. We prefer the former technique with the location of the bowel anastomosis on the posterior aspect of the 3rd or 4th portion of the graft duodenum to promote dependent drainage of the anoxic, denervated graft duodenum when the patient is either in the erect or supine position[121]. Anastomotic length can be variable but usually ranges from 3-5 cm.

Unlike bladder drainage, however, anastomotic bleeding with enteric drainage is more occult and harder to diagnose in the absence of gastric, duodenal, or extreme proximal jejunal diversion or in the absence of a diverting jejunostomy. Because most enteric anastomoses are performed in the middle third of the gastrointestinal tract, endoscopic confirmation and treatment are not available. Consequently, the true incidence of anastomotic bleeding with enteric drainage is probably under-reported and the severity may be under-appreciated because of other causes of anemia in the immediate post-operative period. Fortunately, most cases are self-limited and respond to supportive measures such as decompression of the gastrointestinal tract, administration of blood products, and correction of coagulation parameters. In cases of persistent and significant lower (or rarely upper) gastrointestinal bleeding, administration of octreotide may be helpful by inducing vasoconstriction. Rarely, re-operation with revision of the enteric anastomosis (with or without Roux limb diversion) may be indicated for anastomotic bleeding. For severe gastrointestinal bleeding that occurs more than one week post-transplant, however, one must not assume it is secondary to anastomotic bleeding. In this setting, it is imperative to rule out a leaking pseudoaneurysm, which is best diagnosed and treated with angiographic techniques[124].

When using the retroperitoneal approach to the SMV for portal-enteric drainage, in order to perform an anastomosis to the small bowel, one must make a window in the mesentery of the right colon. Bowel drainage can then be accomplished without or with a diverting Roux limb in a standard side-to-side manner[17,113]. If one initially performs a side-to-side bowel

### Table 8 Portal-duodenal/gastric drainage: Literature review

| Center, authors, year, ref., and study design | Number and type of transplant | Complications | Readmissions and reoperations | 1 yr patient survival | 1 yr pancreas survival |
|-----------------------------------------------|-------------------------------|---------------|-------------------------------|----------------------|-----------------------|
| New York Medical College, Westchester         | DJ: 36; DD: 21, stapled 14, hand-sewn 7 | Thrombosis: None in DJ, 2 in DD (P = NS); Enteric leak and small-bowel obstruction: 3 in DJ, 2 in DD (P = NS); Gastrointestinal bleeding: None in DJ, 4 in DD (P = 0.015) | ND | 94% with DJ, 95% with DD | 89% with DJ, 86% with DD |
| Medical Center, Gunasekaran et al[20], Retrospective | | | | | |
| Louisiana State University, Shokouhi-Amiri et al[23], Retrospective | Group 1: Allograft jejunum to stomach, n = 30; Group 2: Allograft duodenum to jejunum with Roux-en-Y venting jejunostomy, n = 30 | In Group 1: Pancreatectomy in 3, CMV in 7, acute rejection in 4, death in 3; In Group 2: Pancreatectomy in 1, CMV in 2, acute rejection in 6, death in 2 (P = NS) | Major complications: 4 in group 1, 10 in group 2 | 94% in group 1, 96% in group 2 | 85% in group 1, 83% in group 2 |
| Bandeirantes Hospital, Sao Paulo, Brazil, Peraosa et al[26], Retrospective | 43 PAK, 10 PTA with DD | Thrombosis in 5 (9%); 4 additional pancreas graft losses (including 2 deaths with functioning grafts); Acute rejection in 9 (17%); major infection in 24 (45%) | Readmissions: Mean 1.1; Mean length of hospital stay: 11.8 d; Reoperations in 9 (17%) | 96% | 83% |
| University Hospital Bochum, Germany, Walter et al[24], Retrospective | DD in 125 (64% with portal outflow); DJ in 116 (12% with portal outflow) | GI bleeding in 14 with DD, 4 with DJ; Thrombosis in 5 with DD, 18 with DJ (P = 0.002); Acute rejection in 29% in DD vs 31% in DJ | 2 anastomotic leaks with DD, 6 with DJ; Pancreatectomy in 14 with DD, 21 with DJ; Early relaparotomy in 42% DD vs 48% DJ, all P = NS | 96% in both groups | 82% with DD, 78% with DJ |
| Oslo University Hospital, Rikshospitalet, Norway, Homeland et al[22], Retrospective | 20 SPK, 17 PTA, 3 PAK with DD (n = 40); 30 SPK, 7 PTA, 3 APK with DJ (n = 40); In sequential eras | Group 1: 15 DJ; Group 2: 17 DD | Thrombosis in 13% DD vs 5% DJ; Acute rejection in 23% DD vs 28% DJ, both P = NS | 97.5% DD vs 92.5% DJ | Overall pancreas survival was 80% with DD, 87.5% with DJ (P = NS) |
| Scientific Research Institute of Skifosovsky, Moscow, Russia, Khubutia et al[25], retrospective | | | | 93% | 93% DD vs 94% |

DD: Duodeno-duodenostomy; CMV: Cytomegalovirus; ND: Not determined/no data; DJ: Duodeno-jejunostomy; NS: Not significant.
anastomosis, it is relatively straightforward to convert to a diverting Roux limb for whatever reason by separating the afferent limb with a gastrointestinal stapler just proximal to the anastomosis. The stapled and divided proximal limb can then be placed 40 cm or more distal to the anastomosis on the efferent limb and the second proximal limb can then be placed 40 cm or more distal

*Table 9 Systemic vs portal-enteric drainage: Literature review*

| Center, authors, year, ref., study design and follow up | Number and types of transplant | Complications | Length of stay, readmissions and reoperations | 1 yr patient survival | 1 yr kidney and pancreas survival |
|--------------------------------------------------------|--------------------------------|---------------|-----------------------------------------------|----------------------|---------------------------------|
| University of Tennessee, Memphis, Stratta et al[46], Prospective, mean follow-up 17 mo | SE 27; PE 27                   | Incidences of complications: 33% major rejection with 52% similar in both groups; Intraabdominal infections were slightly greater in the SE group (26% vs 11% PE); 2 deaths in SE group compared to one in PE group; Pancreas graft loss in SE vs PE; Pancreatic fistula: 147 in SE vs 41 in PE. | Length of stay - mean 11 d vs 10 d in SE vs PE; Most common causes of death in both groups were myocardial infarction (35%), cerebrovascular accident (13%) and cancer (13%); Most common causes of kidney graft loss in both groups were death with functioning graft (61%) and acute rejection (11%); | SE 96%; PE 95% | Pancreas SE 74%; PE 85%; Kidney SE 96%; PE 93% |
| University of Maryland, Philadelphia, Philosophe et al[47], Retrospective, mean follow-up 23 mo | SE 63 SPK, 42 PAK, 26 PTA; PE 20; | Acute rejection: At 36 mo, the pancreatic rejection rates were 21% for PE vs 52% for SE (P < 0.0001); the kidney rejection rates following SPK were 26% PE vs 43% SE (P = 0.017) | Early relaparotomy no difference: SE 34 d vs PE 20 d; Patient survival did not differ at 5 yr (94% SE vs 89% PE) and 10 yr (85% SE vs 84% PE, P = 0.008) | 36-mo patient survival rates were similar in both groups, 89% for PE vs 93% for SE | 36-mo graft survival rates for all pancreas transplants were 79% with PE vs 65% with SE (P = 0.008) |
| Hospital Juan Canalejo, Coruña, Spain, Alonso et al[48] and Quintela et al[49], Retrospective, mean follow-up 23 mo | PE: 54 SPK, 55 PAK, 40 PTA; SE 18; PE 20; | Incidences of intraabdominal infection and acute rejection episodes were not different between groups; Major infections were not different between groups; 3-mo rejection rate was identical (6%) and the 1-yr rejection rate was 12.2% SE vs 13.3% PE; Most common causes for pancreas graft loss in both groups were death with functioning graft (25%), graft thrombosis (13%), rejection (11%) and duodenal leak (9%); In both groups, a complication occurred in 38% of patients in the first year; | Length of stay - mean 11 d vs 10 d in SE vs PE; Most common causes of death in both groups were myocardial infarction (35%), cerebrovascular accident (13%) and cancer (13%); Most common causes of kidney graft loss in both groups were death with functioning graft (61%) and acute rejection (11%); | PE 80% vs SE 86% | Death-censored pancreas (SPK and PAK) graft survival was 73% for PE and 81% for SE (P = NS) |
| Toronto General Hospital, Bazerbachi et al[50], Retrospective | SE 147; PE 45                  | No significant differences in long-term outcomes but the SE group had a higher incidence of pancreas graft loss secondary to thrombosis | No difference in total surgical complications | 5-yr patient survival 94% | 5-yr pancreas survival 77% PE vs 74% SE |
| Medical University Innsbruck, Austria, Ollinger et al[51], Retrospective, Mean follow-up 8.3 yr | 509 transplants in 4 eras including 34 PE and 146 SE (with DJ) in most recent era (2004-2011) | Thrombosis: 9% PE vs 5% SE, P = NS | Patient survival rates 92% SE vs 95.5% PE | One-, 3-, 5-, and 8-yr pancreas survival rates were 75%, 60.6%, 56.7%, and 44%, respectively, in the SE group compared to 88.6%, 84.1%, 78.4%, and 31.3% in the PE group; One-3-, 5-, and 8-yr kidney survival rates were 91.7%, 78.1%, 74.1%, and 57.9%, respectively, in the SE group compared to 93.2%, 86.6%, 78.4%, and 38.9% in the PE group | One-, 3-, 5-, and 8-yr pancreas survival rates were 75%, 60.6%, 56.7%, and 44%, respectively, in the SE group compared to 88.6%, 84.1%, 78.4%, and 31.3% in the PE group; One-3-, 5-, and 8-yr kidney survival rates were 91.7%, 78.1%, 74.1%, and 57.9%, respectively, in the SE group compared to 93.2%, 86.6%, 78.4%, and 38.9% in the PE group |
| Hôpital Edouard Herriot, Lyon, France, Petrizzu et al[52], Retrospective | SE 36; PE 44; All SPK        | No significant differences in long-term outcomes but the SE group had a higher incidence of pancreas graft loss secondary to thrombosis | No difference in total surgical complications | Patient survival rates 92% SE vs 95.5% PE | One-, 3-, 5-, and 8-yr pancreas survival rates were 75%, 60.6%, 56.7%, and 44%, respectively, in the SE group compared to 88.6%, 84.1%, 78.4%, and 31.3% in the PE group; One-3-, 5-, and 8-yr kidney survival rates were 91.7%, 78.1%, 74.1%, and 57.9%, respectively, in the SE group compared to 93.2%, 86.6%, 78.4%, and 38.9% in the PE group |

SE: Systemic enteric; PE: Portal enteric; ND: Not determined/no data; DJ: Duodeno-jejunostomy; NS: Not significant.
bowel anastomosis can be constructed either in a side-to-side or end-to-side manner with either sutures or a stapler. A potential advantage of accessing the SMV for venous drainage is that the procedure is no longer pelvic but rather mid-abdominal in location, which is helpful in cases of retransplantation or in patients who have had previous pelvic irradiation or procedures\(^{[121]}\).

With any method of enteric drainage, the efferent limb must be placed so as to remove any tension or traction on the bowel anastomosis. By careful positioning, an anastomotic “blow-out” or enteric leak can be averted by preventing bowel angulation just distal to the anastomosis. In addition, it is important close any mesenteric defects and to position the pancreas in such a way that the risk of internal hernia is minimized. Although some surgeons prefer to “wrap” omentum around the bowel anastomosis, we do not advocate this practice because of the concern for liquefaction necrosis that may develop from any fat that comes in direct contact with the pancreas following reperfusion. Fat necrosis may result in peri-pancreatic fluid collections that could subsequently require drainage or become infected.

Alleged gains of pancreas transplantation with portal venous delivery of insulin include immunological, technical, and metabolic, “advantages”. However, neither large registry analyses nor prospective cohort studies have been able to corroborate these purported benefits (Table 9)\(^{[15,23,28-42,44-46,49-53,112-123]}\). Conversely, when comparing the three major techniques of pancreas transplantation, there are likewise no well controlled studies to suggest any major drawbacks of portal-enteric vs either systemic-bladder or systemic-enteric drainage.

One of most recent and exciting innovations in pancreas transplantation is the advent of laparoscopic pancreas transplantation with robotic support\(^{[125-127]}\). With the da Vinci Robotic system, Boggi et al\(^{[125]}\) reported the first three whole pancreas transplants performed by using this technology. Their experience constitutes a proof of concept for pancreas transplantation with robotic-assisted laparoscopic surgery. In these cases, enteric drainage of was accomplished using a circular stapler to create an anastomosis between the proximal recipient small bowel and donor duodenum\(^{[125]}\). However, Boggi et al\(^{[127]}\) have raised concerns regarding the influence of longer warm ischemia duration on viability of the graft because maintaining a cold graft temperature prior to reperfusion is difficult to accomplish laparoscopically. Although several “variations on a theme” exist in the procedural methodology of pancreas transplantation and novel approaches continue to be described, the prevailing viewpoint upholds that the technique with which the individual surgeon feels most confident and comfortable is the best one to be implemented based on donor pancreas quality and recipient anatomic considerations. With improved surgical outcomes over time, exocrine drainage techniques are no longer the “Achilles’ heel” of vascularized pancreas transplantation.

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P- Reviewer: Chen ZS, Keller F, Marino IR, Rydzewski A, Salvadori M
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