**Pancreatic Anastomosis After Pancreatoduodenectomy:**

**A Position Statement By The International Study Group Of Pancreatic Surgery (ISGPS)**

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**ABSTRACT**

***Background:***

Clinically-relevant postoperative pancreatic fistula (grades B and C of the ISGPS definition) or what we will refer to as CR-POPF in this report remains the most troublesome complication after pancreatoduodenectomy (PD). The potential consequences of a CR-POPF are intra-abdominal collections, delayed gastric emptying (DGE), reoperation, post-pancreatectomy hemorrhage (PPH), increased hospital stay, readmission, and increased mortality. The approach to management of the pancreatic remnant via some form of pancreatico-enteric anastomosis (PA) determines the incidence and severity of POPF. Despite numerous trials comparing diverse PA techniques and other technical strategies to minimize the rate of CR-POPF (pancreatic duct stenting, employment of drains, somatostatin analogues, etc.), currently, there is no clear consensus regarding the ideal method of PA.

***Methods:***

An international panel of pancreatic surgeons working in well-known, high volume centers reviewed the best contemporary literature concerning PA and worked to develop a position statement on pancreatic anastomosis after PD.

***Results:***

There is inherent risk assumed by creating a PA based on factors related to the gland (e.g. parenchymal texture, disease pathology). None of the technical variations of pancreaticojejunal or pancreaticogastric anastomosis, such as duct-mucosa, invagination method, and binding technique, have been found to be consistently superior to another. Randomized trials and meta-analyses comparing pancreaticogastrostomy (PG) versus pancreaticojejunostomy (PJ) yield conflicting results and are inherently prone to bias due to marked heterogeneity in the studies. The benefit of stenting the PA to decrease CR-POPF is not supported by high quality evidence. While controversial, somatostatin analogues appear to decrease perioperative complications but not mortality, although consistent data across the more than 20 studies addressing this topic are lacking. The Fistula Risk Score (FRS) is useful for predicting POPF as well as for comparing outcomes of PA across studies.

***Conclusions:***

Currently no specific technique can eliminate development of CR-POPF. While consistent practice of any standardized technique may be a potential strategy to decrease the rate of CR-POPF for any one surgeon early in his/her career, experienced surgeons at high-volume centers can have lower POPF rates performing a variety of techniques depending on the clinical situation. There is no clear evidence on the benefit of internal or external stenting after PA. The use of somatostatin analogues may be important in decreasing morbidity after PD, but even here, strong data supporting their use remains controversial in decreasing morbidity in all patients. The Fistula Risk Score (FRS) is beneficial in predicting CR-POPF as well as for comparing outcomes of PA across studies. Future studies should focus on novel approaches to decrease the rate of CR-POPF and should compare existing approaches using sound methodology that incorporates appropriate risk adjustment according to the situation.

**INTRODUCTION**

Pancreatoduodenectomy (PD) remains the gold standard for management of patients with pancreatic head and periampullary neoplasms and also in managing some benign diseases. The procedure is now safe when performed in most high-volume institutions and has an operative mortality of less than 3-5% 1. Despite the low mortality, overall morbidity remains high principally due to the development of a clinically-relevant, post-operative pancreatic fistula (CR-POPF) in about 11%of patients 2,3. The potential sequelae of CR-POPF are intra-abdominal collections, delayed gastric emptying (DGE), reoperation, post-pancreatectomy hemorrhage (PPH), increased hospital stay, readmission, and increased mortality risk. The well known risk factors for CR-POPF include a soft pancreas, a small pancreatic duct, its posterior location, underlying disease pathology that does not dilate the main pancreatic duct (e.g. bile duct cancer), decreased regional blood supply, and surgeon experience4. The approach to management of the pancreatic remnant and creation of some form of pancreatico-enteric anastomosis (PA) remain key factors in determining the chance of developing a CR-POPF. In an effort to develop evidence-based concepts, several trials have been conducted to study the efficacy of anastomotic technique (invagination *vs*. duct-to-mucosa), site of the enteric connection (pancreaticojejunostomy *vs* pancreaticogastrostomy), use of pancreatic duct stenting, fibrin glue, *etc.*, as well as manipulation using various somatostatin analogues. Despite these efforts, the data are neither consistent nor convincing to the unbiased, critical reader, and there is no clear consensus on how to approach a PA that would best suit a specific situation that would decrease the rate of CR-POPF and its potential sequelae.

**METHODS**

In order to formulate a position statement on the optimum method of PA that should be performed after PD, an extensive search strategy was adapted to identify relevant studies and meta-analyses in PubMed and Cochrane databases (Figure 1). Only articles relevant to PA with English language abstracts and those published from January 1995 until December 2015 were included. Medical subject headings and keywords included pancreatoduodenectomy, pancreaticoduodenectomy, pancreaticojejunostomy, pancreaticogastrostomy, pancreatic fistula, pancreatic stenting, somatostatin, octreotide and fistula risk. Note that every attempt was made to define the rate of pancreatic fistula by the ISGPF definition of a CR-POPF according to the recent update of the original ISGPF definition of 20055. Terms were combined with Boolean operators. The levels of evidence were rated in descending order; the studies reviewed included systematic reviews and meta-analyses of randomized controlled trials (RCTs) comparing anastomotic techniques for the PA, role of stenting and somatostatin analogues; prospective, RCTs comparing anastomotic techniques, stenting versus no stenting; and role of somatostatin analogues; role of prophylactic drains; and lastly, large observational series on anastomotic techniques categorized according to the evidence level of individual studies as per the recommendations of the Centre for Evidence-based Medicine, Oxford, UK (<http://www.cebm.net/>). The search was performed up until December 2015. Title and abstract and subsequently full text articles of all potentially relevant studies were screened by three independent reviewers (SVS, MGS, and MS). The concept of the review and summary of the extracted data was sent to all ISGPS participants. Comments and suggestions were reviewed and multiple drafts that were again circulated to the group until a consensus was achieved. The consensus on the strategy for managing various clinical scenarios during the construction of a PA was derived by the opinion of all ISGPS members by responding to a questionnaire comprising multiple choice answers. The position statement was formulated by the ISGPS study group during the European Pancreatic Club meeting in Liverpool in July 2016 using the guidelines of the Grading of Recommendations Assessment, Development and Evaluation6. The final draft was then read and approved by all the authors.

**RESULTS**

**Technique:**

**Pancreaticojejunostomy (PJ):** The various techniques of pancreaticojejunal anastomosis include end-to-side invagination, duct-to-mucosa, and the “binding technique” using a single- or double-layer technique7,8. Many non-randomized studies have suggested that a duct-to-mucosa anastomosis is associated with a lesser POPF rate compared to an invagination anastomosis; most of these studies, however, are observational studies with fistula rates up to 20% 9, and the definition of a POPF was not consistent. A duct-to-mucosa anastomosis can be difficult technically when dealing with a soft, friable, and fatty pancreas with a small duct. Hence, techniques of an invaginating PA have been recommended when dealing with a soft pancreas 10. In a RCT involving 197 patients by Berger *et al*., the rate of CR-POPF was 17% in the duct-to-mucosa group versus 7% in the invagination group7. The potential criticisms of this study were that the techniques for invagination were not standardized, and unknown surgeon factors such as inter-surgeon variability, varying skill sets and pancreatic surgery experience, could have confounded the outcomes. Bassi *et al*. reported a pancreatic fistula rate of 13% using the duct-to-mucosa technique *vs.* 15% using a single layer (capsule to serosa), end-to-side PJ in a RCT involving 144 patients11; unfortunately and surprisingly, this group did not use the definition of a pancreatic fistula as according to the ISGPF. In another RCT involving 132 patients randomized to invagination *vs.* duct-to-mucosa, the CR-POPF rate was less in the duct-to-mucosa group (3% *vs*. 18%, p = 0.004)12. In another RCT, a binding PJ showed an almost unbelievable decreased pancreatic fistula rate (0% *vs.* 7.2%; note however, that the ISGPF definition of a POPF and the grading was not used), as well as a decreased duration of hospital stay when compared with a conventional PJ technique8. Further trials, however, could not validate the benefit of this binding technique over other techniques13,14.

Optimizing the blood supply to the remnant pancreas has been shown to be associated with a low POPF rate using a cutback technique with again an almost unbelievable fistula rate of 1.6%( the definition of a fistula did not follow the ISGPF definition)15; this strategy however, was an observational cohort study of 123 patients, and further corroborative studies with a higher level of evidence are lacking.

Although high-level evidence on the selection of suture material for the anastomosis is currently lacking, one retrospective study found that the rates of POPF were less with polyester, a synthetic non-absorbable material compared to polydioxanone (PDS), a synthetic absorbable material16 (12% *vs.* 32%, p=0.01)when applied to the outer layers of PJ anastomoses. This effect was thought to be related to slower, progressive resorption of sutures leading to minor, less severe pancreatic leaks, as attested by the fewer grade C POPFs in the polyester group.

On evaluation of the exocrine insufficiency after a pylorus-preserving PD (PPPD) depending on the type of reconstruction, Jang et al compared a cohort of 20 patients of PJ with 14 patients of PG using the stool elastase 1 test and found that 95% of patients in the PJ cohort and 100% of patients in the PG cohort had pancreatic exocrine insufficiency at 22 and 27 months, respectively17.

To summarize, current evidence does not support any specific technique for a PJ predominantly due to lack of standardization, inadequate experimental designs, and various other confounding factors that can affect outcomes substantially. In current practice, both duct-to-mucosa and invagination techniques of PJ are practiced widely by high-volume surgeons across the world with consistent results in experienced hands. In a retrospective study, a standardized technique of PJ resulted in a rate of pancreatic fistula (not the ISGPF definition) of 3.2%, and it was suggested that a standardized technique and consistent practice of a single technique could potentially contribute to a lesser rate of complications18.

**Pancreaticogastrostomy (PG):** Pancreaticogastrostomy was suggested as a potential alternative to PJ with various techniques described in the literature19,20. Several theories never proven in well-designed trials for some of the favorable outcomes after PG include the lack of activation of pancreatic enzymes in the acidic gastric luminal environment, favorable topographic anatomy due to the immediate anatomic proximityof the two organs and therefore, less tension for anastomosis, and the highly vascular stomach promoting healing. Fernandez-Cruz *et al*. described a pancreaticogastrostomy with a gastric partitioning technique, where a sleeve of gastric segment with preservation of the gastroepiploic arcade was prepared with a stapler, and an end to side, duct-to-mucosa PG was constructed21.

In the recent RECOPANC trial that compared PG *vs.* PJ, the authors speculated that although the incidence of CR-POPF was not different after a PG (20% in PG vs 22% in PJ), it may be technically easier for novice surgeons to construct a secure, invaginated PG especially with a soft pancreas22. In a retrospective series involving 944 patients undergoing PD from Germany, 8.4% developed PPH, and successful endoscopic management was more feasible after a PG compared to PJ (31% *vs.* 9%, p=0.026), although the overall outcomes of PPH were not significantly different between the groups23. In a review of observational cohort studies involving PG reconstruction, the pancreatic leak rate was 2.8% (but the definition of a pancreatic leak was vague at best and did not follow the ISGPF definition), and the mortality in this group was 1.6%24. Similar to PJ, the lack of clear, convincing, level 1 evidence favoring PG is due largely to absence of standardization of the technique across various studies. In addition, adequate risk- adjustment approaches have not yet been employed in these comparisons.

In addition to immediate morbidity, long-term consequences of the anastomotic construction have been considered. Exocrine insufficiency after PG was studied using 13-C labeled mixed triglyceride breath tests in a cohort of 61 patients, 62% were diagnosed with pancreatic insufficiency. The independent predictive factors for exocrine insufficiency included preoperative impaired endocrine function, hard pancreatic texture, and MPD dilatation caused by PG stricture25,26.

**Randomized trials of Pancreaticogastrostomy *vs* Pancreaticojejunostomy:**

There are nine, randomized controlled trials that have addressed this issue with varying conclusions. Yeo *et al*. from 1995 found similar rates of pancreatic fistula in both groups, and the data did not suggest that one technique was superior over the other27. Another study by Bassi *et al*. showed no difference in fistula rates, but the primary endpoint was a decrease in postoperative abdominal complications with patients in the PG group showing a decrease in multiple surgical complications (PG 25% *vs.* PJ 68%, p=0.002) 28. A randomized study from France was criticized for the high overall mortality (11%)29, while a Spanish trial was the first to report a much lower incidence of CR-POPF with a PG (4% in PG and 18% in PJ, p<0.01)21.; of note, however, they used a gastric partition technique with preservation of the gastro-epiploic arcade which is technically complex and not always possible oncologically. A German trial did not find any significant difference in the incidence of CR-POPF30 (10% in PG vs 12% in PJ). A Belgian study used a stratified design based on the pancreatic ductal diameter (≤*3mmvs.*>3mm) and showed a lesser rate of CR-POPF in the PG group (OR 2.86, 95%CI 1.38-6.17; p=0.002). In patients with duct diameter of less than or equal to 3mm, the CR-POPF rate was 24.5% in PJ group versus 10.2% in the PG group; however, this apparent improvement did not translate into a statistically significant decrease in morbidity for unclear reasons31. In another Spanish trial randomizing 123 patients, Figueras *et al*. reported a lesser incidence of CR-POPF in the PG group when compared to PJ group (11% vs 33%, p=0.006)32. In the German RECOPANC multicenter trial involving 320 patients, there was no difference in the incidence of CR-POPF between the PG and PJ arms (20*%vs.* 22%, p=0.6)22. In another RCT involving 90 patients randomized to an isolated Roux limb PJ versus PG, there was no statistical difference in the incidence of CR-POPF (8%vs15%, p=0.30).33

These RCTs have shown varied conclusions with respect to incidence of CR-POPF; however, the overall morbidity essentially remained equivalent across the majority of studies.

**Meta-analyses for PG versus PJ:**

There are 17 meta-analyses that have been published on this topic with varied conclusions. The major problem has been the clinical heterogeneity in the individual randomized trials that have been analyzed. The earlier meta-analyses included a number of observational series as well as studies with varied techniques, all adding to this heterogeneity34,35. The characteristics of salient meta-analyses are elaborated in table 1.

In a recent meta-analysis by Menahem *etal*.39comparing PG vs PJ after PD, seven RCTs involving a total of 1121 patients were analyzed; the incidence of POPF was less in patients undergoing PG than in those having PJ ( 11.2% *vs.* 18.7%; odds ratio = 0.53; 95% C.I. 0.38–0.75; p = 0.0003), however the standard definition of POPF as set by the ISGPF was adopted in only four RCTs which made the combined analysis of RCTs using the non-standard definitions problematic and introduced more potential heterogeneity. The other factors which potentially may affect POPF, such as pancreatic duct stenting, octreotide, and extent of resection, were not distributed homogeneously among the RCTs. The differences in outcomes due to these key factors which were distributed unevenly across studies have not been accounted for in the final analysis. There was no statistically significant difference found in the surrogate outcomes of pancreatic fistula, such as delayed gastric emptying, overall morbidity, and mortality among the two groups. Currently, no meta-analyses have included the large RECOPANC trial.

Thus, there are major drawbacks in these meta-analyses that need to be addressed before firm conclusions can be drawn.

**Role of stenting:**

The role of stenting across the PA has been investigated as much for its potential to decrease the rate of POPF as to mitigate the severity of the POPF. The rationale is to divert pancreatic secretions away from the anastomosis as well as allegedly to guide more precise placement of sutures for duct-to-mucosa anastomosis40.

In a RCT involving 120 patients, the patients who had external stenting had a lesser rate of POPF (not defined by the ISGPF definition but by a definition of clinical leakage by symptoms and need for drainage of a fluid collection) when compared to the non-stented group (3% vs 15%, p=0.027), but despite this finding, there were no statistical differences found in overall morbidity or hospital mortality41. In another French RCT involving 158 patients with high-risk prognostic factors for CR-POPF, including soft pancreatic texture and a main pancreatic duct size <3mm, external stenting was found to decrease CR- POPF and overall morbidity. The CR-POPF rate was 25% in the stented group vs 36% in the no-stent group42. In another RCT from Japan involving 93 patients, among the patients with non-dilated ducts, CR-POPFs were shown to be less with external stenting vs no stenting (10% *vs.*40%; p=0.03), while in those patients with a dilated duct, there were no differences (4%vs 8%)43. In another RCT involving 238 patients, internal stenting did not decrease the incidence of a pancreatic leak (non-ISGPF definition); however this study was criticized for non-standardization of the technique of PJ and PG in both groups and the inability to determine the rate of CR-POPFs in the database44. A recent RCT involving 328 patients powered for equivalence between internal and external stenting showed that CR-POPF rates were 18.9% and 24.4% respectively with a conclusion tending to favor internal stenting but with wide confidence limits; the study, however, failed to stratify by fistula risk45.

In a recent (2016) Cochrane systematic review46, the role of stents in decreasing CR-POPF after PD was uncertain due to the low quality of the evidence (RR 0.67, 95% CI 0.39 to 1.14; 605 participants; 4 studies). The effect of external stents on the risk of CR-POPF, reoperation, DGE, and intra-abdominal collections when compared with internal stents was uncertain due to low-quality evidence, and further RCTs were deemed to be necessary. To summarize, the benefit of stenting the PA is not supported by high quality evidence.

**Role of somatostatin analogues:**

There have been numerous studies exploiting the strategy of decreasing pancreatic secretions and thereby possibly the risk of pancreatic fistula by using somatostatin analogues, such as octreotide, pasireotide, *etc.* RCTs have shown conflicting results with regard to the value of perioperative somatostatin analogues. Benefits have been shown in European trials, but contradictory results have been reported in early American trials. In an early European, randomized, multi-center trial involving 246 patients, perioperative use of octreotide was shown to decrease postoperative complications, especially in high risk patients with malignancy (38% in octreotide *vs.* 65% in placebo)47. In another RCT involving 218 patients, prophylactic octreotide was shown to decrease the incidence of POPF rates (9% in octreotide *vs*. 19.6% in placebo; note, the definition of POPF was not the ISGPF one)48. In contrast, in another RCT from the United States involving 211 patients undergoing PD, the rate of POPF (not the ISGPF definition)was not different between the octreotide and placebo group (11% *vs.* 9%,)49. In yet another prospective trial from Barcelona involving 62 patients undergoing PD who were randomized to octreotide vs placebo, there was no difference in the overall morbidity50. Another potent somatostatin analogue, vapreotide, also failed to show any benefit in a RCT involving 275 patients51. These inconsistent results found in these early trials were criticized mainly due to the lack of a standard definition of POPF when these were conducted.

A recent, single institution RCT involving 300 patients comparing prophylactic pasireotide to placebo showed a significant benefit by decreasing CR-POPF rates (7.9% vs 16.9% ; p<0.02) and morbidity (11.2 % vs 25% )52. The cost-benefit ratio of pasireotide has been a potential area of concern, and currently studies are ongoing. Also, pasireotide has not been approved for POPF prophylaxis in many countries.

In an earlier meta-analysis involving 1918 patients, somatostatin analogues did not decrease mortality but did decrease overall morbidity and pancreas-specific complications. (OR 0.56 (0.39 to 0.81); p = 0.002)53.The Cochrane review involving 21 trials concluded that peri-operative somatostatin analogues may decrease peri-operative complications but not mortality54, but further well-designed studies based on risk-adjustment are warranted for appropriate patient selection.

**Role of Dual limb with Isolated Pancreaticojejunostomy:**

Isolation of the PJ from biliary drainage has been studied as a means to decrease POPF rates. The technique is based on the rationale that diversion of biliary secretions from the PA (site of pancreatic secretions into the lumen) may avoid activation of pancreatic pro-enzymes and thereby, protect healing at the site of PJ.A single RCT involving 90 patients assessed this technique, and the isolated PJ was not associated with decreased CR-POPF rate33. A recent meta-analysis which unfortunately used several different definitions of POPF also was unable to demonstrate any statistically significant difference between a single Roux limb and a double Roux limb .55

**Role of prophylactic drainage:**

The benefit of prophylactic drainage after PD has remained highly controversial, although drains often aid in the detection of complications after pancreatic resections56. In a recent, multicenter RCT involving 137 patients randomized to a No Drain and Drain group, PD without drainage was associated with greater morbidity; the study was terminated early in view of an unacceptable increase in mortality from 3% to 12%, thereby concluding that elimination of drainage in PD increased the severity of complications57. The concept of selective drainage in high risk cases has been brought forward by many experts, and the controversy was reappraised58,59. In a RCT assessing early drain removal in patients at low risk of CR-POPF, 114 patients were randomized to early (post-operative day [POD] 3) versus late (POD5 or beyond) and concluded that prolonged retention of a drain was associated with increase in complications, hospital stay, and cost60. In a post hoc reappraisal of the same trial with risk stratification, moderate/high risk patients with POD1 drain amylase <5000U/L had lesser rates of CR-POPF with early drain removal on POD 3 (4.2% *vs.* 38.5%, p=0.003)61 although the number of patients at risk was small. This protocol of selective drain placement and early removal was studied in a prospective study involving 260 patients by the same authors in the United States and Italy and found that overall CR-POPF rates were less after implementation of this protocol (11.2 *vs.* 20.6%, p = 0.001)62. A recent RCT from Germany compared rates of reintervention in 438 patients randomized to drainage *vs.*no drainage; the overall re-intervention rates did not differ between the groups (drain 21.3% *vs.* no-drain 16.6%; p = 0.0004), and there were no differences in morbidity and mortality; the rate of CR-POPF, however, was less in the No drain group (drain 11.9% *vs*. no-drain 5.7%; p = 0.030)63. In the light of the current evidence, we believe that prophylactic drainage can be avoided confidently in negligible/low risk patients and early drain removal on POD3 can be practiced in moderate/high risk patients when the drain fluid amylase activity on POD1 is less than 5000 U/L.

**Role of tissue sealants and patches:**

The role of tissue fibrin sealants has been explored as a strategy to decrease CR-POPF, either by topical application or by duct occlusion. In a RCT involving 125 patients randomized to topical application of fibrin glue *vs*. no glue in the control arm, there was no difference in the rate of a pancreatic fistula (26% in the glue *arm vs.* 30% in the control arm; leak was defined by their definition) and no difference in morbidity and duration of hospital stay64. In another RCT assessing temporary fibrin glue occlusion of main pancreatic duct, 80 patients underwent PD with duct occlusion with no difference in the rate of complications65. In a retrospective study analyzing the use of round ligament as a tissue patch over the PA, 57 PDs were performed with a pancreatic leak rate (local definition of leak, not the ISGPF definition) of 9%, however, further studies are lacking66. Currently, there is no high level evidence in favor of use of fibrin, other substances (such as neoprene or Tissucol), or tissue patches in the prevention of POPF after PD.

**Fistula Risk Score:**

In a prospectively validated trial, recognized risk factors for CR-POPF, such as a small duct, soft pancreatic parenchyma, high risk pathology, and excessive blood loss, were evaluated during PD and a Fistula Risk Sore (FRS) was developed.67 Clinical and economic outcomes were evaluated across four ranges of scores (Negligible risk-0 points; low risk- 1 to 2 points; intermediate risk, 3 to 6 points; and high risk- 7 to 10 points); the FRS correlated strongly with development of a CR-POPF (p<0.001). Clinical outcomes, including complications, duration of stay, and readmission rates, also increased with increasing FRS. The FRS was validated in other multi-institutional studies as well as in other settings (such as laparoscopic PD and cases without drain placement).68,69 The FRS has also been used to assess various strategies to decrease CR-POPF in a risk-adjusted fashion40,70, in assessing surgeon performance *vis-à-vis* CR-POPF outcomes, in augmenting risk prediction for PD, and in predicting cost of care3,71. Thus, the FRS has been validated as a strong tool with widespread applicability in clinical practice to predict the chance of a CR-POPF and also as a tool to compare outcomes across various studies. The FRS can be a reliable method to stratify patients in the future studies.

**Quality of life issues:**

The quality of life after PD with respect to the type of reconstruction is another arena for potential research. In the RECOPANC trial, QOL scores were assessed using the EORTC QLQ-C30 and PAN26 questionnaires at 6 and 12 months postoperatively; the domains of emotional and social functioning fared better in PG compared to PJ group (P=0.039), and financial problems occurred less often in the PG group (p=0.04), however there were no data on comparison of preoperative scores between the two groups22. The other retrospective study comparing PG and PJ found no statistically significant difference in the QOL aspects, but the study was criticized for unbalanced groups72.

**DISCUSSION**

In this era of evidence-based medicine, pancreatic surgeons over the past two decades have rightly embarked on the mission of identifying the ideal method of pancreaticoenteric reconstruction after PD. Despite multiple randomized studies and meta-analyses, there is no clear evidence nor universally accepted guidelines for how to construct the optimal PA after PD. During the past two decades, although the operative mortality has decreased dramatically, the overall morbidity remains high (about 50%), and the serious morbidity from the PA has remained relatively unchanged. It is also interesting to note that experienced high volume pancreatic surgeons and institutions, after their initial publications, have refrained from publishing further on this subject. It seems plausible that these surgeons and their teams matured over time to realize that after the initial refinements ensured improved acceptable outcomes, further refinements were difficult if not impossible and any further work in that direction was deemed essentially ineffective.

The recent additional data have not aided the surgeon today because of the complex interplay of various factors and variables. Many studies have focused on one variable in isolation for what is essentially a complex situation. The multiple studies described above have failed to provide definitive, consistent, and convincing Level 1 evidence that any one technique of PA is better than the others, either during the traditional open PD or more recently with the minimally invasive laparoscopic PD. The same holds true for control of the stump of the pancreatic remnant after a distal pancreatectomy73.

Considerable heterogeneity exists in the practice of PD across the world as shown by a recent survey involving 897 surgeons who perform PD74. The findings reveal that the practices are quite diverse and varied, and this only reflects that no best practice truly exists currently. The survey has also shown considerable regional variations with respect to the use of a stent, somatostatin analogues, drainage practices, and other putative strategies designed to minimize the risk of a CR-POPF. With respect to reconstruction, PJ remains the most common form of reconstruction as practiced by 88.7% of surgeons who participated in the survey.

A consistent practice of a single technique for the PA may lead to lesser rate of complications and therefore, might be preferable. Although this may sound more philosophical and less evidence- based, there is plenty of indirect evidence in the literature where the excellent results of a particular group with a particular technique are often not replicated by other groups, and one probable explanation could be that the comfort level and experience of the surgeon performing a new technique trumps any new and different techniques. Practicing and mastering a repetitive, standardized technique can be a potential solution to evade the problem of CR-POPF especially by surgeons early in their career. In contrast, experienced surgeons in high-volume centers can be expected to utilize different techniques of PA depending on the local characteristics of the operation, anatomy, and consistency of the pancreatic parenchyma in selected situations.

With the rapid advent of minimally invasive technology, laparoscopic and robot-assisted approaches have been explored regarding their possible influence on CR-POPF rates75. Reconstruction with the assistance of surgical microscope has also been shown to decrease pancreatic fistula rates (using a non-ISGPF definition) in one surgeon’s experience76. The precise, fine movement in multiple axes as offered by the robotic technology along with its magnified 3-Dvisual has also been claimed to decrease the incidence of POPFs (using many different definitions of POPF) after pancreatic reconstruction using the robot77,78. Currently, however, due to the complexity of these advanced minimally invasive procedures, there is no robust evidence proving any advantages for these procedures with regard to CR-POPF rates, and the prospects of a randomized trial happening soon also appears doubtful given extremely large cohorts necessary to prove superiority.

The debate concerning the ideal or the “best” form of PA remains unanswered despite the past two decades of RCTs and multiple meta-analyses. The best current technique for pancreatoenteric reconstruction may very well depend more on surgeon experience and comfort using the classic teachings of Halsted (meticulous technique, good blood supply, a tension-free anastomosis) and varying the technique depending on local characteristics of the pancreas and the risk factors in the individual patient. Our review of PJ vs PG, invaginating vs duct to mucosa, stents vs no stents, use or not of somatostatin analogues, and various anatomic constructs of the draining intestinal limbs have not really shown any to be consistently or convincingly better than the other. Perhaps the question “Do we need more studies?” 79 should be asked not concerning the currently described techniques, but rather aimed at radically new and novel approaches or paradigms (as yet undescribed) that lead to better tissue healing of the intestine or stomach to the pancreatic remnant. Currently, it appears that further randomized studies and meta-analyses using our currently described techniques of PA are unlikely to reach a definitive conclusion. Until a truly radically new paradigm becomes available, certain recommendations can be made based on evidence accumulated so far (Table 2).

**POSITION STATEMENT (Table 3)**

1. Neither Pancreaticogastrostomy nor Pancreaticojejunostomy have been shown to make any substantial difference in the incidence of CR-POPF rates after a pancreatico-enteric anastomosis.

2. The outcomes comparing PG and PJ in meta-analyses are associated with substantial heterogeneity in patients, techniques of PA, and definitions of POPF, and have a high degree of bias. A consistent practice of a standardized technique may be a potential strategy to decrease the rate of CR-POPFs for surgeons early in their career, but experienced surgeons at high-volume centers can have lower POPF rates performing a variety of techniques in diverse situations (Table 2).

3. There is no clear evidence on the benefit of internal or external stenting after PA.

4. Certain somatostatin analogues can appear to decrease the perioperative complications after PD in selected, high-risk situations (soft gland, small duct) but not mortality. To this extent, their routine use may be relevant only in high-risk patients.

5. Prophylactic abdominal drainage can probably be avoided in patients with negligible/low risk for POPF. In patients with moderate/high risk, early drain removal on POD 3 appears to be reasonable if drain fluid amylase activity on POD1 is <5000U/L.

6. Currently high level evidence is lacking for the selection of specific suture materials for PA.

7. There is no benefit in the use of tissue sealants and biologic patches as a strategy to prevent POPF.

8. The Fistula Risk Score is a predictive tool for clinically relevant POPF and its incorporation into routine clinical practice may help in managing patients selectively for use of somatostatin analogues and peripancreatic drainage.

9. Future studies should be very high quality multicenter RCTs evaluating specific intraoperative scenarios after eliminating bias and heterogeneity. Furthermore studies should be encouraged for the development and study of truly novel and new paradigms of promoting healing of PA.

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**Table1: Characteristics of Salient Meta-analyses comparing PG vs PJ**

|  |  |  |  |  |  |
| --- | --- | --- | --- | --- | --- |
| # | Author and year | Number of RCT’s included | Number of Observational studies included | Heterogeneity | Conclusion of meta-analysis |
| 1. | McKay 200634 | 1 RCT | 10 OCS | + | PG better than PJ |
| 2. | Wente, 200735 | 3 RCTs | 13 OCS | + | OCS -> PG superior over PJ; RCTS->PG and PJ have equal results. |
| 3. | Clerveus M 201436 | 7 RCTS | - | + | PG cannot be considered superior to PJ due to heterogeneity of trials and absence of difference in morbidity, reoperation rates and mortality |
| 4. | Hallet J 201537 | 4 RCTs | - | + | PG decreases POPF rate. |
| 5. | WeiTao Que MM 201538 | 8 RCTs | - | + | PG preferred over PJ |
| 6. | Benjamin Menahem 201539 | 7 RCTs | - | + | PG-> lower POPF rates and biliary fistula rates |

**Table 2: Suggested recommendations in diverse intra-operative situations**

|  |  |  |  |
| --- | --- | --- | --- |
| **No** | **Scenario** | **Recommended strategy** | **ISGPS concurrence** |
| 1 | Preferred method of PA following PD (PPPD/cW) | PJ with duct-mucosa advised as anastomotic technique | **++** |
| 2 | Preferred method of PA in the presence of high risk features for POPF – soft gland, small duct (<3mm), fatty pancreas and posteriorly located duct etc. | PJ with duct-mucosa advised as anastomotic technique | **++** |
| 3 | Does vascular resection in PD change the strategy of PA? | May not change the strategy | **+++** |
| 4 | a. Preferred suture material for constructing duct-mucosa PA  b. Preferred suture material for pancreatic parenchymal sutures (taken either in dunking or duct to mucosa PA) | Synthetic absorbable ( PDS 5,0)/  Synthetic absorbable (PDS 4,0) | **+++**  **++** |
| 5 | Preferential practice of anastomotic stenting | Stent(external/internal) based on high risk features for POPF | **+** |
| 6 | Preferential practice of using somatostatin analogues | Routine use may be relevant following PD for high risk glands | **++** |
| 7 | Role of isolated Roux-en Y PJ following PD to decrease CR-POPF | Not indicated as a strategy | **+++** |
| 8 | Preferential practice over prophylactic drainage | Routine prophylactic drainage but early removal on POD3 if drain amylase is low | **++** |
| 9 | Tissue sealant/biologic tissue patch usage to reduce CR-POPF | Not indicated as a strategy | **+++** |
| 10 | Following a leak from a PA, when a patient is being re-explored for POPF grade C, role of pancreatic re-anastomosis. | Not advisable as a strategy | **+++** |

***ISGPS concurrence rating:*** *+++ Strong* ***/*** *++ Moderate* ***/*** *+ Weak*

PPPD – Pylorus-preserving pancreatoduodenectomy

cW- Classical Whipple resection

**Table 3: Levels of Evidence and ISGPS recommendation**

|  |  |  |  |  |
| --- | --- | --- | --- | --- |
| **Variables** | **Literature review summary data** | **Level of evidence ( 1 to 5) & Evidence based recommendation (A to D)** | **ISGPS recommendation (Strong, Moderate,Weak)** | **Justification** |
| PG vs PJ | PG apparently seems advantageous over PJ although varied heterogeneity seen in existing RCTs | Level 1B  Grade B | Moderate | High level of heterogeneity observed in evidence. |
| Invagination technique | Safe technique and can be preferred in soft glands with narrow duct | Level 1B  Grade B | Moderate | Adequate evidence observed. |
| Duct to mucosa technique | Safe and common technique of PJ | Level 1B  Grade A | Strong | Adequate evidence observed. |
| Binding PJ | Safe but not associated with lower frequency of CR-POPF, morbidity and mortality. | Level 1B  Grade B | Weak | Consistent evidence is lacking. |
| Dual loop with isolated PJ | Dual loop with isolated PJ is not superior to single loop | Level IA  Grade A | Strong | Consistent evidence observed. |
| Gastric partition technique | New technique of PG but oncologically not always feasible | Level 1B  Grade B | Weak | Adequate evidence is currently lacking. |
| PA stenting | Benefit of stenting PA is not well supported by evidence. No advantage of external over internal stenting | Level 1A  Grade B | Moderate | Moderate level evidence observed. |
| Somatostatin analogues | Somatostatin analogues may reduce perioperative complications but not mortality. | Level 1B  Grade B | Moderate | Adequate evidence observed. |
| Fistula Risk Score | Risk scores correlate with CR-POPF incidence | Level 2A  Grade B | Moderate | Adequate evidence observed |
| Prophylactic drainage | To avoid in negligible/low risk patients and early drain removal in moderate/high risk if POD1 drain amylase is low | Level 2B  Grade B | Moderate | Adequate evidence observed |
| Quality of life | Global QoL is identical in both PG and PJ reconstruction | Level 1B  Grade A | Weak | Lack of adequate evidence |
| Tissue sealant | No advantage of tissue sealants | Level IB  Grade A | Strong | Adequate evidence observed |
| Tissue patches | No advantage of tissue patches | Level 2B  Grade B | Moderate | Lack of adequate evidence |
| Duct occlusion | No advantage of duct occlusion | Level 1B  Grade A | Strong | Adequate evidence observed |

Oxford Centre for Evidence-based Medicine – Levels of Evidence

Level 1A – Systematic review with homogeneity of RCTs

Level 1B - Individual RCT with narrow Confidence Interval

Level 2A – Systematic review with homogeneity of cohort studies

Level 2B - Individual cohort study

Level 3A – Systematic review with homogeneity of case-control studies

Level 3B - Individual Case-Control Study

Level 4 – Case series

Grades of Recommendation

Grade A - consistent level 1 studies

Grade B - consistent level 2 or 3 studies or extrapolations from level 1 studies

Grade C - level 4 studies or extrapolations from level 2 or 3 studies

Grade D - level 5 evidence or troublingly inconsistent or inconclusive studies of any level