



Technical aspects of pancreatic anastomosis

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Summary

Background Despite the significant improvement concerning perioperative mortality, pancreatoduodenectomy is still a challenging procedure. Pancreatic fistula is the most common complication underlying 30-day mortality. More than 61 surgical techniques of pancreatic anastomosis with a vast number of variations have been published. Moreover, various risk factors favoring the development of postoperative pancreatic fistulas have been identified.

Methods This review article presents an outline of ways to achieve the optimal pancreatic anastomosis, concentrating on technical aspects. The following parameters were assessed in this question: pancreatojejunostomy, pancreaticogastrostomy, stents, tissue patches and sealants, surgical experience, and center-specific technique.

Results With regard to current literature, there is no scientific evidence of an optimal pancreatic anastomotic technique. A distinct inhomogeneity among the trials concerning definitions, patient selection, anastomotic technique, and patient management is important to mention.

Conclusion The best strategy for reducing pancreatic fistula rate includes a standardized institutional concept of pancreatic anastomosis, documentation of surgical quality, and continuous enhancement by benchmarking.

Keywords Pancreatic anastomosis · Postoperative pancreatic fistula · Fistula risk score · Pancreatojejunostomy · Pancreatogastrostomy · Surgical technique

Abbreviations

CI	Confidence interval
CR-POPF	Clinically relevant postoperative pancreatic fistula
FRS	Fistula risk score
PG	Pancreatogastrostomy
PJ	Pancreatojejunostomy
POPF	Postoperative pancreatic fistula
RCT	Randomized controlled trial

Main novel aspects

There is no optimal technique for pancreatic anastomosis—a standardized institutional concept leads to low postoperative pancreatic fistula rates.

Introduction

Despite an ongoing significant improvement of perioperative mortality during the past years, pancreatoduodenectomy still remains a challenging procedure. This is reflected in institutional and national series demonstrating a 30-day mortality of up to 5%, which represents a commonly accepted benchmark [1–3]. A closer look at distinct causes of perioperative mortality reveals complications arising from leakage of the pancreatic anastomosis as the underlying problem in 50–80% of deceased patients [4]. Patients with grade C pancreatic fistulas were identified to be at the highest risk, with postoperative mortality rates of 40% [5]. Therefore, it is not surprising that pancreatic anastomosis is estimated to be the Achilles heel of pancreatoduodenectomy and strong efforts have been made to overcome this weak point. The establishment of definitions for pancreatic fistulas as well as their clinical grading regarding therapeutic consequences determined by the International Study Group for Pan-

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Table 1 Postoperative pancreatic fistula risk score according to ISGPS 2005

Risk factor	Parameter	Points
Gland texture	Firm	0
	Soft	2
Pathology	PDAC or chronic pancreatitis	0
	Ampullary, duodenal, cystic, islet cell, etc.	1
Pancreatic duct diameter	≥5 mm	0
	4 mm	1
	3 mm	2
	2 mm	3
	≤1 mm	4
Intraoperative blood loss	≤400 ml	0
	400–700 ml	1
	700–1000 ml	2
	>1000 ml	3
<i>FRS points (out of 10)</i>	<i>Risk zone</i>	<i>Risk of POPF (%)</i>
0	Negligible	Negligible
1–2	Low	6.6
3–6	Negligible	12.9
4–10	High	28.1

ISGPS International Study Group on Pancreatic surgery, *PDAC* pancreatic ductal adenocarcinoma, *FRS* fistula risk score, *POPF* postoperative pancreatic fistula

Table 2 The revised 2016 ISGPS classification and grading of POPF

EVENT	BL ^a (No POPF)	Grade B POPF ^b	Grade C POPF ^b
Increased amylase activity ≥3 times upper limit Institutional normal serum value	Yes	Yes	Yes
Persisting peripancreatic drainage >3 weeks	No	Yes	Yes
Clinically relevant change in management of POPF	No	Yes	Yes
POPF percutaneous or endoscopic specific interventions for fluid collections	No	Yes	Yes
Angiographic procedures for POPF-related bleeding	No	Yes	Yes
Reoperation for POPF	No	No	Yes
Signs of infection related to POPF	No	Yes, without organ failure	Yes, with organ failure
POPF-related organ failure	No	No	Yes
POPF-related death	No	No	Yes

BL biochemical leak, *ISGPS* International Study Group on Pancreatic surgery, *POPF* postoperative pancreatic fistula
^aBL defined by a drain amylase level higher than three times the upper serum amylase level without any clinical symptoms
^bA clinically relevant POPF (grade B and C) is defined as a drain output of any measurable volume of fluid with amylase level higher than 3 times the upper institutional serum amylase level, associated with a clinically relevant development/condition directly related to POPF

creatic Surgery (ISGPS) represented big steps toward to international benchmarking [6, 7].

The burden of pancreatic fistula draws attention to pancreatic anastomosis. More than 61 surgical techniques for pancreatic anastomosis have been published [8–10]. Techniques differ with respect to jejunum or stomach as site of the anastomosis with the pancreatic remnant, one or two-layer suture rows, binding or invagination techniques, and application of transanastomotic drains to mention only some of these technical variations. Furthermore, risk factors have been identified for the incidence of pancreatic fistulas. Soft pancreatic tissue and a diameter of ≤3 mm of the pancreatic duct certainly increase the risk of leakage of the pancreatic anastomosis. Among other factors, patient age and underlying pancreatic

disease as well as institutional patient volume and case load of the surgeon are also discussed to be of importance. The fistula risk score (FRS) has been proven to accurately predict the risk of postoperative pancreatic fistula (POPF) after pancreatoduodenectomy ([11–13]; Tables 1 and 2).

Providing for underlying evidence and measuring pros and cons of the technical aspects, this review article presents an overview of the search for an optimal pancreatic anastomosis. While this review concentrates on technical aspects of the pancreatic anastomosis, other factors of potential impact such as prophylaxis of POPF by somatostatin or analogues are not addressed.

Surgical techniques

Pancreatojejunostomy

In the majority of pancreatoduodenectomies, the pancreatic duct is anastomosed with the jejunum. According to Kennedy, about 90% of surgeons worldwide prefer pancreatojejunostomy over pancreatogastrostomy [14]. In general, four types of PJ may be differentiated, with conventional “classic” PJ, duct-to-mucosa PJ, invagination PJ, and binding PJ [15–21]. For each type, numerous modifications have been described with respect to end-to-side or end-to-end anastomosis, interrupted or running sutures, and suture material and thread size, to name the most affected technical items. Differentiation between types of PJ may be difficult, because techniques overlap to some extent. For example, invagination anastomosis was developed from the classic single-layer PJ to achieve a broader contact between the jejunal wall and the pancreas. Types of PJ differ also with respect to technical complexity. Some variations of invagination PJ and especially duct-to-mucosa PJ in case of a small duct and soft pancreatic tissue may be demanding. On the other hand, binding anastomoses are estimated to be technically easier. Different types of PJ were compared in six randomized controlled trials (RCT) with 1057 patients. There was no significance regarding POPF comparing duct-to-mucosa vs. invagination PJ (14% vs. 10%, RR 1.40, $p=0.54$) in the recent meta-analysis by Daamen [9]. RCTs also compared other types of PJ. A trial comparing duct-to-mucosa PJ with the classic one-layer PJ by Bassi did not detect a significant difference in POPF rate (duct-to-mucosa 13%, single-layer PJ 15%) [16]. Two RCTs were recently published in 2018. Hirono et al. compared a modified Blumgart PJ with the classic single-layer PJ in 224 patients. In the modified Blumgart anastomosis, trans-pancreatic sutures are made to invaginate the jejunum and pancreatic parenchyma with the duct-to-mucosa anastomosis. They resulted in nil postoperative mortality and a similar incidence of grade B/C POPF (invagination PJ 10.3%, classic PJ 6.8%; $p=0.367$) [22]. Another RCT from Japan analyses duct-to-mucosa and invagination PJ. The authors did not find a difference in grade B/C POPF (duct-to-mucosa PJ 23% vs. invagination 10%; $p=0.077$). However, when selecting only patients with a soft pancreas, POPF was significantly decreased in the invagination group (10% vs. 42%, $p=0.01$) [23].

There are numerous variations of PJ with respect to suture material and thread size, but there is no evidence for a distinct setting. In general, there is a tendency toward slowly resorbable monofilament suture material of 4/0 to 6/0 in duct-to-mucosa PJ. Binding techniques and invagination methods sometimes describe the usage of thicker threads.

One retrospective study from China compared continuous versus interrupted sutures in duct-to-mucosa PJ. Clinically relevant postoperative pancreatic fistu-

las (CR-POPF) were observed in 7.5% with continuous and 17% with interrupted sutures ($p=0.022$), major surgical complications decreased from 13.3 to 5% in continuous-suture PJ [24].

Another attempt to mitigate the sequelae of POPF is the reconstruction with two different Roux limbs for pancreatic and biliary anastomosis. There is only one RCT comparing PG with PJ performed with an isolated jejunal limb. The isolated Roux limb PJ could not decrease the rate of POPF [25].

Pancreatogastrostomy

While PJ has been used as the pancreatic anastomosis since the beginning of pancreatoduodenectomy, PG has gained increasing interest as an alternative during past years. Better blood supply of the pancreatic remnant and less demanding surgical technique were some of the subjective arguments in favor of PG. Some surgeons preferred PG when introducing laparoscopic pancreatoduodenectomy, because the stomach seemed to be more easily accessible when performing the pancreatic anastomosis via mini laparotomy [26].

Several modifications of PG have been described. In general, an anterior gastrostomy is performed followed by an incision of the posterior wall of the stomach. The pancreatic body is mobilized as well as the distal stomach and the pancreatic stump is brought into the stomach. The pancreas is secured by a purse-string suture and some additional sutures between the pancreatic capsule and the wall of the stomach [27, 28].

Pancreatojejunostomy–Pancreatogastrostomy

A recent Cochrane Review comparing PJ and PG summarizes 10 RCTs with 1629 patients [29]. There were no significant differences with respect to overall POPF rate and clinically relevant grade B/C fistulas. However, postoperative hemorrhage was found more frequently in the PG group, while more intraabdominal abscesses were observed after PJ. This Cochrane Review is not in line with a recently published meta-analysis of Daamen and the Dutch Pancreatic Cancer Study Group. In their analysis of six RCTs, they found a POPF rate of 12% after PG and 20% after PJ, which is tight to significance ($p=0.05$) [9]. Both Daamen and Cheng state that they found considerable variability in the included studies, hampering reliable analysis and decreasing evidence. Most recently, another meta-analysis was published by Wang et al. comparing PG with different types of PJ. No differences were found in the incidence of POPF between PG, invagination PJ, and duct-to-mucosa PJ [30].

Regarding the most recent RCT, the RECOPANC trial, a German multicenter study, no significant differences in the incidence of grade B/C fistulas and mortality were found between PG (20%; 6%) and PJ

(22%; 5%). The authors also describe a higher incidence of postpancreatectomy hemorrhage, especially grade A/B following PG (overall PPH after PJ 11% vs. PG 21%; $p=0.02$) [31].

Stents

Stenting of pancreatic anastomosis has been proposed as a technical measure to decrease the rate of pancreatic fistulas and attenuate clinical sequelae. The hypothesis behind this concept is to minimize exposition of the anastomosis to the pancreatic secretion by transanastomotic stents. The diameter of these stents is in the range of 5–8 French. Internal drains are placed as lost drains with a length of 5 to 7 cm in the main duct, protruding into the lumen of the jejunum at the anastomotic site. They come off spontaneously, but there is no evidence regarding the time of their loss nor on their patency. Rarely, such internal stents stay in place and are detected during routine controls 6 to 12 months after pancreatoduodenectomy. Some case reports document episodes of acute pancreatitis caused by retained internal stents [32]. Similarly, external stents are placed across the pancreatic anastomosis, but externalized via the jejunal loop beyond the hepaticojejunostomy in a Witzel technique. They are removed within weeks in the short-term postoperative course.

External and internal stents have been analyzed in several RCTs and retrospective series. The scientific evidence has been conflicting since the earlier trials. While Poon et al. reported a significant reduction of POPF with external stenting (6.7% with stent vs. 20% without stent; $p=0.032$), at the same time, an RCT from Johns Hopkins could not detect a reduction of pancreatic fistulas by internal stents, although they stratified for soft and firm pancreas [33, 34]. Neither in firm (stent 1.7% vs. no stent 4.8%) nor in soft pancreas (stent 21% vs. no stent 10%) were internal stents able to reduce the rate of POPF significantly.

Later, in a French multicenter trial, 158 patients with soft pancreatic tissue and a main pancreatic duct <3 mm were randomized to external anastomotic stenting of the PJ versus no stenting [35]. These authors found a significant overall reduction in POPF of 26% in the stenting group vs. 42% ($p=0.03$) without stent. There was no difference, however, with respect to the grading of POPF and mortality. A critical remark was that octreotide was used for 7 days in both groups and may have affected the rate of POPF. In another RCT, external and internal stents were compared. Tani et al. described a reduced hospitalization of 3 days in patients with internal stents, but no difference in fistula rate or mortality [36]. A Cochrane review published in 2016 summarized 8 RCTs including 1018 patients with pancreatoduodenectomy with or without application of stents and external versus internal stents [37]. The effect of stents in reducing the rate of POPF was classified as uncertain when evaluating

four studies with 605 patients due to a wide range of the confidence interval (CI). There was no significant difference regarding mortality (2% without stent versus 3% with stent). Transanastomotic stenting is used particularly in PJ, it is rarely applied in PG [38].

Overall, there is a lack of high-quality evidence due to a wide range of variability of factors with a possible impact on the development of POPF. In a recent multicenter study, inhomogeneity was minimized by analyzing patients within the highest range of the fistula risk score (FRS) [39]. Out of 5323 patients, 9.8% had an FRS of 7–10 and represented the group of interest. Clinically relevant grade B/C fistulas were documented in 15.2% with external stents, 43.8% with internal stents, and 33.8% without stent ($p<0.001$). In multivariate analysis, external stenting still significantly reduced CR-POPF in this group with very high risk (OR 0.45, CI 0.25–0.81).

Tissue patches and sealants

With respect to all the technical issues relevant to performing a safe pancreatic anastomosis, it was obvious to test sealants or patches for mitigation of POPF. However, in the Cochrane Review by Gong, fibrin sealants were not able to decrease the incidence of POPF [40]. In the Austrian P00 study, the effect of a fibrin-coated patch on the rate of POPF was analyzed in a multicenter RCT (Fig. 1 [41]). The overall rate of POPF and grade B/C fistulas was 63% and 23%, respectively, in the patch group compared with 56% and 14% without patch. The patch was not able to decrease fistula formation. Furthermore, no significant differences were observed regarding mortality, postoperative complications, fistula closure, and the length of hospitalization. In multivariate analysis, obesity, pancreatic duct <4 mm, and soft pancreatic tissue were identified as risk factors for POPF in this cohort. Interestingly, application of a patch could not decrease the rate of CR-POPF in this high-risk group either. This is in line with the results of the international multicenter analysis by Ecker et al. [39]. In patients with an FRS of 7–10, neither tissue patches ($p=0.42$) nor biologic sealants ($p=0.08$) were able to decrease the evolution of fistula significantly. However, this finding is limited, because patches were applied in 9.6% and sealants in 1.7% of pancreatoduodenectomies only.

Surgical experience

The technique of how to perform a pancreatic anastomosis is affected by some individual factors. To a certain extent, the more widespread use of PJ over PG is explained by institutional teaching habits. While PJ has been performed for a longer time than the later-developed PG, more surgeons are passing on PJ to their younger colleagues [14].

Table 3 Mitigation strategies to meet high FRS (7–10)

Measure/Factor		POPF rate
Anastomotic technique	Pancreatogastrostomy	↑
	Pancreatojejunostomy	↓
	Binding anastomosis	↔
	Standardization of institutional anastomotic technique	↓
Stent	Externalized stent	↓
	Internal stent	↔
Intraperitoneal drain	–	↓
Medical prophylaxis	Octreotide	↑
Tissue patches and sealants		↑
Surgeons annual case load	<25/year	↑
	25/year	↓
Surgeons career case load	≤50	↑
	50–200	↔
	≥200	↓

Looking at individual surgeons' characteristics such as years in practice, having surpassed the learning curve of 50 pancreatoduodenectomies, performing a high annual case load (>25/year), and high career case load (>200) revealed insight into technical preference. Senior surgeons were more likely to prefer PG, invagination PJ, and external stents. Surgeons having passed the learning curve liked to use two-layer PJ, stents, and the FRS. Surgeons with a high annual volume adhered to the same reconstruction technique in every case and tissue patches, but were less likely to use a separate Roux limb and multiple drains. Finally, surgeons with a career case load >200 PD had a similar behavior to those passing the learning curve, except the use of FRS [42]. In the international multicenter study by Ecker et al., surgeon volume had a significant influence on the development of POPF in high-risk patients. Surgeons with a total volume of 50–199 (RR 0.64, CI 0.28–1.51) and more than 200 PD (RR 0.30, CI 0.14–0.66) had less POPF than those with <50 PD in univariate analysis. However, in the multivariate model for mitigation strategies, this graduation of the case load was not significant anymore and has to be relativized [39].

Center-specific technique

The recently published studies by Ecker and Kennedy may explain to some extent the results of former single-center series reporting low rates of POPF compared with larger multicenter trials [39, 42]. Homogenous patient selection and standardization of surgical technique are more likely given in a single-center setting and may be settled as an institutional concept (Figs. 2 and 3). In combination with prospective documentation and critical assessment of data, surgical technique can be evaluated and possibly im-

proved. After changing from classical single-layer PJ to duct-to-mucosa PJ, we analyzed our results for both periods. To exclude as much variability as possible, we included only patients with ductal pancreatic adenocarcinoma operated on under the responsibility of a single surgeon. There were no differences in overall surgical complications, POPE, and mortality. However, duct-to-mucosa PJ was able to decrease major complications (Dindo–Clavien 3–5) from 36.3 to 4.9% ($p=0.05$) and the incidence of unplanned reoperations and reinterventions from 17.8 to 2.4% ($p=0.02$) [43].

Although such institutional series must be interpreted carefully, they are a solid basis for the development of a center-specific surgical technique of pancreatic anastomosis (Table 3).

Discussion

Overall, considerable efforts have been undertaken to optimize the surgical technique and evolve an optimal pancreatic anastomosis during the past. With respect to more than 60 published techniques and the myriad of variations performed, the only conclusion left is that an optimal technique has not been defined yet. Thinking about the reason for this frustrating fact brings up some considerations.

First, there is a distinct inhomogeneity among trials concerning definitions, patient selection, technique, and patient management. Mixing up fistula definitions, including patients with different risks for POPE, and the use of diverse adjunctive measures like stents, patches, or somatostatin analogues biased trials. Some of these shortcomings have been overcome. Today, the definition of the ISGPF is generally accepted and commonly used [6, 7].

Grading of pancreatic fistulas according to their clinical relevance and reporting systems for surgical complications like the Dindo–Clavien classification are a good standard [44]. Recently, the risk for the

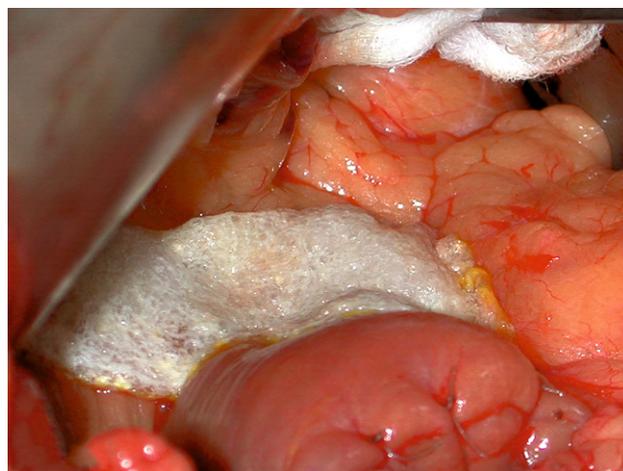


Fig. 1 Fibrin sealant patch on pancreatojejunostomy



Fig. 2 Situs after resection. *P* pancreatic remnant, *VP* portal vein

development of pancreatic fistulas attracted more notice. While soft pancreatic tissue and a small pancreatic duct, normally defined by a diameter up to 3 mm, are generally accepted risk factors for the development of POPE, other possibilities have probably been underestimated. The FRS considers a clinically more realistic pattern and offers models for mitigation of POPF [11, 39]. Ecker et al. identified pancreatoduodenectomy with external stenting, omission of prophylactic octreotide in a setting of PJ, and the use of intraabdominal drains as the best model for minimizing POPF for high-risk patients with an FRS of 7–10. This may be an argument to adapt the anastomotic technique to patient's individual risk. However, this stands in contrast to the practice of high-annual-volume surgeons, who tend to use one reconstruction technique for all patients.

Another item hampering the scientific evidence is a lack of standardization of anastomotic techniques. For example, there are numerous variations on how to perform a PG or a duct-to-mucosa PJ in terms of surgical technique and sutures. These alternative techniques may be due to surgical schools or individual surgeons' preferences. The impact of these individual versions of how to perform a pancreatic anastomosis on perioperative results is not clear. Differing results of multicenter RCTs and single-center studies may be explained by this lack of standardization. Better perioperative results with an exceptionally low incidence of POPF in single-institution trials are possibly caused by a standardized anastomotic technique. Not surprisingly, standardization is easier to achieve in a single institution than in a cluster of international institutions.

Finally, reporting is another striking issue. Looking at published rates of POPF using the ISGPF definition, CR-POPF are reported in a range of 3 to 23% [41, 45]. This is surprising, because these trials stick to a uniform definition. We observe a trend toward higher rates of CR-POPF reported in recently published com-

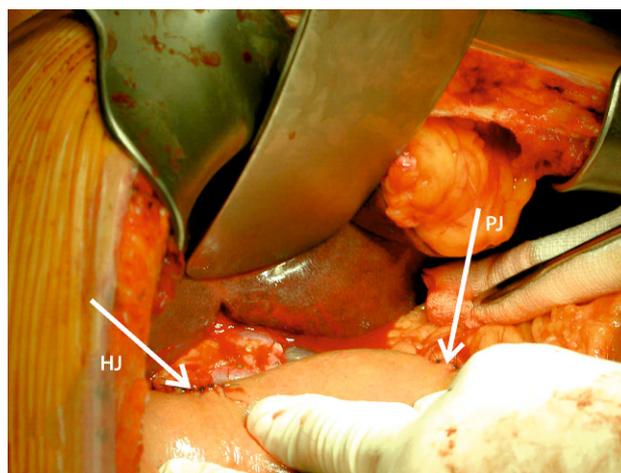


Fig. 3 Situs after reconstruction. *PJ* pancreatojejunostomy, *HJ* hepaticojejunostomy

pared to former studies. Although differing risk factors among trials can be an explanation, skepticism may be appropriate. For example, the rates of CR-POPF and perioperative mortality in the RECOPANC trial were considerably high, although only high-volume centers were involved [31]. It is crucial to look closer at whether underreporting or underestimation of the risk play a role.

In conclusion, there is no scientific proof for an optimal anastomotic technique. Stratification for risk factors and the evaluation of technical measures for mitigation of CR-POPF are the current trends. For surgical practice, a standardized institutional concept of pancreatic anastomosis, documentation of surgical quality, and continuous enhancement by benchmarking are the best strategies in line with current scientific evidence.

Conflict of interest H. Wundsam, C. S. Rösch, I. Fischer, and R. Függer declare that they have no competing interests.

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