Chapter 5

Pancreatic Fistulas

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Introduction

In the literature an objective definition of a pancreatic anastomotic leak is absent; terms like fistula, leak, leakage, focal postoperative pancreatitis, and anastomotic failure or anastomotic insufficiency continue to be used to define pancreatic fistula (PF). A study group has shown that the majority of the pancreatic surgeons prefer to use the term fistula [1]. Regarding pancreatic resections for malignant tumors, the single most significant cause of morbidity and mortality is the appearance of pancreatic leak and PF, and rates of up to 20% are reported from centers specializing in pancreatic surgery [2-4], depending of the type of the resection: pancreatoduodenectomy, central pancreatectomy or corporeo-caudal pancreatectomy. Postoperative PF is one of the most common complications of pancreatic surgery [5]. Despite mortality rate after pancreatic resection has decreased to less than 5%, the morbidity remains high, ranging from 30% to 50% in high-volume centers [2, 3, 6-47].

Despite the main cause of PF is pancreatic resection it can appear also after other surgical procedures like total gastrectomy, pseudocysto-jejuno anastomosis (in case of pancreatic pseudocyst), after splenectomy or endoscopic procedures. Developing PF is causing life-threatening complications and increases the hospitalization and the cost of treatment by the use of additional investigations and procedures. An early recognition of PF and prompt institution of appropriate treatment is the cornerstone in the prevention of potentially devastating consequences [48].

In this chapter we will discuss more of pancreatic fistula after pancreatic resection; the other types of pancreatic fistula will occupy less space, due to the fact that isn’t so common.

Classification

An abnormal communication between the pancreatic ductal epithelium and someother epithelial surface containing pancreas derived, enzyme-rich fluid is define as pancreatic fistula [1].

In what concerns postoperative pancreatic fistula (POPF) and to develop a common system of classifying POPF, the International Study Group on Pancreatic Fistula (ISGPF) in 2005 designed a new and universal set of standards to reconcile the many preexisting definitions (Table 1) [1, 49-52] and since then has been used in most of the studies investigating outcome measures in pancreatic surgery. Based on the level of fluid amylase, POPF are classified as grade A (least severe, biochemical fistulae) or grades B and C, which have a greater clinical impact - also called as clinically relevant post-operative pancreatic fistula (CR-POPF). These grades have been qualitatively validated and generally globally accepted as proper nomenclature for POPF severity.

Table 1. *International Study Group of Pancreatic Fistula definition and grading system [1].*

International Study Group of Pancreatic Fistula definition and grading system			
Definition	*Output via an operatively placed drain (or a subsequently placed percutaneous drain) of any measurable volume of drain fluid on or after post operatory day 3, with an amylase content grater than 3 times the upper normal serum value*		
Grading system			
Grade	**A**	**B**	**C**
Clinical Condition	*Well*	*Often well*	*Bad*
Specific treatment	*No*	*Yes/No*	*Yes*
Ultrasound/CT scan	*Negative*	*Negative/Positive*	*Positive*
Persistent drainage (after 3 weeks)	*No*	*Usually yes*	*Yes*
Reoperation	*No*	*No*	*Yes*
POPF-related death	*No*	*No*	*Possibly yes*
Signs of infection	*No*	*Yes*	*Yes*
Sepsis	*No*	*No*	*Yes*
Readmission	No	Yes/No	Yes/No

A major problem of POPF classification represented the inability to be compared quantitatively [53].

A study published in 2013 by Benjamin C. Miller et al. had reinforce the ISGPF scheme and quantitatively establish a clear clinical impact for each grade of fistula by using Post-operative Morbidity Index (PMI) and a Fistula Risk Score (FRS) model [54, 55] - (Table 2).

Table 2. *Fistula Risk Score for prediction of clinically relevant pancreatic fistula after pancreatoduodenectomy (Adapted from Callery et al.[55]).*

Fistula Risk Score for prediction of clinically relevant pancreatic fistula after pancreatoduodenectomy		
Risk Factor	**Parameter**	**Points**
Gland texture	Firm	0
	Soft	2
Pathology	Pancreatic adenocarcinom or pancreatitis	0
	Ampullary, duodenal, cystic, islet cell	1
Pancreatic duct diameter (mm)	≥5	0
	4	1
	3	2
	2	3
	≤1	4
Intraoperative blood loss (mL)	≤400	0
	401-700	1
	701-1000	2
	>1000	3
Fistula Risk Zones	**Points**	
Negligible	0	
Low	1-2	
Intermediate	3-6	
High	7-10	

In what concerns pancreatic resection, for pancreatic head resection many scoring systems were developed for PD and validated [55-64] in contrast with distal pancreatectomy whereas such a system is missing due to the lack of reproducible risk factors in isolation. Regarding PD, the Fistula Risk Score

(FRS) is the preferred method of individual fistula risk assessment at the authors' institutions, due to the fact that has been the most rigorously scrutinized and applied system thus far in the literature. Using an extensive multivariate analysis of all known endogenous, perioperative, and operative risk factors for fistula (54 variables in total) for the prediction of clinically relevant POPF (CR-POPF) after PD developed this system. After the analysis was done four significant risk factors (Table 2) were weighted and assigned quantitative values: soft gland parenchyma, high-risk pathology (anything other than pancreatic adenocarcinoma or pancreatitis), small duct diameter (<5 mm), and elevated intraoperative blood loss (>400 mL). Other authors have validated this scoring system [59, 60, 62].

Using a protocol based on this FRS system McMillan et al. [65, 66] have applied on 260 PDs to evaluate the necessity of drain placement after PD. In this protocol drains are recommended for moderate/high-risk FRS patients but may be omitted in patients with negligible/low risk. In case of moderate/high-risk patients drain fluid amylase values can then be evaluated on post operatory day 1 to determine the optimal timing for drain removal. This has led to a reduction of CR-POPF in excess of 40% compared with an historic cohort. In particular, no POPF developed in the low/negligible-risk patients where drains had been omitted.

Etiology

In attempt to improve outcomes and since the advent of the ISGPF and standardization of fistula nomenclature, there has been a systematic investigation of risk factors. A multitude of factors are incriminating to favor apparition of PF: endogenous, perioperative, and intraoperative factors (pancreatic duct caliber, pancreatic remnant texture, anastomotic technique, use of trans-anastomotic stent, intraoperative blood loss, operative time, and routine drain placement), including

age, gender, body mass index (BMI), diabetes mellitus, cardiovascular comorbidities, disease pathology, neoadjuvant therapy, use of prophylactic somatostatin analogs. Another new factor incriminated in apparition of PF after PD is body surface area. On a study made on 411 patients with PD [67], body surface area was determined as a significantly factor for PF.

Despite the improvements of long-term survival and mortality in PDs, post-operative morbidity still remains high with rates reported between 30% to 50% in large series [46, 68, 69]. Of these, a POPF still is the clinically most relevant complication after PD with an incidence ranging from 9.9% to 28.5% [1], leading to life-threatening complications such as sepsis, abscesses, early or delayed haemorrhage, the need for a relaparotomy. A French study [70] made on 1325 patients undergoing a PD for ductal adenocarcinoma reported a rate of 14% of PF, comparable with the results of other large institutional studies [71, 72]. In this study, authors analyzed the risk factors for PF and concluded that soft pancreatic parenchyma, the absence of pre-operative diabetes, pancreatojejunostomy and low-volume center are independent risk factors in case of PD for pancreatic adenocarcinoma. Other studies reported a low rate of PF (5%) in patients undergoing PD for pancreatic adenocarcinoma compared with a 15.4% to 18.4% rate in patients operated on for distal cholangiocarcinoma, duodenal carcinoma and ampullary cancer [73, 74]. In these reports up to 75% of patients with adenocarcinoma had pre-operative jaundice.

Patient-Related Risk Factors

In case of PDs from patient characteristics (including male sex, advanced age (>70 years), creatinine clearance abnormality, identifiable jaundice, and intraoperative blood loss and coronary artery disease), majority of the studies concluded that patient's age more than 70 years is the only factor associated with deficient anastomotic healing leading to PF [1, 3, 48, 75-79]. There are

limited studies that have demonstrated the relationship between the rest of the incriminated factors described above and PF. In a multivariate analysis patient with coronary artery disease seems to favor the apparition of PF, due to the impaired visceral perfusion of the anastomotic partners [73]. The duration of the jaundice seems to be another factor that can lead to PF [80]. In the same study, PF was also associated with a significantly lower creatinine clearance.

The association between the presence of pre-operative diabetes and PF is still under debate. While some authors demonstrated the correlation between PF and the presence of pre-operative diabetes [81, 82], other demonstrated that the absence of pre-operative diabetes is a risk factor for PF [73, 83].

Pancreas and Disease-Related Risk Factors

Disease-related risk factors for an increased PF rate after PD mainly include a non-dilated pancreatic duct, a soft pancreatic parenchyma and a fatty pancreatic texture [57, 69, 83, 84]. In a series published of almost 2000 PDs, the authors concluded that a soft pancreas was associated with a 22.6% fistula rate and led to a 10-fold increased risk of PD compared to intermediate or hard gland [73]. Other investigations have similarly reported high rates of PFs when are dealing with soft pancreatic parenchyma [48, 75, 77, 79, 85]. In other reports, none of the patients with hard pancreatic parenchyma developed PF while 25% of patients with soft pancreatic parenchyma were found to be complicated with PF [85, 86].

Another major predictor of PF represents the size of the pancreatic duct [85]. Patients with small no dilated pancreatic ducts, typically defined $\leq$ 3mm in diameter are more predisposed to PF compared to 7% of patients with dilated ducts [48, 75, 77, 79]. Other disease-related risk factors include resection of pathologic lesions like distal cholangiocarcinoma, ampullary or duodenal carcinoma, intraductal papillary mucinous neoplasia, pancreatic cystadenomas, benign islet tumours, duodenal adenomas, and increased pancreatic juice output.

Operative Risk Factors

Many intraoperative factors are incriminated to favor PF. High intraoperative blood loss is an important risk factor for developing PF after PD. This can be secondary to other factors including: advanced stages of disease (portal or superior mesenteric vein invasion, patient obesity, jaundice-associated coagulopathy and concurrent pancreatitis) [48, 77, 80].

The benefit of PJ compared with PG after PD still remains controversial. In four prospective randomized trials comparing PJ and PG, 3 of these studies have reported no difference in the PF rate and one demonstrated significantly lower rate of PF after PG than PJ (4% vs.18%) [45, 87-89]. Results from single institutional centers that are using exclusively telescoping or invaginating techniques supports PG vs PJ [41, 90-95]. Majority of these non-randomized comparative studies have shown a significantly lower PF and relaparotomy rates after invaginated PG compared with PJ [41, 90-93, 95].

Some studies reported high PF after central pancreatectomy (CP) comparing with PD or distal pancreatectomy [96, 97]. In one study comparing the clinical and economic effects of PF among patients with pancreatic resections, revealed that the incidence of clinically relevant fistulae (grades B and C, according to ISGPF grading system) was 16% for PD, 13% for distal pancreatectomy, and 83% for central pancreatectomy [98]. One of the reasons can be that in case of CP there are 2-pancreatic stumps, proximal and distal, thus potentially facilitating the formation of PF. In a meta-analysis published by Yan-Ming Zhou et al. [97] on 867 patients with CP the overall pancreatic fistula rate was 33.4%. Of them, 89.6% (250/279) had grade A or B fistulae of ISGPF, all of which were managed successfully non-operatively; only 10.4% were grade C fistulae. A systematic review of 2706 PDs reported that grade C pancreatic fistula accounted for 15% of all their 479 cases of PF [99]. Other authors [98, 100-102] demonstrated that the occurrence of grade C fistulae of ISGPF with CP was

similar to that with distal pancreatectomy. These data indicate that CP does not seem to increase the severity of PFs. In case of distal pancreatectomy a study published by Distler M. et al. [103] concluded that chronic pancreatitis of the pancreatic remnant is an independent risk factor for postoperatory PF.

According to an Italian study [104], the leakage from the distal pancreatic anastomosis is likely to cause more severe clinical consequences. In their group the distal pancreatic stump was inserted into the peritoneal space through a small transverse mesocolic window and an inframesocolic pancreatojejunostomy was performed while the proximal pancreatic stump was close in the supramesocolic space. Segregation of the two-pancreatic stumps into different body compartments allows for selective identification of the source of a PF.

The two commonly preferred methods for reconstruction of the distal pancreatic remnant are pancreaticojejunostomy and pancreaticogastrostomy, despite a study published by Wayne et al. [105] reported that there was no pancreatic leakage in a series of 10 patients who underwent CP without pancreatico-enteric anastomosis. Xiang et al. [102] reported that pancreaticogastrostomy for the distal pancreatic stump reduced the occurrence of PF, while Venara et al. [106] showed a lower anastomotic leakage rate with pancreaticojejunostomy. Other studies demonstrated that both techniques had an equivalent fistulas rate in CP [107, 108].

Other studies demonstrated that in case of distal pancreatectomy body mass index greater than 25 kg/m^2, transections at the pancreatic body, and absence of pancreatic duct ligation, soft pancreatic tissue, spleen preserving procedures, and the non-use of postoperative prophylactic octreotide favor PF apparition [109-111].

Despite the superiority of laparoscopic distal pancreatectomy (LDP) in preventing PF has not been demonstrated, the PF rate of LDP is similar to that

of open distal pancreatectomy and remains substantial, at up to 21 % [112, 113]. Nakamura et al. [114] demonstrated that in case of LDP by using a special techinque (peri-firing compression method) the incidence of PF is lower that in case of normal technique of LDP. These results were validated by other authors [115].

Another cause for POPF can be surgeries performed in upper part of the abdomen (gastrectomy, splenectomy) and trauma of the abdomen. In one Japanese study on 1341 consecutive patients underwent gastrectomy for gastric cancer, 35 patients (2.6%) develop PF according to the ISGPF classification [116].

Clinical Presentation

The suspicion of PF starts whenever there is a deviation in the normal clinical course of a patient who has just undergone a pancreatic resection. Usually PF is associated with other non-fistulous complications, like delayed gastric emptying, intra-abdominal abscess, pancreatitis, haemorrhage, ileus, wound infection and sepsis. This increases the rate of reoperation and hospital costs.

The diagnosis of post-operatory PF may be suspected on the basis of the many clinical or biochemical findings. A general definition begins with the following criteria: output via an operatively placed drain (or a subsequently placed, percutaneous drain) of any measurable volume of drain fluid on or after postoperative day 3, with amylase contents 3 times greater than the normal amount [1].

The aspect of drain fluid could vary from a dark brown to greenish bilious fluid (provided by the anastomosis that is near or abroad to a biliojejuno-anastomosis) to milky water to clear ‘‘spring water’’ that looks like pancreatic juice [1]. Abdominal pain and distention with impaired bowel function, delayed gastric emptying; fever (>38 ℃), serum leukocyte count

greater than 10,000 cells/mm^3, and increased C-reactive protein may also be present. Radiologic documentation is not necessarily and it isn't recommended for diagnosis [37].

Treatment

Conservative Treatment

In over 90% of the patients with PF a conservative treatment is successful [117, 118], especially after PD. This means that patients should be evaluated at short period of time. If the patient does not have any fever, tachycardia, leucocytosis, severe wound infection, and the abdomen is soft (with functioning bowel), and no signs of peritonitis, it is safe to continue with conservative measures. The measure should include maintenance of enteral nutrition (through an operatively placed nasojejunal tube or a feeding jejunostomy), nasogastric suction (in the presence of delayed gastric emptying secondary to PF). Total parenteral nutrition should be considered for patients who have not tolerated oral feeding or in situations where the abdomen has not "really settled".

In case of signs of infection (i.e., fever, warmth, tenderness, leukocytosis, purulent discharge, erythema) empiric antibiotics should be given and adjusted depending on information from gram stains or cultures.

Drainage should be management by caution and intra-peritoneal drains should be left in situ until daily drainage volumes approach 50mL per day; patients can be discharged at home as long the liquid drain is not purulent. Therapeutic octreotide can be administered to reduce pancreatic secretions despite its administration is debatable.

Endoscopic Treatment

The first-line treatment of pancreatic fistulae is endoscopic treatment, which tries to restore the continuity of the pancreatic duct by placing a stent that

crosses the ductal disruption. As in the case of biliary drainage, the purpose of pancreatic duct stenting is to lower the pressure inside the Wirsung duct, favoring the drainage of pancreatic secretion inside the duodenum and reducing its exteriorization through the fistulous opening. In some cases, when the fistula has a low output, performing only a pancreatic sphincterotomy may suffice. Routine biliary sphincterotomy for patients undergoing pancreatic sphincterotomy is not recommended, and should be reserved for patients in whom there is evidence of coexisting bile duct obstruction or biliary sphincter of Oddi dysfunction [119].

From a technical standpoint, this is achieved by endoscopic retrograde pancreatography. After endoscopic visualization of the papilla, a guidewire is inserted into the main pancreatic duct under radiologic guidance. The stent is then placed on a pushing catheter and deployed under radiologic guidance, after which the guidewire and catheter are removed. Although transpapillary passage of a stent through the pancreatic sphincter reduces ductal pressure to promote flow toward the duodenum and away from the fistula tract, the passage of a stent through the disruption may be somewhat more effective than transpapillary stenting alone [120-123].

Pancreatic plastic stents are similar to biliary ones and are mainly made of polyethylene, with sizes ranging from 2 to 25 cm in length and 3F to 11.5F in diameter. Similar to their biliary counterparts they can be either straight, curved, wedged, or single pigtail, most having side holes to aid in draining the pancreatic secondary ducts [124].

Because of the smaller diameter of the pancreatic duct, pancreatic fistulae are usually managed using plastic stents. Stent selection depends upon the size of the lumen and length to be traversed. A study showed that smaller diameter stents (3-4 Fr) were significantly less likely to be associated with ductal changes than 5-6 Fr stents [125]. These, particularly when bridging the entire leak is

possible, are effective in treating pancreatic duct leak in 77% to 94% of cases [122, 126, 127]. Effectiveness is reduced in complete duct disruption. Stents are usually retrieved after four to six weeks.

A special consideration should be given to disconnected pancreatic duct syndrome (DPDS), which describes the most severe form of a pancreatic leak and occurs when the pancreatic duct is completely transected, usually at the pancreatic neck, in the setting of necrotizing pancreatitis or trauma (Figure 1). Patients can develop abdominal fluid collections, including walled-off pancreatic necrosis. In these cases, transmural endoscopic drainage of the collection should be performed alongside transpapillary stenting (Figure 2). Newly developed lumen-apposing metal stents (Axios stent - Boston Scientific, Spaxus - Taewoong Medical) have been shown to be very effective in draining pancreatic fluid collections, but their role in long-term stenting for DPDS is uncertain and cannot be recommended at this time [128].

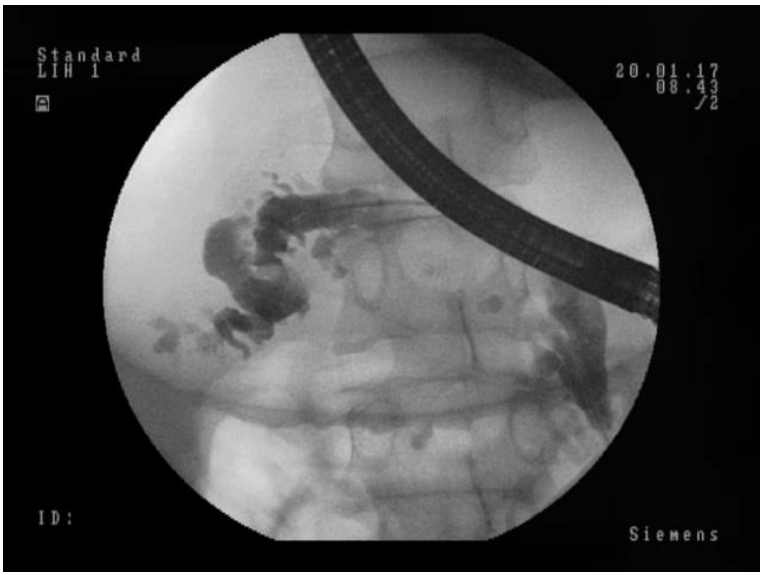

Figure 1. *Chronic pancreatitis in a young patient, with a dilated Wirsung duct.*

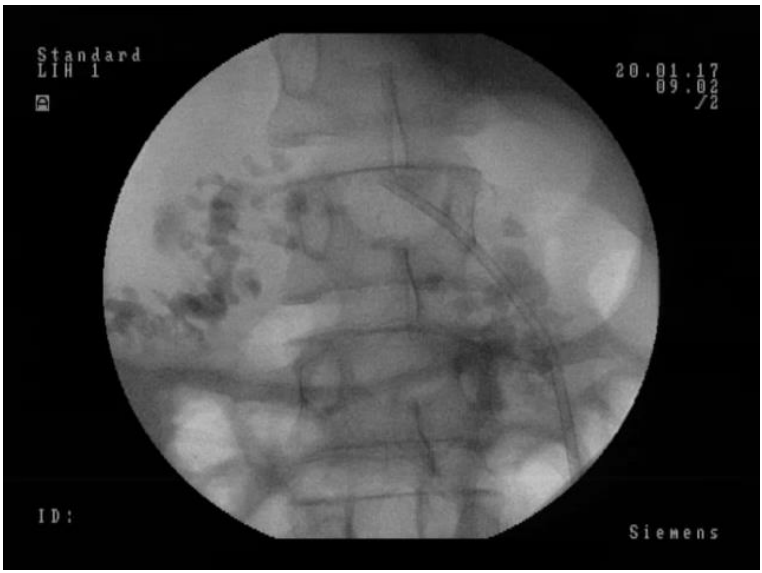

Figure 2. *Plastic stent placed in the main pancreatic duct, in order to decompress it and allow for the fistula to close.*

Early complications related to stent placement include acute pancreatitis, bleeding and guidewire fracture inside the pancreatic duct. Acute cholangitis is also possible and is caused by the stent obstructing the common bile duct. Late complications related to pancreatic stents are the development of changes that resemble chronic pancreatitis, related to stent occlusion. Migration and clogging also occur in more than 50% of patients, and can be managed endoscopically [129].

Interventional Imaging Treatment

The interventional radiologist is playing a crucial role by image-guided repositioning of operatively placed drains or for insertion of percutaneous catheters to drain collections seen in CT scan [22, 118]. CT (Figure 3 and 4) or ultrasound- guided percutaneous drainage can drain intra-abdominal collection; this decision should belong to the surgeon.

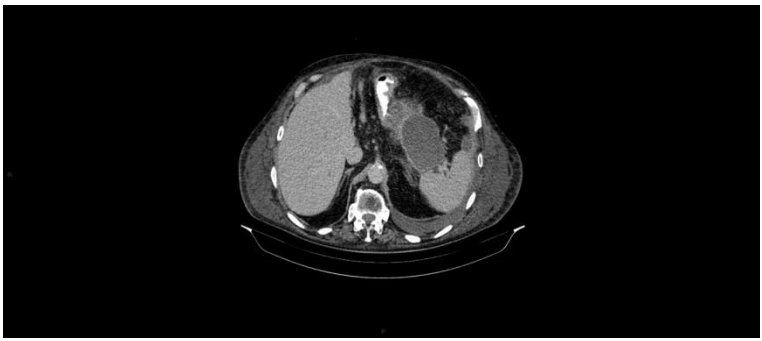

Figure 3. *Collection in rapport with greater curvature of the stomach after a pancreato-gastro anastomosis after duodenopancreatectomy.*

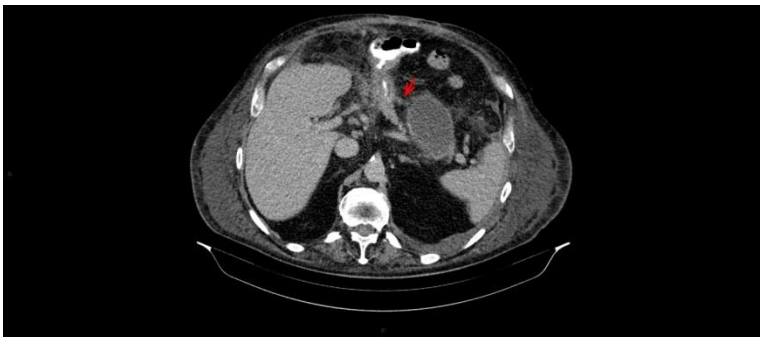

Figure 4. *Fistulas traject (the arrow).*

Surgical Treatment

When there is an anastomotic dehiscence suspected and patients are clinically deteriorated surgical exploration is necessary. The surgical options include wide peripancreatic drainage of an abscess or fluid collection, revision of the initial pancreaticoenteric anastomosis, conversion to an alternative pancreaticoenteric anastomosis, or completion pancreatectomy. Simple peripancreatic drainage might not be effective in patients with severe postoperative pancreatic fistula with disruption of the pancreaticojejunostomy [85]. If completion of total pancreatectomy is necessary this can lead to high perioperative mortality ranging from 75% to 100% with severe morbidity of brittle diabetes [85, 130].

Conclusions

Knowing and identify the risk factors for PF preoperatively is essential. Special attention should be taken to prevent POPF. In case of PF apparition a correct management is essential and should be address in correlation with PF grade.

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