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PREVENTION AND TREATMENT OF COMPLICATIONS IN PANCREATIC CANCER SURGERY

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Pancreatic cancer is the fifth leading cause of cancer-related death in men and women in Europe, being resistant to non-surgical forms of oncological treatment such as radio-, chemo-, and immunotherapy. Surgery remains the only curative treatment for pancreatic tumors. These patients typically present in a malnourished and advanced state of the disease. Most of the improved survival achieved over the past three decades has been related to improved perioperative management, and earlier recognition and treatment of post-operative morbidity. Malnutrition leads to a vicious cycle, as complications are detrimental to the nutritional state of the patient, with postoperative morbidity rates being still substantial. Whilst the majority of perioperative complications are not life-threatening, they can, however, amount to increased lengths of stay, costs and delays in adjuvant therapy. This article reviews the current literature, the prevention and treatment of most common four postoperative complications after pancreatic surgery for cancer, namely pancreatic leakage, delayed gastric emptying, intra-abdominal abscess and hemorrhage. Literature search in PMC, PubMed, NCBI, Cochrane databases, between 1990 and 2015, using as keywords pancreatic surgery, postoperative complications, pancreatic cancer, fistula, treatment, multidisciplinary, perioperative and management was used.

Keywords: complications, cancer, perioperative, pancreatic

INTRODUCTION

Pancreatic cancer is the fourth and fifth leading cause of cancer-related death in men and women respectively in the United States[1,2], as in Europe[3], being one of the most aggressive malignancies, making each pancreatic surgery for cancer – pancreatoduodenectomy (PD), central or distal pancreatectomy, or, in particular cases – total pancreatectomy, a "formidable operation"[1]. It is resistant to non-surgical forms of oncological therapy. The only treatment that can offer potential cure and long-term survival is the resection of the cancer, completed by adjuvant chemotherapy. Although extensive preoperative investigations are made, more than one third of the patients present with locally advanced cancer, with invasion of adjacent organs or major blood vessels and with a malnourished state[4]. This involves multivisceral resection or pancreatic resection along with the involved vessels, with or without vascular reconstruction, which increases postoperative complications (grade III or higher Clavien-Dindo scale). It is resource consuming for the patients, needs advanced logistics from the medical staff and represents a provocative and technical challenge for surgeons. Often, these patients receive only palliative treatments, such as bilio-digestive double bypass for nonresectable pancreatic cancer or endoscopic stenting.

In 1930's Whipple popularized the standard pancreatic resection for cancer of the head, uncinate process, periampullary or distal bile duct tumors. Modifications were lately adopted, such as duodenum preserving pancreatic head resection (DPPHR) or pylorus preserving pancreatoduodenectomy (PPPD). Central pancretectectomy, reserved for selective management of pancreatic neck cancer, is sparingly being used[5]. Distal pancreatectomy with or without splenectomy is used for resecting lesions located in the tail or body of the pancreas. Priestley reported the first successful total pancreatectomy in 1944[6] (Table 1).

1884 : Billroth reported first distal pancreatectomy[1]
1909: Kausch 2-stage procedure for pancreatoduodenectomy, first cholecystectomy, followed 6 weeks later by resection of the head of pancreas, pylorus, first and second half of duodenum, with gastroenterostomy, closure of common bile duct and anastomosis of pancreas and the third part of duodenum[1]
1935: Whipple 2-stage procedure for pancreatoduodenectomy, first posterior gastroenterostomy, ligation and division of the common bile duct with cholecystogastrostomy, followed by resection of the duodenum and pancreatic head, with closure of pancreatic stump[1, 14, 15].
1940: Whipple completed the procedure in a single stage, in 1942. modification of the procedure with pancreaticojejunostomy[15]
1944 : Priestley reported the first total pancreatectomy[6]
1957 : Guillemin and Bessot reported first central pancreatectomy[5, 6, 7]
1946: Waugh and Clagett first used pancreaticogastrostomy after pancreatoduodenectomy[19]
1978: Taverso and Longmire reported pylorus preserving pancreaticoduodenectomy[12]
1994 : Gagner and Pomp – first laparoscopic pancreatoduodenectomy [9, 15]
1996 : Gagner reported first 5 cases of laparoscopic spleen preserving pancreatectomy [15]
2003 : Giulianotti reported first robotic pancreatoduodenectomy [1, 15, 34, 38]

Table 1 History and evolution of pancreatic surgery for cancer

During the late 1960s, studies reported high postoperative morbidity rates of more than 60 % and a mortality rate between 20-25 %, substantial progress being made since, with gradual reduction of mortality and complications. Recent studies from specialized surgical centers show mortality rates following pancreatic surgery for cancer less than 5 % [7, 8, 9, 10]. Morbidity rates , in spite of the progress made, remain high, reported between 30 and 60 % [11, 12]. Early recognition and treatment of the postoperative complications, sustained by efficient perioperative management, leads to less morbidity and improved outcome for procedures with such high risks. Malnutrition has been documented to be an independent risk factor in surgical procedures outcome for nearly 80 years, thus identifying patients at risk prior to surgery by screening for nutritional risk may be critical to improving outcomes. The most frequent and high morbidity-related complications after pancreatic resection for cancer are delayed gastric emptying, postoperative intra-abdominal abcess, hemorrhage and the most important, pancreatic fistula. Focused strategies based on preventing, early recognition and treatment, consequently lead to low morbidity, lengths of stay and costs , with no delay in adjuvant therapy[1].

Evidence based pancreatic resection for cancer shows that curative resection is the single most important factor determining the outcome in patients with pancreatic adenocarcinoma[13]. Therefore, despite its risks, surgery offers the only chance for cure and continues to be a viable undertaking in patients with cancer [14, 15].

Pancreatic fistula is an abnormal communication between the pancreas and other organs due to internal or external leakage of pancreatic secretions from damaged pancreatic ducts. Postoperative pancreatic fistula (POPF), still regarded as a major complication, according to International Study Group for Pancreatic Fistula (ISGPF) represents a failure of healing/sealing of a pancreatic-enteric anastomosis or a parenchymal leak not directly related to an anastomosis. An all-inclusive definition is a drain output of any measurable volume of fluid on or after postoperative day 3 with an amylase content greater than 3 times the serum amylase activity[16]. Three different grades of POPF (grades A, B, C) are defined according to the clinical impact on the patient's hospital course (Table 2).

The Achilles heel in pancreatic surgery is represented by the pancreaticoenetric anastomosis , with higher rates of grade B and C fistula after central and distal pancreatectomy[18]. Reported rates of pancreatic fistula varies widely, perhaps due to different definitions, surgical technique and no report of postoperative pancreatic leakage. Risks for developing the fistula can be divided into a few groups: patient, pancreas or procedure related[19, 20, 21] (Table 3) .

Criteria for Grading Pancreatic Fistula (ISGPF Classification Scheme)				
Criteria	**No Fistula**	**Grade A Fistula**	**Grade B Fistula**	**Grade C Fistula**
Drain amylase	< 3 x normal serum amylase	>3 x normal serum amylase	>3 x normal serum amylase	>3 x normal serum amylase
Clinical conditions	Well	Well	Often well	Ill appearing/bad
Specific treatment	No	No	Yes/no	Yes
US/CT (if obtained)	Negative	Negative	Negative/positive	Positive
Persistent drainage (>3 wk)	No	No	Usually yes	Yes
Signs of infection	No	No	Yes	Yes
Readmission	No	No	Yes/no	Yes/no
Sepsis	No	No	No	Yes
Reoperation	No	No	No	Yes
Death related to fistula	No	No	No	Yes

Table 2 Classification of pancreatic fistula according to ISGPF [16] .

Pancreas related
Soft pancreatic parenchyma
Small size pancreatic duct (<3 mm)
Ampullary, duodenal, cystic and bile duct neoplasms
Patient related
Male sex
Age >70 years
Cerebrovascular disease
Duration of jaundice
Procedure related
Type of pancreatic anastomosis
Use of somatostatin
Surgeon's experience
Intraoperative blood loss

Table 3 Risk factors for pancreatic leak

An essential point in the management of POPF is prevention, early recognition and treatment of clinically relevant POPF, which separates asymptomatic patients from those who require therapeutic intevertion or are at risk of death[22,14,17]. A multi-center international study conducted by Callery et al[23] confirmed that a simple 10-point Fistula Risk Score (based on small pancreatic duct, soft texture pancreas, high-risk pathology and high operative blood loss volume) is a valid tool for predicting development of grade B and C POPF after pancreatoduodenectomy for cancer. This prediction strategy is easy and convenient and amenable to being broadly deployed, offering surgeons an important tool to anticipate, diagnose, and manage this severe complication in a timely manner[24]. A great deal of research has been conducted over the years aimed at decreasing the risk of pancreatic fistula occurrence, with some commonly solutions adopted for pancreatic leak, namely use of somatostatine and analogues, pancreaticogastrostomy, binding or invaginating pancreaticojejunostomy, pancreatic duct stentig or occlusion, total pancreatectomy (Table 4). In the approach to pancreatic leaks, prevention is certainly better than cure. The use of surgical drains has been considered mandatory after pancreatic surgery, remaining a crucial step[25,17]. Usually, most leaks run a benign course, requiring just maintenance of intraoperatively placed drains to fistula closure. However, if it leads to septic complications such as retroperitoneal abcess, may finally result in late postoperative massive hemorrhage, which requires immediate diagnostic workup and therapy[26]. In such particular cases it is the major cause of postoperative mortality.

Use of Somatostatin & analogues
Pancreaticogastrostomy
Binding or invaginating pancreaticojejunostomy
Pancreatic duct stenting
Pancreatic duct occlusion
Total pancreatectomy

Table 4 Solutions for pancreatic leak

Essential to a succesfull management of pancreatic leakage is early recognition, with treatment guided and dictated by

patient's condition[1]. Surgical interventions for complications after pancreatoduodenectomy are nowadays rare[7], with general consensus for successful conservative management for the majority of cases (over 70 %) with low-output fistula in the absence of peritonitis, sepsis, hemorrhage or organ failure[8,27]. This consists in surveillance and effective control of the pancreatic leak by intraoperative or percutaneous placed drainages, large spectrum intravenous antibiotics, fluid management, intensive parenteral and enteral nutrition and close monitoring by well-trained multidisciplinary team[28,29]. Repeated abdominal ultrasound and computed tomography is mandatory in order to exclude intra-abdominal collections or abcess. Studies show conflicting results regarding value of somatostatine and analogues such as octreotide in the treatment of established pancreatic fistula [30,31,32,33]. When major complications such as massive hemorrhage, abdominal abcess with signs of spreading peritonitis, total wound dehiscence or uncontrollable fistula occurs, with clinical deterioration of the patient, early intervention is indicated[28, 19, 35]. Delayed hemorrhage can be managed, if a patient is stable, by angiographic embolization of the bleeding vessel. The type of surgical procedure depends on the underlying cause, and includes procedures such as peripancreatic drainage, control of hemorrhage, disruption of the pancreatic anastomosis without a new anastomosis or a conversion in another type of pancreatic anastomosis and a completion total pancreatectomy said to be able to salvage up to 50% of patients[19, 29, 34, 35].

Postoperative **delayed gastric emptying** (DGE) is one of the most common complications after PD and is a potentially serious event that may lead to patient discomfort, prolonged hospitalization and increased hospital costs. With the decline in the incidence of pancreatic leaks, DGE has emerged as the leading procedure-related morbidity. The reported incidence ranged from 8% to 45% [7, 8, 36]. DGE is a complex phenomenon with a multifactorial genesis and is believed to be associated with other major intra-abdominal complications, including pancreatic fistula and infected collections[7, 50, 1].

There are eight studies (evidence level I and II) comparing PD and PPPD. While three studies showed no difference, three favored PPPD, and two showed lower DGE rates after PD compared to PPPD[38,39,40,41,43]. Furthermore, several technical aspects, such as the type of resection (Whipple PD vs. pylorus-preserving PD [PPPD]), the method of reconstruction of gastric drainage (antecolic vs. retrocolic) and mechanical dilatation of the pylorus (in cases of its preservation) have been shown to influence DGE[44,50].

A wide range of mechanisms has been proposed to cause DGE, including the absence of hormonal stimulation caused by the resection of the duodenum, and the denervation/ischaemia of the antropyloric region resulting from the interruption of vagal branches and the ligation of gastric pedicles[37]. In 2007, the International Study Group of Pancreatic Surgery (ISGPS) proposed a consensus definition based on severity and clinical impact, which has been recently validated in a small number of reports (Table5)[37].

Presence of postoperative complications other than DGE and extended radical surgery significantly increased the rates of DGE[45, 46]. Horstmann *et al.* showed that patients without any complications had a DGE rate of 1%>. But this climbed to 28% and 43% in the presence of moderate and severe postoperative complications[39]. Cameron *et al.* demonstrated that extended lymphadenectomy not only did not translate into longer survival, it significantly increased the rate of complications including DGE (16% versus 6%)[45]. A mechanical etiology for DGE has also been proposed, and this relates to the method of reconstruction of the gastrointestinal continuity, which may cause transient torsion or angulation of the duodenojejunostomy (in case of PPPD). Postoperative gastroparesis may lead to temporary gastric distension, which can then potentially lead to angulation of the anastomosis because it lies relatively fixed through its retrocolic position. Additionally, the close proximity of the duodenojejunostomy to the pancreatico-jejunostomy also predisposes the incidence of DGE in the event of a small pancreaticojejunostomy leak or a transient postoperative remnant pancreatitis[47]. Adopting an antecolic technique, the incidence of DGE can drop from 28% to 12% [48,50].

By placing the duodenojejunstomy in the infracolic compartment through a mesenteric window, and away from the pancreatic and biliary anastomosis, which lie in the supracolic compartment, the risk of DGE caused by local inflammation is reduced.

Whilst DGE mostly resolves spontaneously, it is still a major source of discomfort to the patients because of the prolonged gastric decompression, not to mention prolonged hospital stay and higher healthcare costs.

Yeo et al. [49] have shown that DGE could be reduced by up to 37% following PD with intravenous erythromycin, a motilin agonist.

But if such measures still fail, the immediate task is to exclude concomitant intra-abdominal complications, since DGE may herald an otherwise undetected pancreaticoenteric or bilioenteric anastomotic leak. Treatment consists of nasogastric decompression, attention to nutritional support, reassurance and watchful waiting. Using ISGPS definitions, the diagnosis of DGE can be established earlier in the postoperative course, thus enabling the selective care of DGE patients and the implementation of fast-track pathways for subjects who do not develop this complication[50].

DGE grade	Nasogastric tube required	Unable to tolerate solid oral intake by POD	Vomiting/gastric distension	Use of prokinetics
A	4–7 days or reinsertion > POD 3	7	±	±
B	8–14 days or reinsertion > POD 7	14	+	+
C	>14 days or reinsertion > POD 14	21	+	+
DGE - delayed gastric emptying; POD - postoperative day				

Table 5 International Study Group of Pancreatic Surgery definition of delayed gastric emptying after pancreatic surgery

Hemorrhagic complications of PD occur in 3-13 % of patients[8,51]. The incidence of bleeding complications appears to be related to the type of resection. The duodenum-preserving procedures (Beger and Frey) tend to be associated with a slightly increased rate of gastrointestinal hemorrhage, ranging from 5% to 10%[52]. Postoperative hemmorhage can be classified as early, occuring during the first 24 hours postoperatively or late, 1-3 weeks after surgery[53, 8]. The source of early, as well as late hemmorhage can be either intraluminal (gastrointestinal hemmorhage) or from the large surface of retroperitoneal dissection (intraoperative field hemmorhage)[54]. Early hemmorhage can be the result of intraoperative techinal mishap such as inadequate hemostatis, a slipped vascular ligature, anastomotic bleeding or diffuse retroperitoneal hemmorhage, usually as a result of an missdiagnosed or aquired coagulopathy (in cases of jaundiced patients or patients receiving massive blood transfusion on the operating table), large raw surface of the operative field after extensive lymphadenectomy[1]. In most of these cases, the complication is swiftly diagnosed and prompt management is established (interventional endoscopy, embolization or relaparotomy), due to the patient being under close postoperative monitoring. Stress ulcer can be prevented by prophylactic use of acid secretion inhibitory agents. In any case, it usually can be managed medically and/or endoscopically[54]. Coagulation disturbances are frequently seen in jaundiced patients. This hypothesis is supported by a multiple-variant regression analysis which identified jaundice (bilirubin level >5.8 mg/dl) as a significant risk factor for postoperative hemorrhage[55]. Late hemmorhage is a more dreaded complication, with a much more difficult and often late diagnosis. This type of bleeding is closely linked to pancreatic leakage which causes the erosion of ligated or retroperitoneal vessels. Other causes include pseudoaneurysms and bleeding from the pancreaticojejunostomy. Pancreaticojejunal dehiscence should always be ruled out before turning to other causes. Management includes conservative approach or laparotomy with the formation of a new anastomosis or in reserved cases the completion of pancreatectomy[1]. Close monitoring of the patient is crucial in detecting the early signs of a late hemmorhage such as a "sentinel bleeding" even in patients diagnosed with a pancreatic leakage which were initially treated conservatively. Mortality rates in late hemmorhage range between 15% and 58 % [56].

Hemmorhagic complications of PD can be prevented and more easily managed, if they arise, by correct preoperative preparation and assesment of the patient, meticulous hemostatis and accurate technique during surgery and close monitoring of the patient in the postoperative period for up to 2-3 weeks. Management of this type of complication includes endoscopic haemostasis, interventional embolization and more often relaparotomy[57, 1].

Intraabdominal abscess

The incidence of intra-abdominal abscess after pancreaticoduodenectomy ranges from 1%-12% [27] and are usually ascociated with anastomotic leakage (at the site of the pancreaticojejunostomy, hepaticojejunostomy, gastro-jejunostomy or duodenojejunonstomy)[51] and less frequently with the length of time which abdominal drainages are kept in situ. The most common sites of intraabdominal absccess following PD are subhepatic and left subdiafragmatic[51]. These collections may be suspected in a patient with abdominal pain, fever, general malaise and change in the aspect of abdominal drainage. Whenever a complication like this is suspected a contrast-enhanced CT should be performed[58].

Management of intra-abdominal abscess can be achieved conservatively with antimicrobial therapy and maintaining the abdominal drain in place. If the collection persists it usually requires drainage. This can be achieved by percutaneous radiologically-guided technique. The persistance of any abdominal collection correlated with the patient state could hint at an underlying cause such as leakage or fistula, which, being effectively controlled, conservative measures are usually adequate. If the

subsequent cause cannot be managed, surgical exploration and drainage becomes necessary[28]. Prophylactic drainage can evacuate anastomotic leakage fluid and abdominal collections. Drainage fluid can serve as a warning sign of anastomotic leakage, intra-abdominal hemorrhage, and abdominal infection. Therefore, it can facilitate the early detection and timely management of postoperative complications[59]. However, abdominal drainages can potentially be utilized by various pathogens and increase the risk of infection, which will subsequently lead to the formation of an abdominal abscess[60]. This controversial aspect of drainage tubes has led to a series of studies which tried to ascertain the necessity of prophylactic drainage after PD. Callery et al proposed a clinical risk score predicting pancreatic fistula after PD based on intraoperative bleeding, diameter of the pancreatic duct, texture of the pancreas, and pathologic diagnosis[23]. Early conclussions suggest that it is safe to abandon the practice of prophylactic drainage for patients with low risk of developing postoperative pancreatic fistulas. It is predicted that in the future patients will be evaluated using risk scores for developing postoperative complications and an adopt an appropriate drainage strategy for each patient.

CONCLUSIONS

Pancreatic resections can be performed with considerable safety and a low rate of pancreatic complications. The dramatic decline in mortality after PD represents the most impressive advance of pancreatic surgery during the past two decades. Many factors have contributed to this phenomenon, including better understanding of pancreatic diseases, careful preoperative assessment, advances in diagnostics, better patient selection, improvements in perioperative care and, perhaps one of the most critical contributing factors, the concept of centralization[61,62]. High-volume hospitals have a broader range of specialist and technology-based services, better-staffed intensive care units, and other resources that are not available at smaller centers. In addition, such referral centers tend to have a higher level of experience in the various departments involved in the detection and management of postoperative complications, such as gastroenterology and radiology[61,63]. Adjunctive therapeutics like the use of octreotide and preoperative biliary drainage have yet to be unequivocally proven to be beneficial. Increasingly, the duct-to-mucosa pancreaticojejunostomy is recognized to be a safe anastomotic technique[64]. Consequently DGE has now emerged to be the most common postoperative morbidity. While distal pancreatectomy has low mortality rates, the incidence of complications and, in particular, pancreatic leaks are still substantial[66]. Further studies and research will, no doubt, be focused on strategies to lower the morbidity rates of pancreatic surgery.

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