A Review of Methods for Preventing Pancreatic Fistula after Distal Pancreatectomy

INTRODUCTION

Pancreatic fistula is a complication that may occur after injuries, inflammation, surgeries or endoscopic procedures of the pancreas. The mechanism of fistula formation is associated with damage to the main pancreatic duct and small pancreatic ducts or anastomotic leakage. Effective methods to prevent pancreatic fistula are still sought. The incidence of fistula is particularly high (60%) after distal pancreatectomy, with mortality rates < 2%.1 Indications for this procedure include benign and malignant tumours of the pancreatic body and tail. Due to the fact that distal pancreatectomy has become an increasingly common procedure, it seems necessary to develop methods to effectively reduce the risk of postoperative pancreatic juice leakage. Pancreatic fistula involves the risk of secondary complications, such as fluid collection, intra-abdominal abscess, sepsis, septic haemorrhage and, consequently, death. We present a review of different techniques reported in the literature to prevent post-distal pancreatectomy pancreatic fistula, considering the risk factors for this complication. The first documented distal pancreatectomy was performed 100 years ago by Mayo.2 Indications for this procedure have changed since that time. In the 1960s and 1970s, distal pancreatectomy was the gold standard for chronic pancreatitis. Currently, it is performed mainly in patients with primary adenocarcinoma, neuroendocrine tumours, metastases (mainly the clear cell renal cell carcinoma, melanoma, breast cancer, lung cancer, gastric cancer, colorectal cancer, gallbladder cancer), cystic tumours, intraductal papillary mucinous neoplasm (IPMN), pseudocysts or traumatic lesions and, less commonly, in chronic pancreatitis. Distal pancreatectomy may involve splenectomy or may be spleen-sparing. Malignancy is an indication for splenectomy.3 The development of minimally invasive techniques has allowed for laparoscopic pancreatic surgeries, including distal pancreatectomy.

DEFINITION OF PANCREATIC FISTULA

In 2005, the International Study Group of Pancreatic Surgery (ISGPS) proposed a new definition of pancreatic fistula defined as a threefold increase in the level of amylase in the drainage fluid compared to its normal serum levels on day 3 post surgery.4 The definition was widely accepted, which allowed for inter-centre comparison of results. Three grades of pancreatic fistula were distinguished: A, B and C. Grade A pancreatic fistula, also called a “biochemical leak”, does not involve a higher risk of secondary complications, transfusions of blood products or transfers to Intensive Care Unit. Patients with grade B fistula present with clinical symptoms, such as abdominal pain, fever, increased inflammatory parameters. The drainage fluid contains pancreatic leakage, and peripancreatic fluid collections may be revealed by imaging. Therefore, antibiotic therapy, enteral or parenteral nutrition and somatostatin analogue administration may be necessary. Grade C pancreatic fistula is associated with severe general condition of the patient, sepsis and multiorgan failure. Such patients require aggressive treatment in Intensive Care Units and surgical intervention.5 In 2017 the updated definition and grading of pancreatic fistula was published in Surgery. There is no clinical importance of grade A pancreatic fistula, for this reason is no longer referred to a true pancreatic fistula. Only Grade B and C pancreatic fistula should be taken into consideration during diagnosing and treatment pancreatic fistula.6

RISK FACTORS FOR Pancreatic FISTULA

The risk factors for pancreatic fistula may be patient- or surgery-related. The first group includes male gender, high BMI, age, the so-called soft pancreas, low albumin levels, high ASA (American Society of Anesthesiologists) score, smoking tobacco, pathology of
the hepatopancreatic ampulla, cystic and neuroendocrine tumours. It is believed by most investigators that the younger the patient, the higher the risk of pancreatic fistula. However, Kleeff et al. believe that patients below the age of 50 years are at a lower risk of this complication. The second group of risk factors includes excessive blood loss during surgery, prolonged surgery time, non-underpinning of the pancreatic duct, extensive lymphadenectomy, extensive resections, large pancreatic stump. Goh et al. included 232 patients after distal pancreatectomy (some patients also underwent splenectomy) in their analysis. Their findings indicate that splenectomy involves a higher risk of clinically significant pancreatic fistula (grade B and C). Kleeff et al. also showed in their study including 302 patients that splenectomy was associated with a higher rate of fistula compared to spleen-sparing procedures (11.2% vs. 5.1%, p=0.0480). Opposite results were obtained by Ridolfini et al.

**Techniques for pancreatic transection:**

Transsection of the pancreas with a scalpel leaves a smooth surface and facilitates the identification of the pancreatic duct, which should always be closed (pancreatic underpinning and suturing, tissue adhesives, coverage with intestinal loop). Suzuki et al. compared pancreas transection using scalpel and ultrasonic knife in their randomised study. During transection using the ultrasonic knife, the main pancreatic duct was identified and managed separately. However, the remaining pancreatic parenchyma was left intact. After transection with a scalpel, the pancreatic duct was underpinned and the remaining pancreatic parenchyma was sewn using a mattress suture. Pancreatic fistula was observed in 4% of patients after ultrasonic knife procedure and in 26% of patients after conventional transection technique (p=0.02). In addition to the ultrasonic knife, other surgical tools, such as radiofrequency ablation device, bipolar tweezers, LigaSure or coagulation, are also used.

**THE MANAGEMENT OF PANCREATIC STUMP**

Although a number of techniques for stump management after distal pancreatectomy may be found in the literature, new approaches are still sought. Stump management techniques include underpinning of the pancreatic duct and hand sewing of the stump; transecting and closing the pancreas with a linear stapler; pancreaticoenteral anastomosis; coverage of the stump with a fragment of the greater omentum or a serous-muscular flap (e.g. gastric); the use of biological adhesive, wrapping the stump with a mesh; coverage of the pancreatic stump with falciform or round ligament flap. Stenting of the pancreatic duct before or during surgery is also performed.

Current studies, including randomised trials, do not clearly determine which of the above mentioned techniques is superior; therefore the question which of these methods should be chosen is still open.

**Hand-sewn and stapled management of the pancreatic stump**

After underpinning of the pancreatic duct, the pancreatic stump may be sutured in two ways: using single sutures or U-sutures in a ‘fish-mouth’ fashion. The underpinning itself has significant effects on the reduced risk of fistula, as confirmed by Bilimoria et al. Additionally, the method is simple and inexpensive; however, it is ineffective in the case of a “soft pancreas” as well as in laparoscopic procedures. Pancreatic division with a stapling device is used in minimally invasive procedures. The lack of immediate management of the pancreatic duct and high costs are disadvantages of this method. Using a stapler for the transection of the so-called “thick pancreas” is also questionable. According to Kawai et al., pancreatic thickness of more than 12 mm increases the risk of fistula after distal pancreatectomy using stapler. A multicentre DISPACT trial (2011), which showed no statistically significant superiority of stapler, is the most important randomised study including 450 patients and comparing stapler versus hand-sewn closure after distal pancreatectomy. Also, no differences were shown in the incidence of complications such as wound dehiscence or infection, intra-abdominal fluid collections, and diabetes. The duration of surgery and hospital stay as well as postoperative mortality were comparable in both treatment arms. Zhang et al. performed a meta-analysis including, among others, 31 studies comparing stapler versus hand-sewn closure of the pancreatic stump, and obtained statistically significant results indicating superior of the stapler method. Similar, though statistically non-significant, findings were obtained by Zhou et al. in their meta-analysis of 16 studies as well as by Kaebel et al., who included 2 randomised trials and 8 observational studies in their analysis. However, the latter study was published before the initial approval of the current definition of pancreatic fistula by the ISGPF. This was also the case of a randomised single-centre trial conducted by Bassi et al., who demonstrated the superiority of stapler over hand-sewn closure. According to Kleeff et al., however, the use of stapler may cause focal pancreatic necrosis in the surroundings of tissue stapling site and, consequently, an impaired outflow of the pancreatic juice through the Wirsung’s duct. The author believes that this is the direct cause of an increased number of postoperative complications following stapler closure. These findings correspond to a prospective study conducted by Reeh et al., whose results were, however, statistically non-significant. The above cited findings do not provide grounds for recommending staple closure of the pancreatic stump.

**Staple reinforcement**

A 2013 meta-analysis compared standard metal staples vs. reinforced staples. The analysis included 5 retrospective and 5 prospective observational studies. A total of 483 stapler distal pancreatectomies, including 249 procedures using metal staples and 234 procedures using reinforced staples, were performed. The incidence of pancreatic fistula was 24% and 17%, respectively. Despite the lack of statistical significance, the study has provided important information regarding the benefits of the above mentioned method. Jimenez et al. achieved a significantly lower rate of fistula using reinforced staples vs. metal staples (8% vs. 39%), which also resulted in a shorter hospital stay. This data also conforms the benefits of reinforced staples. A study using two-row absorbable lactomer staples for distal pancreatectomy is also worth noting. Their use was associated with pancreatic fistula occurrence in only 0.6% of patients (general complication rate was 3.3%). No deaths were reported. In addition to modified staples, biodegradable meshes are also used to cover staple lines. The aim of this method is to prevent pancreatic tearing and accelerate wound healing by bringing the tissues together. Easy placement of the mesh in open and laparoscopic surgeries is also a significant advantage. A single-centre randomised study conducted by the Washington University in St. Louis compared pancreatic closure using staples and staples reinforced with a biodegradable mesh. The study included 100 patients subjected to laparoscopic and open distal pancreatectomy. Clinically significant fistula (grade B and C) occurred in only 2% of treated patients when the staple was reinforced with the mesh and in up to 20% of patients receiving staples.
alone (p=.0007). Additionally, safety and ease of laparoscopic mesh placement were demonstrated.26 This study confirms previous reports by Thaker et al. (2007).27

Pancreateoenteral anastomosis

The technique of covering the pancreatic stump with an intestinal loop was introduced in 1950’s by Duval for the surgical treatment of chronic pancreatitis.24 The Roux-en-Y anastomosis is performed in an end-to-end or an end-to-side fashion, depending on the surgeon’s preference. In 2007, Wagner et al. assessed whether stump drainage by intestinal loop coverage may reduce the risk of pancreatic fistula. Although the group included only 23 patients and the control group included 20 patients (hand-sewn closure of the pancreatic stump alone), the obtained findings indicate that pancreateoenteral anastomosis prevents fistula (0% vs. 20% p< 0.05). All patients included in the study were postoperatively administered octreotide for 5-7 days, which could have had some effects on the final outcome. No difference was found in the incidence of non-surgical complications or the time of hospital stay between the two groups.29 Very optimistic results were obtained by Klein et al. who compared pancreateoenteral anastomosis and hand-sewn or staple closure of the pancreatic stump. Pancreatic fistula was observed in 11% of patients after the use of the first technique and in up to 22% of patients treated with the latter method. However, these results were statistically non-significant.30 Maniconi et al. compared pancreateoenteral anastomosis and a hand-sewn closure; pancreatic fistula was observed in none of the patients with pancreateoenteral anastomosis, whereas it was reported in 29.1% of patients with hand-sewn closure of the pancreatic stump (p= 0.005).31 Kawi et al. did not confirm such high efficacy of pancreateoenteral anastomosis in their randomised trial; their findings indicate that this technique is non-superior to staple closure (38.7% vs. 37.7% p=0.332). However, it seems that pancreateoenteral anastomosis may prove beneficial in patients with thick pancreas (>12 mm) as the intestinal loop drains the pancreatic juice from the lateral branches more effectively.32

Tissue adhesives

Prevention of pancreatic fistula also involves the use of tissue adhesives. Their use in pancreatic surgery was first investigated and described by Kram et al. Tissue adhesive was applied on traumatic pancreatic lesions, in the region after hand-sewn and stapled closure as well as onto the pancreatic anastomosis. None of the patients was affected by pancreatic fistula, abscess or pseudocyst.33 A Japanese study conducted by Suzuki et al. assessed the efficacy of tissue adhesive in the prevention of pancreatic fistula only after distal pancreatectomy. Tissue adhesive was applied in 26 patients after the underpinning of the pancreatic duct, whereas the other 30 patients were included in the control group. Pancreatic fistula occurred in 15.4% of patients receiving tissue adhesive and 40% of controls (p=.04).34 Ohwada et al. described an interesting correlation between a reduced rate of pancreatic fistula and the treatment of pancreatic stump with tissue adhesive prior to suturing (9% vs. 27 p= 0.01).35 However, most published studies using tissue adhesives were conducted in patients subjected to pancreateoduodenectomy with an evaluation of pancreatic anastomosis healing; some of these refer to different pancreatic surgeries, but with no reference to particular procedures. In 2016, Cheng et al. compared the incidence of pancreatic fistula after different pancreatic procedures in their meta-analysis. A total of 9 randomised studies were included in the study. No significant differences in the incidence of pancreatic fistula were observed between the tissue adhesive group and controls (29.6% vs. 31 %), however, most of the studies did not analyse the incidence of clinically significant pancreatic fistula (grade B and C). There were no differences between the two groups in relation to the rate of postoperative complications, resurgeries, the length of hospital stay or the incidence of pancreatic fistula.36

Serous-muscular flap (intestinal loop/stomach flap)

A single-centre randomised trial published in 2009 by Olah et al. demonstrated that a serous-muscular intestinal flap reduces the rate of pancreatic complications, including the risk of pancreatic fistula following distal pancreatectomy.37 Similar results were obtained in a randomised study by Isserkutz et al. The rate of pancreatic fistula was 8.7% after flap plasty and 33% in controls (p= 0.0458).38 Kuroki et al. used flaps from the posterior gastric wall to cover pancreatic stumps and confirmed their efficacy in the prevention of pancreatic fistula (5% vs. 36.4% p= 0.01). No prolonged surgery time, increased blood loss or differences in the structure of the pancreatic stump were observed.39 Since the studies investigating this surgical technique are sparse, it is difficult to conclusively determine its efficacy.

Coverage of the pancreatic stump with the round/falciform ligament flap

The efficacy of round/falciform ligament or greater omentum flaps has been investigated in recent years. The technique was for the first time described in 2006 by Iannitti et al., with the rate of pancreatic fistula of 5.3% (the follow-up period was only 5 days, and the definition of pancreatic fistula was different than the current one). According to the authors, this type of flap not only allows for the closure of the lateral branches of the main pancreatic duct, but it also provides additional blood supply, which accelerates the healing process.40 Hassenplug et al. emphasised in their study that the use of falciform ligament flap after distal pancreatectomy reduced the rate of clinically significant fistula (grade B and C), which was associated with shorter hospital stay and lower treatment costs.41 Wu et al. found that although round ligament flap does not prevent pancreatic fistula, it accelerates its healing (10.8 +/- vs. 16.4 +/- 3.5 days).42 A very interesting, though incomplete, study was presented by Carter et al., who in addition to hand-sewn or stapled closure of the pancreatic stump, used a fragment of the falciform ligament in combination with fibrin adhesive. It was found at one stage of the study that the incidence of pancreatic fistula, complications and hospitalisation length was similar in both groups; therefore the study was discontinued. Many authors point out that flap perfusion is undoubtedly of key importance for the healing of tissue it covers; therefore it should not come as a surprise that the above authors did not achieve a reduced rate of pancreatic fistula and related complications.43 A prospective, single-centre, randomised trial (DISCOVER) has been published in 2016. The study lasted from October 2010 to July 2014 and included 152 patients subjected to distal pancreatectomy. The patients were classified into two groups: with the pancreatic stump covered with a round ligament flap (n=76) and with no flap (n=76). The epidemiology (age, gender, BMI), surgical parameters (surgery length, blood loss, surgical technique, additional surgical procedures) as well as histopathological diagnosis were comparable in both groups.
This way of planning a study is very important as it allows for the elimination of the impact of the above-mentioned factors on the final outcomes, thus increasing their reliability. General mortality reported during the hospital stay was only 0.6%, which corresponded to one death in 152 patients. A clear difference for the benefit of patients with round ligament flap was observed for resurgery rates (1.3% vs. 13% p= 0.009), hospital readmissions (13.1% vs. 31.5% p= 0.011) and finally the incidence of clinically significant pancreatic fistula (grade B and C) (22.4% vs. 32.9% p= 0.20). Based on the above data, the authors concluded that although pancreatic stump closure using a round ligament flap is not associated with a decrease in the total rate of pancreatic fistula, it has significant effects on the risk of clinically significant pancreatic fistula and related complications.

### Pancreatic duct stenting

As shown by some investigators, endoscopic stenting of the pancreatic duct is an effective method for the treatment of pancreatic fistula. An incision of the ampulla of Vater followed by pancreatic duct stent placement reduces the pressure gradient between the pancreatic duct and the duodenum, which facilitates drainage of the pancreatic contents and accelerates fistula healing. Therefore, attempts are made to perform preoperative pancreatic duct stenting and to assess the effects of this procedure on the incidence of pancreatic fistula following distal pancreatectomy. Although a meta-analysis conducted by Wu et al. covered only four studies, including one randomised trial, it showed that pancreatic duct stenting is associated with a reduced rate of pancreatic fistula. Abe et al. placed a stent in the main pancreatic duct in 10 patients scheduled for distal pancreatectomy, and none of these patients was affected by pancreatic fistula. Gupta et al. demonstrated that transampullary pancreatic duct stent placement is associated with a reduced rate of clinically significant pancreatic fistula (grade B and C). Intraoperative stenting was also attempted, which was described by Fisher and Oida. In both cases, the incidence of pancreatic fistula was lower in patients with stents. However, a Swedish single-centre study did not confirm the efficacy of stenting in the prevention of clinically significant pancreatic fistula. On the contrary, grade B and C fistula was more common (42.3% vs. 22.2% p= 0.122) and the hospital stay longer (13.4 +/- 6.4 vs. 19.4 +/- 14.4 p= 0.071) in patients with stenting.

### Administration of somatostatin analogues

Data on the efficacy of octreotide in the prevention of postoperative fistulas are contradictory. Early reports, including randomised trials, were very promising. They came from four European studies and referred to different pancreatic procedures. A study conducted by Buechler et al. in 246 patients after various pancreatic surgeries demonstrated a significantly lower rate of postoperative complications in patients who were postoperatively administered octreotide (32% vs. 55% p< 0.005), as well as lower incidence of pancreatic fistula (17.6% vs. 38% p< 0.05) vs. controls. The other three studies were similar to the German study, both in terms of sample size as well as study design and findings, which indicated the efficacy of octreotide in the prevention of postoperative complications and pancreatic fistula. The efficacy of octreotide was not confirmed in a randomised trial by Yeo et al. and Lowy et al., however, both of these studies limited the study group to patients after pancreateoduodenectomy. In the study by Yeo et al., the incidence of pancreatic fistula was 11% in the octreotide group vs. 9% in controls, with no statistical significance; while in the latter study, the rate of pancreatic fistula was 12% in the octreotide group vs. 6% in controls (p=0.23). A large sample size (n=211) was an advantage of the study by Yeo et al.; furthermore, the control group received placebo, whereas Lowy et al. included 110 patients (n=110) in their study, and the control group did not receive placebo. A meta-analysis conducted in 2010 by Koti et al., which included 17 randomised trials, showed that the incidence of complications after pancreatic procedures was lower in the octreotide group (RR 0.71, 95% CI 0.62-0.82); however, no differences were observed for the general perioperative mortality (RR 1.04, 95% CI 0.53-0.78), resurgery rate (RR 1.15, 95% CI 0.56-2.36) or the length of hospital stay (MD-1.04 days, 95% CI- 2.54 up to 0.46). Pancreatic fistula was less common in the octreotide group (RR 0.64, 95% CI 0.53-0.78), while the rate of clinically significant pancreatic fistula (grade B and C) was similar in both groups. The meta-analysis did not allow to distinguish patients after distal pancreatectomy alone due to the missing data in the analysed studies. A randomised study by Droeser et al. confirmed the lack of efficacy of octreotide in the prevention of clinically significant postoperative pancreatic fistula (72.7 vs. 35.7%; RR 4.8; CI 1.6-14.2; p 0.005). In recent years, a large number of studies assessing the efficacy of octreotide in the prevention of pancreatic fistula were related to pancreateoduodenectomy. A multicentre study conducted by McMillan et al. demonstrated the lack of beneficial effects of octreotide on the risk of clinically significant fistula (21% vs. 7.0% p< 0.001). It was even suggested that octreotide may promote clinically significant fistula in patients with risk factors. A similar relationship was shown by Rohatgi et al. In addition to octreotide, longer-acting somatostatin analogues are also used. Allen et al. reported that pasireotide significantly reduced the rate of
pancreatic fistula in the group of patients after distal pancreatectomy (7% vs. 23%; relative risk, 0.32; 95% CI, 0.10 to 0.99). However, a study using vaptatoide, which included patients after pancreaticoduodenectomy and distal pancreatectomy, showed no differences in the rate of pancreatic complications between the vaptatoide group and the placebo group.61

**SUMMARY**

Pancreatic fistula involves the risk of secondary complications, including sepsis and intra-abdominal bleeding, prolonged hospital stay, increased treatment costs, decreased life quality and, in the case of patients with malignancies, delayed anticancer therapy.

Although there are many techniques for the prevention of pancreatic fistula, as described above, there is no one fully effective method. This is a serious problem, especially in the case of distal pancreatectomy, as the incidence of fistula after this procedure reaches up to 60%. Distal pancreatectomy has become more common due to improved diagnosis of, among other things, cystic and endocrine tumours of the pancreas. A unified definition and grading of pancreatic fistula, which was introduced by the International Study Group of Pancreatic Surgery (ISGPS) in 2005 and updated in 2017, has allowed for an easier, correct diagnosis as well as for a reliable comparison of data between different pancreatic surgery centres. Coverage of the pancreatic remnant with the round ligament following to reduce the rate of grade B and C pancreatic fistula.

**REFERENCES:**

5. Eguchi H, Nagano H, Tanenura M I wsp.: „A thick pancreas is a risk factor for pancreatic fistula after a distal pancreatectomy: selection of closure technique according to the thickness” Dig Surg. 2011;28:50-6
10. Ridolfini MP, Alferri S, Gourgiotis S I wsp. „Risk factors associated with pancreatic fistula after distal pancreatectomy, which technique of pancreatic stump closure is more beneficial?” World J Gastroenterol.2007;13(38):5096-100
33. Kram HB, Clark SR, Ocampo HP, et al.: „Fibrin glue sealing of pancreatic injuries as well as for a reliable comparison of data between different pancreatic surgery centres.” Pancreatic fistulas following distal pancreatectomy ” Arch Surg 2012;255:1037-42


