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REVIEW

Prevention and treatment of pancreatic fistula after pancreatic body and tail resection: current status and future directions

Li Jiang[1], Deng Ning[1], Xiao-ping Chen (✉)[2]

[1]*Department of Biliary and Pancreatic Surgery, Tongji Hospital, Tongji Medical College, Huazhong University of Science and Technology, Wuhan 430030, China;* [2]*Hepatic Surgery Center, Tongji Hospital, Tongji Medical College, Huazhong University of Science and Technology, Wuhan 430030, China*

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Abstract **Postoperative pancreatic fistula (POPF) is the most common and critical complication after pancreatic body and tail resection. How to effectively reduce the occurrence of pancreatic fistula and conduct timely treatment thereafter is an urgent clinical issue to be solved. Recent research standardized the definition of pancreatic fistula and stressed the correlation between POPF classification and patient prognosis. According to the literature, identification of the risk factors for pancreatic fistula contributed to lowering the rate of the complication. Appropriate management of the pancreatic stump and perioperative treatment are of great significance to reduce the rate of POPF in clinical practice. After the occurrence of POPF, the treatment of choice should be determined according to the classification of the pancreatic fistula. However, despite the progress and promising treatment approaches, POPF remains to be a clinical issue that warrants further studies in the future.**

Keywords pancreatic fistula; pancreatic body and tail resection; distal pancreatectomy

Introduction

Distal pancreatectomy (DP) is a standard surgical procedure for removing pancreatic body and tail lesions. In recent years, the prognosis of benign and malignant diseases of the body and tail of the pancreas has significantly improved by the advancement of surgical methods and proposal of new concepts. Nevertheless, the incidence of postoperative complications (especially pancreatic fistula) remains high, which has been troubling clinical surgeons all along. Therefore, how to prevent the occurrence of postoperative pancreatic fistula (POPF) and standardize the treatment of choice have attracted research interest in recent years.

This review aims to provide an overview of the recent advances in the field of prophylaxis and management of pancreatic fistula after laparoscopic DP and discuss potential future developments.

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Correspondence: Xiao-ping Chen, chenxpchenxp@163.com

Definition of pancreatic fistula

Pancreatic fistula can be diagnosed on the basis of clinical manifestations and the level of amylase in drainage fluid. However, it should be differentiated from other diseases with similar clinical manifestations, such as intestinal fistula, bilioma, abdominal abscess, and intestinal obstruction [1,2]. In light of the confusion over the definition and classification of pancreatic fistula, the International Study Group of Pancreatic Fistula (ISGPF) issued the diagnostic criteria for pancreatic fistula in 2005 [3]; that is, the peritoneal drainage fluid after operation can be measured, in which the amylase concentration exceeds the upper limit of normal serum amylase level by three times or more than 300 IU/L. These criteria have been widely accepted. The ISGPF further updated the definition of pancreatic fistula in 2016 [4], emphasizing the correlation between pancreatic fistula and clinical prognosis in addition to the original definition.

The ISGPF classifies pancreatic fistula into two categories (biochemical pancreatic fistula and clinically relevant pancreatic fistula) and three grades (A, B, C) according to the clinical manifestations, imaging manifestations, drainage duration, necessity of reoperation, pancreatic fistula-related death, infection signs, sepsis, and re-admission. Class A pancreatic fistula is now referred to as biochemical pancreatic fistula because there are no clinical symptoms. Class B and C pancreatic fistulas are defined more strictly than before. Class B pancreatic fistulas require significant clinical interventions such as continuing drainage for more than three weeks or endoscopic and percutaneous drainage [5]. Class C pancreatic fistulas refer to pancreatic fistulas requiring further surgical intervention. Patients with class C pancreatic fistulas have organ failure, which can lead to death.

Risk factors and prediction of pancreatic fistula

Identifying the risk factors of pancreatic fistulas and actively predicting and preventing them in clinical practice are important. Literature reports indicate that patient characteristics, operation approaches, and techniques are correlated to the occurrence of pancreatic fistula (Table 1).

Previous studies that reported the risk factors of pancreatic fistula focused almost exclusively on the operation-related index, such as long operation time (more than 480 min), intraoperative blood loss of more than 1000 mL, and combined splenectomy [6–8]. All of them were listed as the risk factors of pancreatic fistula after operation. With the development of surgical techniques and experience, researchers have gradually excluded the factors of surgical techniques and sought to find possible risk factors from patient characteristics; for example, BMI > 25 is generally considered as an independent risk factor for pancreatic fistula after operation [9–11].

Recent studies tend to focus on pancreatic features per se. An analysis of 41 patients by Arai *et al*. [12] showed that pancreatic thickness (> 15 mm) was an independent risk factor for pancreatic fistula after pancreatectomy. Consistently, a retrospective analysis by Chang *et al*. in 2017 [13] predicted the risk of pancreatic fistula by measuring the thickness and sectional area of pancreas with imaging technology. They concluded that thicker pancreas and larger pancreatic cross-section are risk factors for pancreatic fistulas after operation. The reason may be that a thick pancreas is predisposed to insufficient stapled disclosure during clamping, and large residual pancreatic volume leads to the preservation of most pancreatic exocrine function. In the same year, Fukuda *et al*. [14] determined the thickness of the pancreas, pancreatic index (CT value of pancreas/CT value of spleen), and the ratio of pancreatic thickness to pancreatic index by using digital imaging technology. They verified that pancreatic thickness was an independent risk factor for pancreatic fistulas after DP through multivariate analysis. Most recently, an analysis of 157 patients by Sivesri *et al*. [15] showed that

Table 1 Risk factors of postoperative fistula after distal pancreatectomy

Author (year)	Cases (*n*)	Risk factor		Postoperative pancreatic fistula (%)	Complications (%)	Mortality (%)
		Patient related	Technique related			
Kleeff, 2007 [6]	302	N/A	Closure with a stapler and an operating time$\geqslant$480 min, multivisceral	11.6	35.4	2
Goh, 2008 [7]	232	Overweight, hypoalbuminemia	High ASA score, blood loss greater than 1 L, increased operation time, decreased albumin levels, and sutured closure of the stump without main duct ligation, combined with splenectomy	31	47	3
Seeliger, 2010 [9]	110	BMI>25 kg/m^2	N/A	11	18	N/A
Kawai, 2013 [10]	122	Pancreatic thick ness>12 mm	N/A	36.9	N/A	0
Kowalsky, 2017 [11]	310	N/A	Postoperative narcotic use	21.6	N/A	N/A
Arai, 2015 [12]	41	Pancreatic thickness$\geqslant$15 mm and SI ratio$\geqslant$1.3	N/A	19.5	36.6	0
Chang, 2017 [13]	60	Pancreatic thickness>17.6 mm, cross-sectional area>377 mm^2	N/A	20	N/A	N/A
Fukuda, 2017 [14]	122	TP, PI, TPIR	N/A	19.7	19.7	0

SI ratio, pancreas-to-muscle signal intensity (SI) ratio on MRI; TP, thickness of the pancreas; PI (pancreatic index), calculated by dividing the pancreatic CT by the splenic CT density; TPIR, TP-to-PI ratio.

the pancreatic division level did not affect the rate of POPF after comparing the outcomes of DP by body/tail division (body–tail group) with those by neck division (neck group). Concerning the tissue texture of the pancreas and the diameter of the pancreatic duct, soft tissues and small pancreatic ducts are regarded as culprits for pancreatic fistulas after pancreaticoduodenectomy; however, no significant relationship between them and pancreatic fistula after DP was observed [16]. The results also implied that the mechanism of pancreatic fistula after the two procedures was different.

With the rapid development of imaging technology in recent years, computed tomography and magnetic resonance imaging have become more effective in the diagnosis and classification of various pancreatic diseases, thereby provide more guidance for the surgical methods of choice and help to reduce the occurrence of pancreatic fistulas and other complications [17,18].

Prevention and management of pancreatic fistulas

Since the pancreatic fistula after operation often lead to catastrophic consequences, how to find appropriate ways to reduce the occurrence of POPF has become a hot topic in recent years (Table 2).

Management of pancreatic stump

Closure of the pancreatic stump directly —transition from handsewn to stapled closure

Closing the pancreatic stump properly is the most critical step to prevent the occurrence of pancreatic fistula. Manual suture is a classical approach for the closure of pancreatic stump; however, the incidence of pancreatic fistula remains high from traditional handsewn technique. In recent years, with the rapid development of minimally invasive technology, surgical instruments, biological materials, and other surgical techniques have been constantly improved and optimized.

Management of the main pancreatic duct

Unlike pancreaticoduodenectomy, pancreatic body–tail resection retains the function of the Oddi sphincter, which leads to high intrapancreatic duct pressure. This explains why the incidence of pancreatic fistula after DP is significantly higher than that after pancreaticoduodenectomy [19]. Bilimoria *et al*. [20] retrospectively analyzed 126 cases of pancreatic body and tail resection in 2003. They found that the incidence of pancreatic fistula in the pancreatic duct ligation group was significantly lower than that in the non-ligation group (9.6% vs. 34%). Multivariate analysis also indicated that non-ligation of the pancreatic duct was an independent risk factor for POPF, with some studies supporting this view [7,11]. By contrast, the series from Ferrone *et al*. [21] in 2008 failed to confirm the prophylactic role of transfixion of the pancreatic duct for fistula development. Thus, a definitive conclusion cannot be reached given these inconsistent findings.

Due to the rapid implementation of minimally invasive DP, stapled closure of the pancreas has emerged as the preferred method for parenchymal division, which leads to the difficulty of finding and ligating the pancreatic duct during operation. Nevertheless, while laparoscopic DP is performed in many centers, the operation of open DP in the same period mostly includes finding the main pancreatic duct and ligating it [22–24].

Application of pancreatic stump-covering material

During DP, the hepatic round ligament and falciform ligament can be freed and sutured through the lesser omentum to reinforce the closure of pancreatic stump. The buttressing of pancreatic closures with autoplasty has been reported mostly as anecdotal evidence [24–27]. A randomized controlled trial (RCT) by Carter *et al*. [26] in 2012 randomized 109 patients into two groups: closure of the pancreatic remnant with or without falciform ligament patch and fibrin glue. The trial failed to show any benefit of falciform ligament patch and fibrin glue in terms of pancreatic fistula in DP. To address the inconsistence in the literature, Hassenpflug *et al*. [27] completed a relevant randomized controlled clinical study (the DISCOVER Randomized Controlled Trial) in 2016. In their study, the research group was treated only by hepatic round ligament and falciform ligament covering and fixing the closure of the pancreatic stump, without additional bioglue treatment. The incidence of grades B and C pancreatic fistulas in the study group was 10% lower than that in the control group although no statistical difference was observed. The multivariate regression analysis showed that the use of this autologous material to cover the pancreatic stump was one of the protective factors to prevent the occurrence of clinically relevant pancreatic fistula. Chen *et al*. [28] also believe that this method can help to reduce the occurrence of pancreatic fistula, and further clinical studies may be needed in the future to address this issue in depth and standardize the operation process.

In addition to the hepatic round ligament, other autologous tissues with serous surface have been proposed to cover the pancreatic stump. In Oláh *et al*.'s study [29], 70 patients were randomly divided into two groups: the pancreatic stump was closed by staples alone in one group (35 cases), whereas part of the jejunal loop was freed and covered the stapled pancreatic stump with jejunal serosa

Table 2 Reports on the treatment of pancreatic stump

Author (year)	Study design	Study group (*n*)	Postoperative pancreatic fistula (%)	Mortality (%)
Kleeff, 2007 [6]	Retrospective	Anastomosis (24) vs. seromuscular patch (36) vs. stapler (145) vs. suture (97)	0 vs. 8.3 vs. 15.9 vs. 9.3	0 vs. 0 vs. 2.8 vs. 2.1
Johnston, 2008 [8]	Retrospective	Mesh (70) vs. stapler (44) vs. suture (55)	10 vs. 16 vs. 33	0 vs. 0 vs. 0
Diener, 2011 [39]	Prospective	Stapler (177) vs. suture (36)	36 vs. 37	0 vs. 1
Ban, 2012 [77]	Retrospective	Stapler (177) vs. non-stapler (36)	21 vs. 50.6	0 vs. 0
Kawai, 2013 [10]	Retrospective	Handsewn closure (32) vs. bipolar scissors (45) vs. stapler closure (45)	18.7 vs. 17.7 vs. 11.1	0 vs. 0 vs. 0
Karabicak, 2017 [22]	Retrospective	DP-TF (89) vs. DP-PG (44) vs. DP-ST (36)	11.3 vs. 20.5 vs. 27.8	2.3 vs. 2.4 vs. 0
Cunha, 2015 [23]	Prospective	TachoSil (134) vs. non-TachoSil (136)	30.6 vs. 24.3	0.7 vs. 1.5
Hassenpflug, 2012 [25]	Retrospective	Coverage (73) vs. non-coverage (44)	14 vs. 34*	0 vs. 1
Carter, 2012 [26]	Prospective	FF (50) vs. SS (51)	18 vs. 18	0 vs. 0
Hassenpflug, 2016 [27]	Prospective	Coverage (76) vs. non-coverage (76)	22.4 vs. 32.9	0 vs. 1.3
Oláh, 2009 [29]	Prospective	Stapling + seromuscular patch (35) vs. stapling alone (35)	2.8 vs. 8.6	0 vs. 2.8
Fujii, 2015 [30]	Retrospective	EJ patch (42) vs. non-EJ patch (39)	10 vs. 35	0 vs. 3
Park, 2016 [33]	Prospective	TachoSil[l®]patch (48) vs. control (53)	22.9 vs. 28.3	0 vs. 0
Shubert, 2016 [34]	Prospective	SEAMGUARD (32) vs.TissueLink (35)	12.5 vs. 22.9	0 vs. 0
Kawai, 2017 [51]	Prospective	Reinforced staplers (105)	12.4	0
Montorsi, 2012 [32]	Prospective	TachoSil[l®] patch (145) vs. standard (130)	8 vs. 14	0 vs. 0
Hamilton, 2012 [44]	Prospective	Mesh reinforcement (54) vs. non-staple-line reinforcement (46)	1.9 vs. 20*	1.8 vs. 2.2
Sudo, 2011 [48]	Retrospective	Duct-to-mucosa pancreaticogastrostomy (21)	0	0
Yanagimoto, 2013 [49]	Retrospective	DP-PG (21) vs. DP (26)	5 vs. 12	0 vs. 4
Klein, 2012 [50]	Retrospective	Pancreatoenteral anastomosis (PE) (47) vs. direct closure (DC) (51)	11 vs. 22	2 vs. 4
Kawai, 2015 [51]	Prospective	Pancreaticojejunostomy (62) vs. stapler closure (61)	9.7 vs. 16.4	0 vs. 0
Uemura, 2016 [52]	Prospective	Duct-to-mucosapancreaticogastrostomy (36) vs. handsewn closure with pancreatic duct ligation (37)	19.4 vs. 18.9	2.7 vs. 0

*$P < 0.05$. SS, stapled or sutured closure; FF, stapled or sutured closure plus falciform patch and fibrin glue reinforcement; EJ, elevated jejunum; PG, duct-to-mucosa pancreaticogastrostomy.

suture in the other group (35 cases). The total POPF rate in the jejunal-covering group was low, but it did not affect the clinical process (no difference was observed between the two groups in terms of grades B and C fistulas). In 2015, Fujii *et al*. [30] proposed an improved Blumgart stump closure method: the pancreatic stump was embedded in the seromuscular layer of the jejunum after the elevated jejunum (EJ) was free. The results showed that this method could reduce the incidence of POPF, and multivariate analysis proved that this EJ embedding approach was an independent protective factor for POPF. In addition, Wang *et al*. [31] proposed to cover the pancreatic stump with the greater omentum during DP, which can reduce the incidence of pancreatic fistula and is less expensive, practical, and safe.

At present, the following biomaterials are used for closing the pancreatic stump: fibrin glue with or without material covering, absorbable gasket suture wrapping pancreatic stump, synthetic gasket assisted reinforced staplers. Recent randomized controlled clinical studies have confirmed that the use of absorbable fibrin glue (TachoSil) to cover (without suture) the pancreatic stump cannot reduce the incidence of pancreatic fistula [23,32–35]. Matsumoto *et al*. reported in 2016 [36] that the use of absorbable Vicryl gasket suture to cover the pancreatic stump can help reduce the risk of pancreatic fistula after DP. An RCT exploring the efficacy of polyglycolic acid (PGA) mesh for the prevention of pancreatic fistula following DP was conducted by Jiang *et al*. [37] in the same year. In this study, patients in the PGA group underwent transection of the pancreas. After application of the fibrin glue, the PGA mesh was wrapped around the remnant pancreatic stump. The results of this trial offered high-quality evidence supporting that wrapping of the cut surface of the pancreas with PGA mesh was associated with a significantly reduced rate of clinically relevant POPF [37].

Although the effect of biological materials on the prevention of pancreatic fistula is still controversial, further research on improving suture technology combined with more reasonable and effective new materials for the prevention of pancreatic fistula is still promising.

Stapled closure of pancreatic remnant

Given the wide application of laparoscopic techniques in pancreatic surgery and the continuous advancement of surgical instruments in recent years, laparoscopic and robot-assisted approaches are increasingly being used for DP. However, whether stapled closure can replace traditional manual suture still needs to be elucidated. In addition, the safety and impact of stapled approach on postoperative complications are unknown.

Researchers once found that stapled closure of pancreatic stump resulted in a higher incidence of pancreatic fistula compared to classical manual suture [6,38]. This phenomenon may be related to the imperfect design of early staplers and inexperience of surgeons. Diener *et al.* [39] conducted a double-blind randomized controlled clinical trial of 352 patients in 21 European hospitals (DISPACT) in 2011. In this trial, 352 patients were divided into the stapled closure group (177 cases) and manual suture group (175 cases). The results showed no significant difference in the incidence of pancreatic fistula and mortality between the two groups. In the following years, reports indicated that stapler transaction provided equal rate of pancreatic fistula compared with handsewn approach, or even lower rate of clinically significant fistula. This finding was further supported by a meta-analysis in 2015, which included 191 patients with stapled closure and 190 patients with handsewn closure. The fistula rates were 34% for the stapled group and 41% for the handsewn group, indicating no statistical difference ($P = 0.66$) [40].

Slow parenchymal flattening technique was first described in 2008 by Okano *et al.* [41].In this technique, the closure jaw was clamped carefully and slowly, taking more than 5 min at a fixed speed, with the jaws of the stapler being held shut for 2 min after firing [41]. Nakamura *et al.* reported a similar prolonged peri-firing compression technique in 2011 [42]. Both techniques were formulated to reduce the pancreatic fistula by avoidance of tearing and destruction of the pancreatic capsule and parenchyma during transaction. This finding was further supported by the study of Hirashita *et al.* [43] in 2018. This approach has been widely accepted in recent studies comparing the handsewn and stapled closure of the pancreatic remnant, which yielded no difference between the two approaches in terms of POPF [10,22].

In recent years, most authors advocated the use of synthetic gasket-assisted reinforced stapler to strengthen the closure of pancreatic stump to prevent POPF occurrence. An RCT in 2012 by Hamilton *et al.* [44] found that mesh reinforcement of stapled pancreatic transection decreases the incidence of pancreatic leakage for DP. In the series, the authors used mesh reinforcement of the staple line with either SEAMGUARD® or Peri-Strips Dry®. ISGPF grades B and C fistulas were found in 1.9% (1/53) of patients undergoing resection with mesh reinforcement and 20% (11/45) of patients without mesh reinforcement ($P = 0.0007$). Most recently, however, another RCT by Kondo *et al.* [45] failed to show any advantages of mesh reinforcement in terms of POPF over stapled closure without mesh. In the study, they used PGA (Neoveil) as the mesh, a bioabsorbable recombinant membrane made of a synthetic polymer. No significant difference in the incidence of clinically relevant pancreatic fistula was observed between the reinforced stapler and stapler groups (16.3% vs. 27.1%, $P = 0.15$). Further high-power studies with various kinds of meshes could help to clarify this topic in the future.

The stapler size of choice remained to be an issue during laparoscopic distal pancreatectomy (LDP). Kim *et al.* found that there is no suitable-sized cartridge for a pancreas thicker than 12 mm [46]. Most recently, Dokmak *et al.* [47] reviewed 130 patients who underwent stapler closure during left pancreatectomy. Multivariate analysis suggested that the stapler cartridge size did not influence the development of clinically significant POPF.

Pancreatic–digestive tract anastomosis

The anastomosis of pancreatic stump with the intestine or stomach can avoid hemorrhage and necrosis of abdominal tissue and organs caused by pancreatic fistula from pancreatic stump to the abdominal cavity. Moreover, it can retain the drainage of pancreatic fluid to the digestive tract to maintain pancreatic exocrine function. Pancreatic–digestive tract anastomosis was first used for digestive tract reconstruction after pancreaticoduodenectomy. In 2011, Sudo *et al.* [48] first proposed the anastomosis of the pancreatic stump with the posterior gastric wall during DP. Among the 21 patients who underwent this operation, no grades B and C pancreatic fistulas were observed, and the incidence of grade A pancreatic fistulas was 21%. Yanagimoto *et al.* [49] also reported reduced POPF by pancreaticogastrostomy during DP compared with closure of the pancreatic stump. However, inconsistent results have been reported in literature. Klein *et al.* [50] retrospectively analyzed 198 cases of pancreatic body and tail resection in 2012. They found no significant difference in the incidence of pancreatic fistula between the pancreatic stump–digestive tract anastomosis group and the stump closure group. A randomized controlled clinical study by Kawai *et al.* [51] in 2016 showed that pancreaticojejunostomy did not reduce the incidence of pancreatic fistula after DP compared with the stump closure approach. A multi-center randomized controlled clinical study by Uemura *et al.* [52] in 2017 compared 36 cases of pancreaticogastrostomy with 37 cases of manual suture of pancreatic stump after DP. The results showed that the operation time of pancreaticogastrostomy group was longer, but the incidence of peritoneal effusion was lower. No significant difference in the incidence of pancreatic fistula and other complications were observed between the two groups. To address this inconsistence within the literature, pancreaticojejunostomy was applied in 18 patients in our institute to manage the pancreatic remnant after DP during the past two years. In this series, we introduced a new technique: invaginated end-to-end pancreaticojejunostomy with transpancreatic transverse U-sutures [53]. Of note, only two patients developed grade A-type POPF, and no patients developed grade B/C-type POPF. The result of this pilot study seems promising. Overall, whether the management of pancreatic stump–digestive tract anastomosis can reduce the incidence of pancreatic fistula may depend on the detail technique of the approach.

Other intraoperative management

To reduce the incidence of pancreatic fistula, some researchers have proposed to use special instruments, such as radiofrequency energy instruments or LigaSure, to treat pancreatic stump besides conventional surgical scalpel, electrotome, ultrasound scalpel, and stapler to cut the pancreas. However, these instruments are still limited to animal experiments or sporadic small-sample clinical reports [54–57].

A prospective multi-center study in 2015 [58] revealed that the routine use of intraperitoneal drainage during DP increased the rate of pancreatic fistula formation. Another multi-center randomized controlled study reported by Van Buren *et al*. [59] in 2017 showed that routine placement of abdominal drainage after pancreatectomy had no effect on the frequency of postoperative imaging, percutaneous drain placement, reoperation, readmission, or quality of life scores of patients after DP, but was related to the occurrence of peritoneal effusion. More recently, Seykora *et al*. found that early drain removal after DP is associated with better outcomes compared with late removal and no drain placement for POPF [60].

Perioperative clinical management

Regulation of intrapancreatic pressure during perioperative period

In light of the correlation between pancreatic duct pressure and the occurrence of pancreatic fistula, some researchers proposed to take measures to reduce intrapancreatic pressure to prevent POPF. In a non-randomized prospective cohort study from 2010, Rieder *et al*. [61] found that no pancreatic fistula occurred in 25 patients who underwent preoperative pancreatic duct stent placement, whereas five (22%) of 23 patients who did not receive stent placement developed pancreatic fistula after DP. This finding indicated that preoperative pancreatic duct stenting can effectively prevent POPF. In a later series, Hashimoto *et al*. [62] retrospectively analyzed 223 cases of pancreatic body and tail resection and found that preoperative endoscopic pancreatic duct stenting is a protective factor that could reduce the incidence of pancreatic fistula. By contrast, a randomized controlled clinical study by Frozanpor *et al*. [63] in 2012 analyzed the use of pancreatic duct stents before pancreatic body and tail resection and showed that preventive drainage by pancreatic duct stents did not reduce the incidence of pancreatic fistula after pancreatic surgery. The authors believe that this may be due to the inflammation of pancreatic duct caused by stent placement, which leads to increased pancreatic duct pressure. To avoid the impact of stent-related complications on pancreatic fistula, Hackert *et al*. [64] completed a prospective clinical trial in 2017. They injected a smooth muscle relaxant into the pancreatic duct before operation. Preliminary results confirmed that this procedure could reduce the incidence of POPF after DP.

Other clinical treatments, such as drug use and diet control

Octreotide has been widely used in pancreatic diseases and post-pancreatic operation. Although the overall incidence of pancreatic fistula can be reduced, no evidence suggests that octreotide can effectively prevent the occurrence of clinically relevant pancreatic fistula [65]. In recent years, a new somatostatin analog, pasireotide, has been reported to effectively reduce the incidence of pancreatic fistula after DP [66,67].

Opioid analgesics have long been used in postoperative analgesia, especially after pancreatic surgery. Recent reports recommended to reduce the use of narcotics as opioid analgesics can cause Oddi sphincter contraction, which will increase intrapancreatic pressure and lead to pancreatic fistula after surgery [11,64].

Nowadays, preoperative neoadjuvant therapy (chemotherapy and/or radiotherapy) has been increasingly used in patients with pancreatic cancer. Literature reports [68,69] show that preoperative neoadjuvant therapy can reduce the incidence of pancreatic fistula after operation due to the change of pancreatic tissue texture and the inhibition of pancreatic exocrine function. Antibiotic treatment may benefit the outcome of DP; positive result of drainage culture was identified as a new independent risk factor for POPF, and detection of microorganisms in the fluid collection of POPF resulted in high morbidity and mortality [70,71].

Comprehensive management should be taken for the prevention and treatment of pancreatic fistula after operation. The physical condition of preoperative patients, risk factor assessment, and management after operation have a great impact on the incidence of POPF. At the same time, once pancreatic fistula occurs, timely diagnosis and effective treatment are the key factors affecting patient prognosis.

Comprehensive management of pancreatic fistula of DP

The treatment of choice for POPF is determined by the PF grades [7]. Most pancreatic fistulas belonging to A and B grades could be managed through conservative treatments, such as nutritional support, somatostatin and its analogs, and sufficient drainage [6,28,29]. However, some grades B and C POPF require interventional therapy, such as endoscopic or percutaneous procedures [66,68,69], and a few patients should receive re-operation [70–72].

Non-surgical treatment

Sufficient drainage is the basis of treatment for POPF. In most cases, peritoneal fluid collection caused by pancreatic fistula could be effectively managed through routine abdominal drainage [6,29], percutaneous peritoneal drainage under CT or ultrasound guidance [29,33,47,73], and internal drainage using endoscopic ultrasonography by placing pancreatic duct stents [17,29]. With sufficient drainage combined with nutritional support [73], antibiotic therapy [74], and inhibition of pancreatic secretion, most patients would recover uneventfully from POPF.

Postoperative feeding time and route of nutritional treatment have always been the key issues of postoperative nutritional support for pancreatic surgery. Premature feeding or enteral nutrition may promote the secretion of pancreatic juice, which may hamper the healing of pancreatic fistula. On the other hand, fasting or long-term parenteral nutrition can also lead to dystrophy, healing difficulties, and parenteral nutrition-related complications [75,76]. In 2006, a retrospective study conducted by Pannegeon *et al*. [76] confirmed that POPF could be relieved by conservative treatment including enteral and parenteral nutrition and abdominal drainage. As fasting is sometimes considered necessary to suppress the secretion of pancreatic juice in patients with POPF, a multi-center RCT in 2015 proved that food intake did not aggravate POPF, which indicated that there may be no need to avoid oral dietary intake in patients with POPF [75].

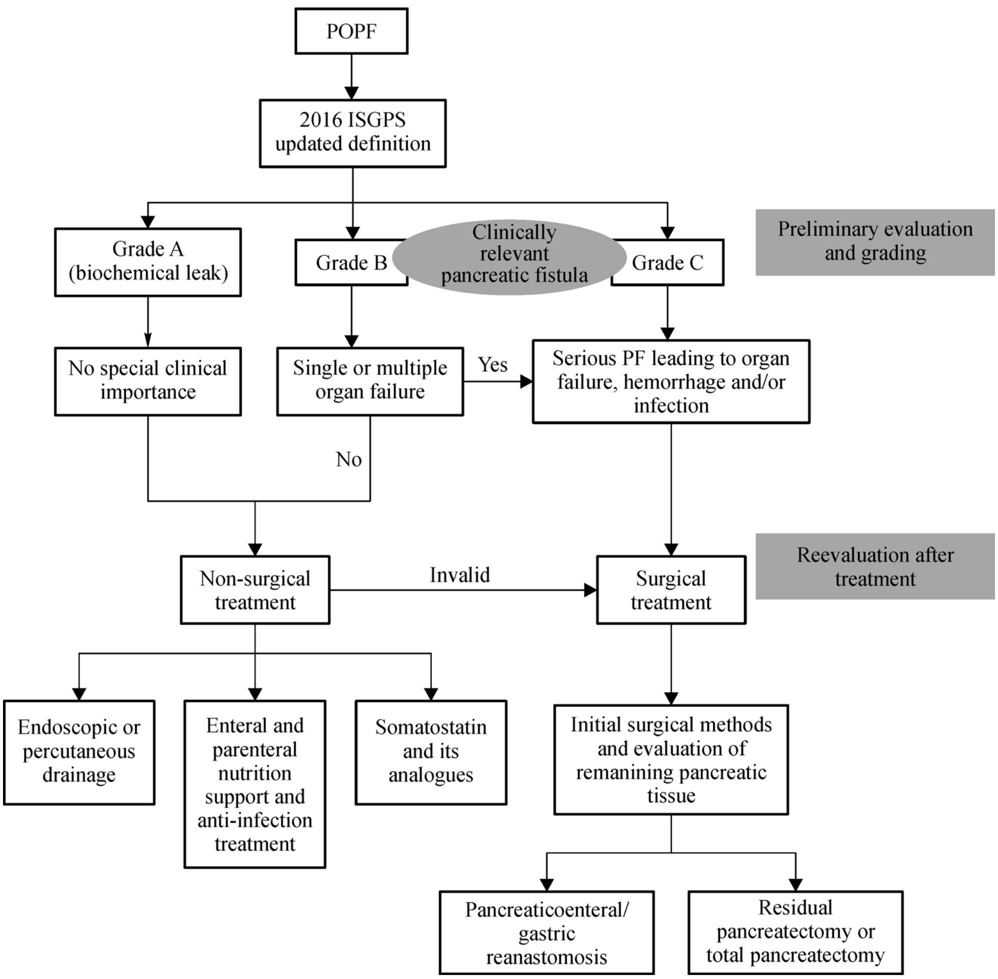

Fig. 1 Flow chart of treatment for pancreatic fistula after distal pancreatectomy.

Surgical treatment

Surgical treatment should be considered for patients with POPF who fail to respond to conservative treatment. After non-surgical treatment, patients that still have persistent pancreatic fistula, abdominal bleeding, abdominal abscess, sepsis, and other critical situations require further surgical treatment [24,29,39,47,73].

Reoperation approach includes placement of drainage in the vicinity of pancreatic stump or anastomosis site (the pancreatic stump could be further resected and sutured again) [73,74], anastomosis of pancreatic stump and digestive tract, and removing a part of pancreatic tissue or even the whole pancreas. In case of ischemic necrosis of other organs, combined resection of vessels and organs is even required [29].

Summary

With the development of minimally invasive surgery, the surgical technique of pancreatic body and tail resection is also constantly improving. Minimally invasive radical resection is gradually being popularized and has achieved good results in clinical practice. POPF is still the most common and dangerous complication of pancreatic body and tail resection. Experts and scholars are attempting to standardize the definition of pancreatic fistula in order to diagnose, prevent, and treat pancreatic fistula more reasonably. They are continuously studying the risk factors of pancreatic fistula so as to avoid its occurrence at an early stage. Many new approaches (e.g., pancreatic disconnection and stump closure) and materials are being developed and utilized to prevent pancreatic fistula.

Prospective and randomized controlled studies on body and tail pancreatectomy are relatively few, and this should be the direction of future research and development.

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Compliance with ethics guidelines

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References

1. Pratt WB, Callery MP, Vollmer CM Jr. The latent presentation of pancreatic fistulas. Br J Surg 2009; 96(6): 641–649
2. Facy O, Chalumeau C, Poussier M, Binquet C, Rat P, Ortega-Deballon P. Diagnosis of postoperative pancreatic fistula. Br J Surg 2012; 99(8): 1072–1075
3. Bassi C, Dervenis C, Butturini G, Fingerhut A, Yeo C, Izbicki J, Neoptolemos J, Sarr M, Traverso W, Buchler M; International Study Group on Pancreatic Fistula Definition. Postoperative pancreatic fistula: an international study group (ISGPF) definition. Surgery 2005; 138(1): 8–13
4. Bassi C, Marchegiani G, Dervenis C, Sarr M, Abu Hilal M, Adham M, Allen P, Andersson R, Asbun HJ, Besselink MG, Conlon K, Del Chiaro M, Falconi M, Fernandez-Cruz L, Fernandez-Del Castillo C, Fingerhut A, Friess H, Gouma DJ, Hackert T, Izbicki J, Lillemoe KD, Neoptolemos JP, Olah A, Schulick R, Shrikhande SV, Takada T, Takaori K, Traverso W, Vollmer CR, Wolfgang CL, Yeo CJ, Salvia R, Buchler M; International Study Group on Pancreatic Surgery (ISGPS). The 2016 update of the International Study Group (ISGPS) definition and grading of postoperative pancreatic fistula: 11 Years After. Surgery 2017; 161(3): 584–591
5. Maggino L, Malleo G, Bassi C, Allegrini V, McMillan MT, Borin A, Chen B, Drebin JA, Ecker BL, Fraker DL, Lee MK, Paiella S, Roses RE, Salvia R, Vollmer CM Jr. Decoding grade B pancreatic fistula: a clinical and economical analysis and subclassification proposal. Ann Surg 2019; 269(6): 1146–1153
6. Kleeff J, Diener MK, Z'graggen K, Hinz U, Wagner M, Bachmann J, Zehetner J, Müller MW, Friess H, Büchler MW. Distal pancreatectomy: risk factors for surgical failure in 302 consecutive cases. Ann Surg 2007; 245(4): 573–582
7. Goh BK, Tan YM, Chung YF, Cheow PC, Ong HS, Chan WH, Chow PK, Soo KC, Wong WK, Ooi LL. Critical appraisal of 232 consecutive distal pancreatectomies with emphasis on risk factors, outcome, and management of the postoperative pancreatic fistula: a 21-year experience at a single institution. Arch Surg 2008; 10(143): 956–965
8. Johnston FM, Cavataio A, Strasberg SM, Hamilton NA, Simon PO Jr, Trinkaus K, Doyle MBM, Mathews BD, Porembka MR, Linehan DC, Hawkins WG. The effect of mesh reinforcement of a stapled transection line on the rate of pancreatic occlusion failure after distal pancreatectomy: review of a single institution's experience. HPB (Oxford) 2009; 11(1): 25–31
9. Seeliger H, Christians S, Angele MK, Kleespies A, Eichhorn ME,

Ischenko I, Boeck S, Heinemann V, Jauch KW, Bruns CJ. Risk factors for surgical complications in distal pancreatectomy. Am J Surg 2010; 200(3): 311–317

10. Kawai M, Tani M, Okada K, Hirono S, Miyazawa M, Shimizu A, Kitahata Y, Yamaue H. Stump closure of a thick pancreas using stapler closure increases pancreatic fistula after distal pancreatectomy. Am J Surg 2013; 206(3): 352–359
11. Kowalsky SJ, Zenati MS, Dhir M, Schaefer EG, Dopsovic A, Lee KK, Hogg ME, Zeh HJ, Vollmer CM, Zureikat AH. Postoperative narcotic use is associated with development of clinically relevant pancreatic fistulas after distal pancreatectomy. Surgery 2018; 163 (4): 747–752
12. Arai T, Kobayashi A, Yokoyama T, Ohya A, Fujinaga Y, Shimizu A, Motoyama H, Furusawa N, Sakai H, Uehara T, Kadoya M, Miyagawa S. Signal intensity of the pancreas on magnetic resonance imaging: prediction of postoperative pancreatic fistula after a distal pancreatectomy using a triple-row stapler. Pancreatology 2015; 15 (4): 380–386
13. Chang YR, Kang JS, Jang JY, Jung WH, Kang MJ, Lee KB, Kim SW. Prediction of pancreatic fistula after distal pancreatectomy based on cross-sectional images. World J Surg 2017; 41(6): 1610–1617
14. Fukuda Y, Yamada D, Eguchi H, Iwagami Y, Noda T, Asaoka T, Wada H, Kawamoto K, Gotoh K, Mori M, Doki Y. A novel preoperative predictor of pancreatic fistula using computed tomography after distal pancreatectomy with staple closure. Surg Today 2017; 47(10): 1180–1187
15. Silvestri M, Coignac A, Delicque J, Herrero A, Borie F, Guiu B, Fabre JM, Souche R. Level of pancreatic division and postoperative pancreatic fistula after distal pancreatectomy: a retrospective case-control study of 157 patients with non-pancreatic ductal adenocarcinoma lesions. Int J Surg 2019; 65: 128–133
16. Martin AN, Narayanan S, Turrentine FE, Bauer TW, Adams RB, Zaydfudim VM. Pancreatic duct size and gland texture are associated with pancreatic fistula after pancreaticoduodenectomy but not after distal pancreatectomy. PLoS One 2018; 13(9): e0203841
17. Flohr TG, Schaller S, Stierstorfer K, Bruder H, Ohnesorge BM, Schoepf UJ. Multi-detector row CT systems and image-reconstruction techniques. Radiology 2005; 235(3): 756–773
18. Yang W, Fan Z, Deng Z, Pang J, Bi X, Fraass BA, Sandler H, Li D, Tuli R. Novel 4D-MRI of tumor infiltrating vasculature: characterizing tumor and vessel volume motion for selective boost volume definition in pancreatic radiotherapy. Radiat Oncol 2018; 13(1): 191–198
19. Jimenez RE, Hawkins WG. Emerging strategies to prevent the development of pancreatic fistula after distal pancreatectomy. Surgery 2012; 152(3 Suppl): S64–S70
20. Bilimoria MM, Cormier JN, Mun Y, Lee JE, Evans DB, Pisters PW. Pancreatic leak after left pancreatectomy is reduced following main pancreatic duct ligation. Br J Surg 2003; 90(2): 190–196
21. Ferrone CR, Warshaw AL, Rattner DW, Berger D, Zheng H, Rawal B, Rodriguez R, Thayer SP, Fernandez-del Castillo C. Pancreatic fistula rates after 462 distal pancreatectomies: staplers do not decrease fistula rates. J Gastrointest Surg 2008; 12(10): 1691–1697, discussion 1697–1698
22. Karabicak I, Satoi S, Yanagimoto H, Yamamoto T, Yamaki S, Kosaka H, Hirooka S, Kotsuka M, Michiura T, Inoue K, Matsui Y, Kon M. Comparison of surgical outcomes of three different stump closure techniques during distal pancreatectomy. Pancreatology 2017; 17(3): 497–503
23. Sa Cunha A, Carrere N, Meunier B, Fabre JM, Sauvanet A, Pessaux P, Ortega-Deballon P, Fingerhut A, Lacaine F; French Fédération de Recherche EN Chirurgie (FRENCH). Stump closure reinforcement with absorbable fibrin collagen sealant sponge (TachoSil) does not prevent pancreatic fistula after distal pancreatectomy: the FIABLE multicenter controlled randomized study. Am J Surg 2015; 210(4): 739–748
24. Walters DM, Stokes JB, Adams RB, Bauer TW. Use of a falciform ligament pedicle flap to decrease pancreatic fistula after distal pancreatectomy. Pancreas 2011; 40(4): 595–599
25. Hassenpflug M, Hartwig W, Strobel O, Hinz U, Hackert S T, Fritz MW, Büchler J, Werner. Decrease in clinically relevant pancreatic fistula by coverage of the pancreatic remnant after distal pancreatectomy. Surgery 2012; 152(3 Suppl): S164–S171
26. Carter TI, Fong ZV, Hyslop T, Lavu H, Tan WP, Hardacre J, Sauter PK, Kennedy EP, Yeo CJ, Rosato EL. A dual-institution randomized controlled trial of remnant closure after distal pancreatectomy: does the addition of a falciform patch and fibrin glue improve outcomes? J Gastrointest Surg 2013; 17(1): 102–109
27. Hassenpflug M, Hinz U, Strobel O, Volpert J, Knebel P, Diener MK, Doerr-Harim C, Werner J, Hackert T, Büchler MW. Teres ligament patch reduces relevant morbidity after distal pancreatectomy (the DISCOVER Randomized Controlled Trial). Ann Surg 2016; 264(5): 723–730
28. Chen S, Chen G, Zhao Y. Comment on 'Teres ligament patch reduces relevant morbidity after distal pancreatectomy (the DISCOVER Randomized Controlled Trial)'. Ann Surg 2018; 267(5): e93–e94
29. Oláh A, Issekutz A, Belágyi T, Hajdú N, Romics L Jr. Randomized clinical trial of techniques for closure of the pancreatic remnant following distal pancreatectomy. Br J Surg 2009; 96(6): 602–607
30. Fujii T, Yamada S, Murotani K, Sugimoto H, Hattori M, Kanda M, Takami H, Nakayama G, Nomoto S, Fujiwara M, Nakao A, Kodera Y. Modified Blumgart suturing technique for remnant closure after distal pancreatectomy: a propensity score-matched analysis. J Gastrointest Surg 2016; 20(2): 374–384
31. Wang M, Zhu F, Peng F, Tian R, Shi C, Xu M, Li X, Wang X, Shen M, Qin R. Greater omentum binding: a simple technique to cover the pancreatic remnant after distal pancreatectomy. J Am Coll Surg 2014; 219(2): e19–e23
32. Montorsi M, Zerbi A, Bassi C, Capussotti L, Coppola R, Sacchi M; Italian Tachosil Study Group. Efficacy of an absorbable fibrin sealant patch (TachoSil) after distal pancreatectomy: a multicenter, randomized, controlled trial. Ann Surg 2012; 256(5): 853–859, discussion 859–860
33. Park JS, Lee DH, Jang JY, Han Y, Yoon DS, Kim JK, Han HS, Yoon Y, Hwang D, Kang CM, Hwang HK, Lee WJ, Heo J, Chang YR, Kang MJ, Shin YC, Chang J, Kim H, Jung W, Kim SW. Use of TachoSil® patches to prevent pancreatic leaks after distal pancreatectomy: a prospective, multicenter, randomized controlled study. J Hepatobiliary Pancreat Sci 2016; 23(2): 110–117
34. Shubert CR, Ferrone CR, Fernandez-Del Castillo C, Kendrick ML, Farnell MB, Smoot RL, Truty MJ, Que FG. A multicenter

randomized controlled trial comparing pancreatic leaks after TissueLink versus SEAMGUARD after distal pancreatectomy (PLATS) NCT01051856. J Surg Res 2016; 206(1): 32–40
35. Kawai M, Hirono S, Okada KI, Satoi S, Yanagimoto H, Kon M, Murakami Y, Kondo N, Sho M, Akahori T, Toyama H, Fukumoto T, Fujii T, Matsumoto I, Eguchi H, Ikoma H, Takeda Y, Fujimoto J, Yamaue H. Reinforced staplers for distal pancreatectomy. Langenbecks Arch Surg 2017; 402(8): 1197–1204
36. Matsumoto I, Takeyama Y, Kamei K, Satoi S, Nakata Y, Ishikawa H, Murase T, Matsumoto M, Nakai T. Transpancreatic mattress suture with Vicryl mesh around the stump during distal pancreatectomy: a novel technique for preventing postoperative pancreatic fistula. J Am Coll Surg 2016; 223(2): e1–e5
37. Jang JY, Shin YC, Han Y, Park JS, Han HS, Hwang HK, Yoon DS, Kim JK, Yoon YS, Hwang DW, Kang CM, Lee WJ, Heo JS, Kang MJ, Chang YR, Chang J, Jung W, Kim SW. Effect of polyglycolic acid mesh for prevention of pancreatic fistula following distal pancreatectomy: a randomized clinical trial. JAMA Surg 2017; 152 (2): 150–155
38. Harris LJ, Abdollahi H, Newhook T, Sauter PK, Crawford AG, Chojnacki KA, Rosato EL, Kennedy EP, Yeo CJ, Berger AC. Optimal technical management of stump closure following distal pancreatectomy: a retrospective review of 215 cases. J Gastrointest Surg 2010; 14(6): 998–1005
39. Diener MK, Seiler CM, Rossion I, Kleeff J, Glanemann M, Butturini G, Tomazic A, Bruns CJ, Busch OR, Farkas S, Belyaev O, Neoptolemos JP, Halloran C, Keck T, Niedergethmann M, Gellert K, Witzigmann H, Kollmar O, Langer P, Steger U, Neudecker J, Berrevoet F, Ganzera S, Heiss MM, Luntz SP, Bruckner T, Kieser M, Büchler MW. Efficacy of stapler versus hand-sewn closure after distal pancreatectomy (DISPACT): a randomised, controlled multicentre trial. Lancet 2011; 377(9776): 1514–1522
40. Probst P, Hüttner FJ, Klaiber U, Knebel P, Ulrich A, Büchler MW, Diener MK. Stapler versus scalpel resection followed by hand-sewn closure of the pancreatic remnant for distal pancreatectomy. Cochrane Database Syst Rev 2015; 6(11): CD008688
41. Okano K, Kakinoki K, Yachida S, Izuishi K, Wakabayashi H, Suzuki Y. A simple and safe pancreas transection using a stapling device for a distal pancreatectomy. J Hepatobiliary Pancreat Surg 2008; 15(4): 353–358
42. Nakamura M, Ueda J, Kohno H, Aly MYF, Takahata S, Shimizu S, Tanaka M. Prolonged peri-firing compression with a linear stapler prevents pancreatic fistula in laparoscopic distal pancreatectomy. Surg Endosc 2011; 25(3): 867–871
43. Hirashita T, Ohta M, Yada K, Tada K, Saga K, Takayama H, Endo Y, Uchida H, Iwashita Y, Inomata M. Effect of pre-firing compression on the prevention of pancreatic fistula in distal pancreatectomy. Am J Surg 2018; 216(3):506–510
44. Hamilton NA, Porembka MR, Johnston FM, Gao F, Strasberg SM, Linehan DC, Hawkins WG. Mesh reinforcement of pancreatic transection decreases incidence of pancreatic occlusion failure for left pancreatectomy: a single-blinded, randomized controlled trial. Ann Surg 2012; 255(6): 1037–1042
45. Kondo N, Uemura K, Nakagawa N, Okada K, Kuroda S, Sudo T, Hadano N, Matstukawa H, Satoh D, Sasaki M, Abe T, Fukuda S, Oshita A, Nakashima A, Hashimoto Y, Ohdan H, Murakami Y. A multicenter, randomized, controlled trial comparing reinforced staplers with bare staplers during distal pancreatectomy (HiSCO-07 Trial). Ann Surg Oncol 2019; 26(5): 1519–1527
46. Kim H, Jang JY, Son D, Lee S, Han Y, Shin YC, Kim JR, Kwon W, Kim SW. Optimal stapler cartridge selection according to the thickness of the pancreas in distal pancreatectomy. Medicine (Baltimore) 2016; 95(35): e4441
47. Dokmak S, Ftériche FS, Meniconi RL, Aussilhou B, Duquesne I, Perrone G, Romdhani C, Belghiti J, Lévy P, Soubrane O, Sauvanet A. Pancreatic fistula following laparoscopic distal pancreatectomy is probably unrelated to the stapler size but to the drainage modality and significantly reduced with a small suction drain. Langenbecks Arch Surg 2019; 404(2): 203–212
48. Sudo T, Murakami Y, Uemura K, Hayashidani Y, Hashimoto Y, Nakashima A, Ohge H, Sueda T. Distal pancreatectomy with duct-to-mucosa pancreaticogastrostomy: a novel technique for preventing postoperative pancreatic fistula. Am J Surg 2011; 202(1): 77–81
49. Yanagimoto H, Satoi S, Toyokawa H, Yamamoto T, Hirooka S, Yamao J, Yamaki S, Ryota H, Matsui Y, Kwon AH. Pancreaticogastrostomy following distal pancreatectomy prevents pancreatic fistula-related complications. J Hepatobiliary Pancreat Sci 2014; 21 (7): 473–478
50. Klein F, Glanemann M, Faber W, Gül S, Neuhaus P, Bahra M. Pancreatoenteral anastomosis or direct closure of the pancreatic remnant after a distal pancreatectomy: a single-centre experience. HPB (Oxford) 2012; 14(12): 798–804
51. Kawai M, Hirono S, Okada K, Sho M, Nakajima Y, Eguchi H, Nagano H, Ikoma H, Morimura R, Takeda Y, Nakahira S, Suzumura K, Fujimoto J, Yamaue H. Randomized controlled trial of pancreaticojejunostomy versus stapler closure of the pancreatic stump during distal pancreatectomy to reduce pancreatic fistula. Ann Surg 2016; 264(1): 180–187
52. Uemura K, Satoi S, Motoi F, Kwon M, Unno M, Murakami Y. Randomized clinical trial of duct-to-mucosa pancreaticogastrostomy versus handsewn closure after distal pancreatectomy. Br J Surg 2017; 104(5): 536–543
53. Chen X. Chen's continuous transpancreatic transverse U-sutures technique for end-to-end invaginated pancreaticojejunostomy. J Abdom Surg (Fu Bu Wai Ke) 2019; 32(2): 77–79 (in Chinese)
54. Hartwig W, Duckheim M, Strobel O, Dovzhanskiy D, Bergmann F, Hackert T, Büchler MW, Werner J. LigaSure for pancreatic sealing during distal pancreatectomy. World J Surg 2010; 34(5): 1066–1070
55. Rostas JW, Richards WO, Thompson LW. Improved rate of pancreatic fistula after distal pancreatectomy: parenchymal division with the use of saline-coupled radiofrequency ablation. HPB (Oxford) 2012; 14(8): 560–564
56. Blansfield JA, Rapp MM, Chokshi RJ, Woll NL, Hunsinger MA, Sheldon DG, Shabahang MM. Novel method of stump closure for distal pancreatectomy with a 75% reduction in pancreatic fistula rate. J Gastrointest Surg 2012; 16(3): 524–528
57. Dorcaratto D, Burdío F, Fondevila D, Andaluz A, Quesada R, Poves I, Caceres M, Mayol X, Berjano E, Grande L. Radiofrequency is a secure and effective method for pancreatic transection in laparoscopic distal pancreatectomy: results of a randomized, controlled trial in an experimental model. Surg Endosc 2013; 27(10): 3710–3719
58. Behrman SW, Zarzaur BL, Parmar A, Riall TS, Hall BL, Pitt HA.

Routine drainage of the operative bed following elective distal pancreatectomy does not reduce the occurrence of complications. J Gastrointest Surg 2015; 19(1): 72–79, discussion 79
59. Van Buren G 2nd, Bloomston M, Schmidt CR, Behrman SW, Zyromski NJ, Ball CG, Morgan KA, Hughes SJ, Karanicolas PJ, Allendorf JD, Vollmer CM Jr, Ly Q, Brown KM, Velanovich V, Winter JM, McElhany AL, Muscarella P 2nd, Schmidt CM, House MG, Dixon E, Dillhoff ME,Trevino JG, Hallet J, Coburn NSG, Nakeeb A, Behrns KE, Sasson AR, Ceppa EP, Abdel-Misih SRZ, Riall TS, Silberfein EJ, Ellison EC, Adams DB, Hsu C, Tran Cao HS, Mohammed S, Villafañe-Ferriol N, Barakat O, Massarweh NN, Chai C, Mendez-Reyes JE, Fang A, Jo E, Mo Q, Fisher WE. A prospective randomized multicenter trial of distal pancreatectomy with and without routine intraperitoneal drainage. Ann Surg 2017; 266(3): 421–431
60. Seykora TF, Liu JB, Maggino L, Pitt HA, Vollmer CM Jr. Drain management following distal pancreatectomy: characterization of contemporary practice and impact of early removal. Ann Surg 2019 Jan 30. [Epub ahead of print] doi:10.1097/SLA.0000000000003205
61. Rieder B, Krampulz D, Adolf J, Pfeiffer A. Endoscopic pancreatic sphincterotomy and stenting for preoperative prophylaxis of pancreatic fistula after distal pancreatectomy. Gastrointest Endosc 2010; 72(3): 536–542
62. Hashimoto Y, Traverso LW. After distal pancreatectomy pancreatic leakage from the stump of the pancreas may be due to drain failure or pancreatic ductal back pressure. J Gastrointest Surg 2012; 16(5): 993–1003
63. Frozanpor F, Lundell L, Segersvärd R, Arnelo U. The effect of prophylactic transpapillary pancreatic stent insertion on clinically significant leak rate following distal pancreatectomy: results of a prospective controlled clinical trial. Ann Surg 2012; 255(6): 1032–1036
64. Hackert T, Klaiber U, Hinz U, Kehayova T, Probst P, Knebel P, Diener MK, Schneider L, Strobel O, Michalski CW, Ulrich A, Sauer P, Büchler MW. Sphincter of Oddi botulinum toxin injection to prevent pancreatic fistula after distal pancreatectomy. Surgery 2017; 161(5): 1444–1450
65. Gurusamy KS, Koti R, Fusai G, Davidson BR. Somatostatin analogues for pancreatic surgery. Cochrane Database Syst Rev 2013; (4): CD008370
66. Kunstman JW, Goldman DA, Gönen M, Balachandran VP, D'Angelica MI, Kingham TP, Jarnagin WR, Allen PJ. Outcomes after pancreatectomy with routine pasireotide use. J Am Coll Surg 2019; 228(2): 161–170.e2
67. Allen PJ, Gönen M, Brennan MF, Bucknor AA, Robinson LM, Pappas MM, Carlucci KE, D'Angelica MI, DeMatteo RP, Kingham TP, Fong Y, Jarnagin WR. Pasireotide for postoperative pancreatic fistula. N Engl J Med 2014; 370(21): 2014–2022
68. Takahashi H, Ogawa H, Ohigashi H, Gotoh K, Yamada T, Ohue M, Miyashiro I,Noura S, Kishi K, Motoori M, Shingai T, Nakamura S, Nishiyama K, Yano M, Ishikawa O. Preoperative chemoradiation reduces the risk of pancreatic fistula after distal pancreatectomy for pancreatic adenocarcinoma. Surgery 2011; 150(3): 547–556
69. Czosnyka NM, Borgert AJ, Smith TJ. Pancreatic adenocarcinoma: effects of neoadjuvant therapy on post-pancreatectomy outcomes — an American College of Surgeons National Surgical Quality Improvement Program targeted variable review. HPB (Oxford) 2017; 19(10): 927–932
70. Loos M, Strobel O, Legominski M, Dietrich M, Hinz U, Brenner T, Heininger A, Weigand MA, Büchler MW, Hackert T. Postoperative pancreatic fistula: microbial growth determines outcome. Surgery 2018; 164(6): 1185–1190
71. Yang F, Jin C, Hao S, Fu D. Drain contamination after distal pancreatectomy: incidence, risk factors, and association with postoperative pancreatic fistula. J Gastrointest Surg 2019 Feb 27. [Epub ahead of print] doi:10.1007/s11605-019-04155-7
72. de Rooij T, van Hilst J, van Santvoort H, Boerma D, van den Boezem P, Daams F, van Dam R, Dejong C, van Duyn E, Dijkgraaf M, van Eijck C, Festen S, Gerhards M, Groot Koerkamp B, de Hingh I, Kazemier G, Klaase J, de Kleine R, van Laarhoven C, Luyer M, Patijn G, Steenvoorde P, Suker M, Abu Hilal M, Busch O, Besselink M; Dutch Pancreatic Cancer Group. Minimally invasive versus open distal pancreatectomy (LEOPARD): a multicenter patient-blinded randomized controlled trial. Ann Surg 2019; 269(1): 2–9
73. Hirashita T, Ohta M, Yada K, Tada K, Saga K, Takayama H, Endo Y, Uchida H, Iwashita Y, Inomata M. Effect of pre-firing compression on the prevention of pancreatic fistula in distal pancreatectomy. Am J Surg 2018; 216(3): 506–510
74. Idrees K, Edler JR, Linehan DC, Strasberg SM, Jacques D, Hamilton NA, Fields RC, Lambert D, Kymes S, Hawkins WG. Cost benefit analysis of mesh reinforcement of stapled left pancreatectomy. HPB (Oxford) 2013; 15(11): 893–898
75. Fujii T, Yamada S, Murotani K, Okamura Y, Ishigure K, Kanda M, Takeda S, Morita S, Nakao A, Kodera Y. Oral Food intake versus fasting on postoperative pancreatic fistula after distal pancreatectomy: a multi-institutional randomized controlled trial. Medicine (Baltimore) 2015; 94(52): e2398
76. Pannegeon V, Pessaux P, Sauvanet A, Vullierme MP, Kianmanesh R, Belghiti J. Pancreatic fistula after 340 proximal and distal pancreatectomy. Pancreatology 2017; 17(4 Supplement): S15–S16
77. Ban D, Shimada K, Konishi M, Saiura A, Hashimoto M, Uesaka K. Stapler and nonstapler closure of the pancreatic remnant after distal pancreatectomy: multicenter retrospective analysis of 388 patients. World J Surg 2012; 36(8): 1866–1873