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CASE STUDY

REVIEW ARTICLE ON THE MANAGEMENT OF PANCREATIC FISTULAE

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ABSTRACT

Introduction: The most significant cause of morbidity and mortality after pancreatic resection, either for malignancy or certain benign disorders, is the development of pancreatic leak and pancreatic fistula. Fistula formation is multifactorial and is often influenced by patient-specific anatomic features of the pancreas and operative techniques at the time of resection.Various strategies have been employed to decrease its incidence including pharmacologic manipulation, and modifications and refinements in surgical technique.

Methods: A broad PubMed and Cochrane database search was conducted, on pancreatic fistula, post-operative fistula, and the various techniques in management.

Conclusions: It is clear that early recognition of pancreatic fistula (PF) and prompt institution of appropriate treatment is the cornerstone in the prevention of potentially devastating consequences. While there are multiple surgical techniques and novel therapies, none have proven to be the gold standard thus far.

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INTRODUCTION

Pancreatic cancer is the fourth most common cause of cancer-related deaths in USA and eighth world-wide. Median survival in locally advanced and metastatic diseaseis ten and six months respectively.At diagnosis, more than 85% of pancreatic tumours are at an advanced stage. Thus, the chances of possible potentially curative resections are only in 10%-15% patients (Wagner *et al.,* 2004, De Souza *et al.,* 2008).The standard surgical procedure for a lesion in the pancreatic head is pancreatico-duodenectomy (PD), while distal pancreatectomy (DP) with or without splenectomy, is performed for tumours in the body and tail. At experienced high-volume centres, mortality after PD is currently 3-5%. At present, the development of pancreatic leak and pancreatic fistula (PF)after PD remain, the most significant cause of morbidity and mortality with rates of up to 20%-50%reported from centres specializing in pancreatic surgery (Schmidt *et al.,* 2004, Bassi *et al.,* 2001, Balcolm *et al.,* 2001, Shrikande *et al.,* 2008). The highest leak rate of PF follows central pancreatectomy, which ranges from 20% to 63% among specialized centres (Sauvanet *et al.,* 2002), in contrast to 5% following distal pancreatectomy (Lillamoe *et al.,* 1999). Distal pancreatectomy is a relevant procedure for chronic pancreatitis, other benign diseases, cysts of the pancreas, malignant diseases, and pancreatic parenchymal damage after abdominal trauma (Balcom *et al.,* 2001, Fahy *et al.,* 2002, Neoptolemos *et al.,* 1997). DP was first performed successfully by Trendelenburg in 1882(Finney *et al.,* 1910) and has long since become a standard procedure. It is now widely performed with a very low morbidity and mortality. However, perioperative morbidity remains substantial from the very first reported cases to the most recent large series (Nathan *et al.,* 2009, Seeliger *et al.,* 2010), the most important cause being pancreatic fistula. In particular, pancreatic leak following distal pancreatic resection has been the foremost complication in terms of frequency and associated morbidity (Montorsi *et al.,* 1995, Fernandez *et al.,* 1995, Ohwada *et al.,* 1998). It is believed that patients with a non-dilated Wirsung's

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duct and a soft friable pancreatic gland are especially susceptible to this complication (Sato *et al.,* 1998, Marcus *et al.,* 1995, Hamanka *et al.,* 1996, Suzuki *et al.,* 2002).

MATERIALS AND METHODS

A literature review was conducted using Medline, PubMed and the Cochrane Database, with the keywords post-operative pancreatic fistula, pancreatic leak, pancreatic anastomotic failure, pancreatic occlusion failure, pancreatico-duodenectomy, pancreatico-gastrostomy, pancreatico-jejunostomy, distal pancreatectomy, total pancreatectomy, pancreatic duct stenting, pancreatic duct occlusion, anastomotic sealants, sero-muscular patch, mesh patch and somatostatin analogues. Only published research was utilised in our paper. A secondary source search was also done for relevant articles, and these were cited as necessary. The aim of this review is to increase awareness about the variety of current techniques available for management of pancreatic leak and pancreatic fistula.

DISCUSSION

Definitions of pancreatic fistula

There is no single universally-accepted definition of PF. Mostly; it is based on the amylase content from an intra-abdominal drain as well as the daily volume of effluent. However, the debate continues as to what threshold of amylase level defines a PF (Bassi *et al.,* 2001, Shrikande *et al.,* 2008, Callery *et al.,* 2009, Yang *et al.,* 2005) Different groups have their own definitions of post-operative pancreatic fistula (POPF). The Heidelberg and Johns Hopkins groups usea definition of POPF as drainage of more than 50 mL of fluid in 24 hours, with an amylase content of more than 3 times the serum level (more than 10 days postoperatively) (Yeo *et al.,* 1995). German and Italian studies (Buchler *et al.,* 1992) used a definition of POPF as drainage more than 10 mL of fluid in 24 hours with the amylase at least 3 times the serum activity (3 or 4 days postoperatively). The Japanese group used a less-strict definition (Suzuki *et al.,* 1995)- fluid drainage for more than 7 days postoperatively with fluid amylase level more than 3 times the serum level. Some groups also suggest that for a definitive diagnosis, radiologic imaging is necessary (Bassi *et al.,* 2001, Takano *et al.,* 2000, Cullen *et al.,* 1994). Furthering this concept, in 1997, Lowy *et al.,* introduced the ‘‘clinically significant leak’’ defined as fever (>38ºC), leukocyte count of greater than 10,000 cells/mm3, sepsis, and/or the need for drainage (Lowy *et al.,* 1997). Between 1991 and 2000, 26 definitions of PF were examined and published, and each arbitrarily assigned a score based on daily fluid output criteria and the timing of fistula development. The results revealed wide variations in the incidence of PF from 10% to 29% depending upon the definition (Pecorelli *et al.,* 2011). Prior to the new grading system by the International Study Group for Pancreatic Fistula (ISGPF), the four most commonly used definitions of PF were:

- Output >10 mL/day of amylase rich fluid on postoperative day 5 or for >5 days
- Output >10 mL/day of amylase rich fluid on postoperative day 8 or for 8 days
- Output of >50 mL/day of amylase rich fluid after postoperative day 11 or for more than 11 days
- Output between 25 mL-100 mL/day of amylase rich fluid after post-operative day 8 or for > 8 days.

The ISGPF, which includes 37 notable pancreatic surgeons from 15 countries, came up with a definition of PF to facilitate comparison of various studies (Bassi *et al.,* 2005) as well as standardizing of postoperative treatment. The essential component of an anastomotic leak was the high amylase content (more than 3 times the upper limit of normal serum value) of the drain fluid (of any measurable volume), at any time on or after the 3rd postoperative day.

Grading of pancreatic fistula- figure (a) & (b)

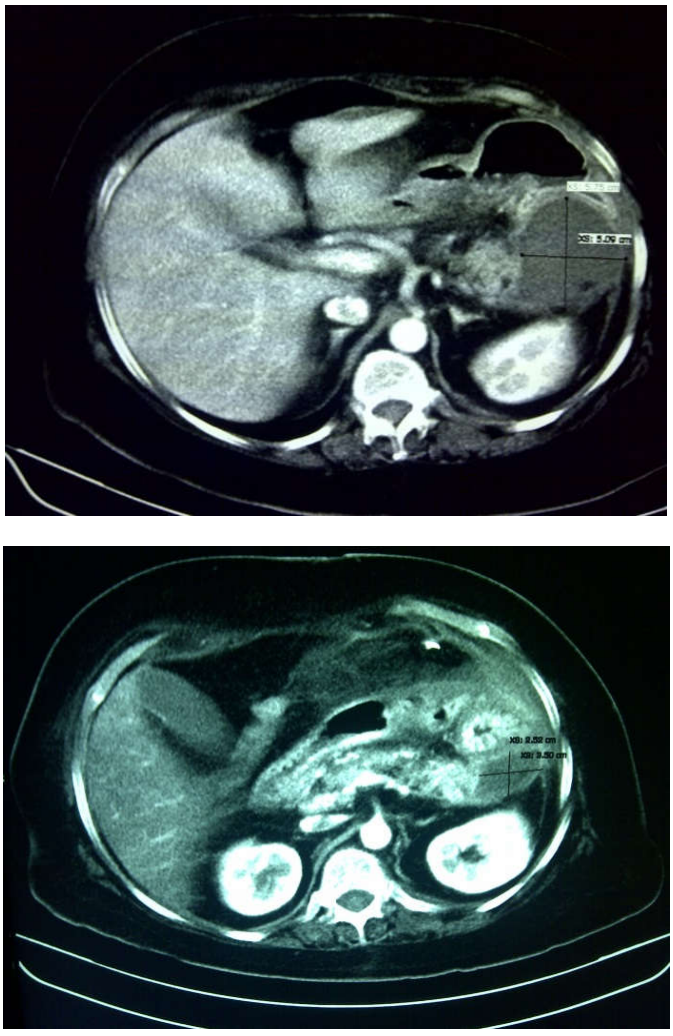


Figure (a)& (b): Two separate fluid collection in lesser sac and in LUQ close to abdominal wall (Two weeks post op)after distal pancreatectomy

The ISGPF has also graded PF according to the clinical impact on the patient’s hospital course and eventual outcome. This is determined by various clinical criteria (patient’s condition, persistent drainage longer than 3 weeks, use of specific treatment, ultrasound and/or CT findings, reoperation, death, signs of infection, sepsis, and re-admissions (Shrikande *et al.,* 2008, Callery *et al.,* 2009, Yang *et al.,* 2005). More recently, Pratt *et al.,* sought to validate the ISGPF classification in 176 patients who underwent DP and concluded that there was a negative clinical and economic impact on patients and their healthcare resources with increasing fistula grades (Pratt *et al.,* 2007).

POPF grade A- The most frequently seen grade (transient fistula) and has no clinical impact. It requires little change in management. The patient is fed orally and remains clinically well, and the use of antibiotics, total parenteral nutrition, or somatostatin analogues are not indicated.

POPF grade B- This requires adjustment in the patient's clinical pathway. Often the patient is kept NPO and supported with partialenteral or total parenteral nutrition. The peri-pancreatic drains are usually maintained in place, but if they do not fully drain the fistula, a CT scan may show peri-pancreatic collection(s) requiring repositioning of the drains. Antibiotic therapy is started if the patient develops fever, abdominal pain with leucocytosis; somatostatin analogues may also be used. Prolonged hospital stay, or readmission after a previous discharge is not uncommon. Many of these patients can be discharged with drains in-situ andoutpatient observation. However, if an invasive procedure is needed, the POPF graduates to grade C.

POPF grade C- In this situation, a major change in clinical management occurs. Clinical stability may be borderline. The patient is kept NPO, and total parenteral nutrition or enteral nutrition, intravenous antibiotics, and somatostatin analogues instituted, often in an ICU setting. A CT scan usually reveals peri-pancreatic fluid collection(s) that require percutaneous drainage. An extended hospital stay with a major delay in hospital discharge is common. However, if patient's clinical condition deteriorates along with notable sepsis and organ dysfunction; further options may require re-exploration. Such as:

(1) An attempt to repair the site of leakage with wide peri-pancreatic drainage
(2) Conversion to alternative means of pancreatic-enteric anastomosis (e.g. conversion of pancreatico-jejunostomy to pancreatico-gastrostomy)
(3) and the last resort completion pancreatectomy

Fistula type based on operative procedure performed

Fistulas can be secondary to either pancreatic anastomotic failure (PAF) or pancreatic occlusion failure (POF). Recently Strasberg *et al.,* proposed that intra-abdominal collections along with peritonitis and haemorrhage are the result of PAF. This includes all clinically relevant problems associated with loss of integrity of the pancreatico-enterostomy (Strasberg *et al.,* 2007). They also sought to categorise fistulas that occur after segmental resection or distal pancreatectomy (DP) or enucleation (situations that do not involve pancreatico-enterostomy) as a distinct entity from fistula occurring after PD. These were termed pancreatic occlusion failure, and generally has a benign course compared to PAF, since enzyme activation does not occur in the absence of pancreatico-enteric anastomosis.In terms of a clinical definition, PAF has been described as "drainage of greater than 50 mL amylase-rich fluid (more than 3-fold elevation above the upper limit of normal in serum) per day on or after postoperative day 10, or radiological evidence of pancreatic anastomotic disruption "(Strasberg *et al.,* 2007).

PAF is graded as

- *Grade 1*-deviation from normal postoperative course without any pharmacologic, radiologic, endoscopic, or surgical interventions (certain drugs are allowed)
- *Grade 2*-pharmacologic treatment needed, includes blood transfusion and total parenteral nutrition.
- *Grade 3*–radiological, endoscopic andsurgical interventional are needed
  - a)undergeneral anaesthesia
  - b) not under general anaesthesia
- *Grade 4*–usually have life threating complications along with organ dysfunction
  - a) single
  - b) multi-organ
- *Grade 5*- death due to PAF

Complications and long-term effects of pancreatic fistula

The reported incidence of PF following pancreatico-duodenectomy ranges from 6% to 14% and mortality from 1.4% to 3.7% (Schmidt *et al.,* 2004, Bassi *et al.,* 2008, Shrikande *et al.,* 2008, Callery *et al.,* 2009, Yang *et al.,* 2005, Lowy *et al.,* 1997, Pecorelli *et al.,* 2011, Bassi *et al.,* 2005, Strasberg *et al.,* 2007, Cameron *et al.,* 2006, Bassi *et al.,* 2004, Lin *et al.,* 2004). Increased morbidity, mortality and prolonged hospital stay are all consequences of PF. In addition, PF is associated with other non-fistulous complications, particularly delayed gastric emptying, paralytic ileus, wound infections, intra-abdominal abscess formation, pancreatitis, haemorrhage and sepsis. The hospital costs, rate of reoperation and hospital readmission rate are significantly increasedin patients after pancreatico-duodenectomy rather than after distal pancreatectomy. Patients after DP seldom require aggressive management approaches or experience prolonged hospital stays, and can be discharged home rather than to rehabilitation facilities (Pratt *et al.,* 2006). On the contrary, patients after PD usually require prolonged drainage of intra-abdominal collections, multiple hospital readmissions and multiple radiological and surgical interventions(Schmidt *et al.,* 2004, Bassi *et al.,* 2008, Shrikande *et al.,* 2008, Callery *et al.,* 2009, Yang *et al.,* 2005, Bassi *et al.,* 2005, Cameron *et al.,* 2006).

Risk factors for pancreatic fistula after pancreatico-duodenectomy

Several risk factors for pancreatic anastomotic leakage have been documented in the literature - general patient-related risk factors, disease-related risk factors and procedure-related factors. In addition, surgeon experience and in some cases, the use of somatostatin prophylactically, has been shown to correlate with the pancreatic anastomotic leakage rate(Schmidt *et al.,* 2004, Bassi *et al.,* 2008, Shrikande *et al.,* 2008, Callery *et al.,* 2009, Yang *et al.,* 2005, Bassi *et al.,* 2005, Cameron *et al.,* 2006).

Patient-related risk factors

Among all patient characteristics, several factors have been well documented as predictors of pancreatic fistula formation including male sex, advanced age (>70 years), identifiable jaundice, abnormal creatinine clearance, intraoperative blood loss and coronary artery disease (Bassi *et al.,* 2008, Shrikande *et al.,* 2008, Callery *et al.,* 2009, Yang *et al.,* 2005, Pecorelli *et al.,* 2011, Bassi *et al.,* 2005, Cameron *et al.,* 2006, Ulrich *et al.,* 2010).Central obesity and low serum albumin are also responsible for poor healing, leading to PF formation. Several authors have recently documented that high Body Mass Index (BMI)> 25kg/m^2 is an independent and important predictor of PF formation after distal pancreatectomy. This was seen in a

retrospective series that combined a total of 236 consecutive patients after distal pancreatectomy (Seeliger *et al.,* 2010, Ulrich *et al.,* 2012).A number of studies, including prospective ones, have found that patient age > 70 years as the only factor associated with poor anastomotic healing, leading to PF. A fourfold increased likelihood has been found in patients with coronary artery disease (Lin *et al.,* 2004, Ulrich *et al.,* 2010, Matsusue *et al.,* 1998). Jaundice and creatinine clearance have been previously reported as patient-related risk factors, predisposing to PF after PD. The duration, rather than the extent of jaundice was found to be of greater influence on this poor outcome. Yeh *et al.,* demonstrated that the average duration of jaundice was two times longerin pancreatic fistula patients compared to no fistula group: 45 +-21 days versus 23 +-11 days (P = 0.018).However, the author noted no significant impact of serum bilirubin level on fistula development in them (Yeh *et al.,* 1997).A significantly lower creatinine clearance was also associated with the pancreatic fistula:59 +-18 mL/min versus 71+-14 mL/min. The impaired creatinine clearance (<50 mL/min) precipitates intra-abdominal bleeding, acute renal failure, and sepsis, processes that predispose patients to PF (Yeh *et al.,* 1997).Interestingly patients with diabetes mellitus and smoking are relatively low risk,and a history of weight loss and pancreatitis constituted as protective factors. Similarly, neo-adjuvant chemo-radiation therapy has been shown to offer a protective benefit against PF, presumably causing a decrease in pancreatic exocrine secretion (Ulrich *et al.,* 2010, Ishikawa *et al.,* 1991, Hoffman *et al.,* 2006).

Pancreatic texture and disease-related risk factors- figure (2a&2b)

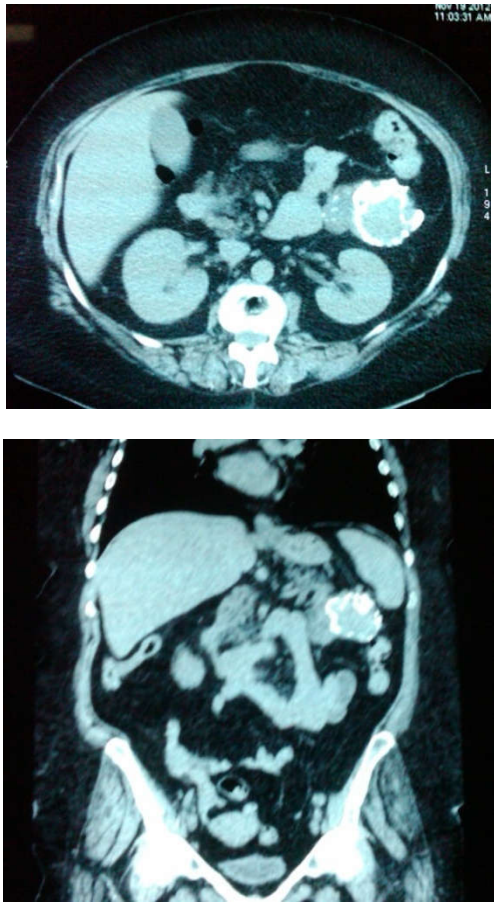


Figure 2(a) &2(b): CT scan of abdomen showing a heterogeneous cystic mass in the tail of pancreas with calcification

The most widely recognized risk factors for pancreatic fistula are directly linked to the state and disease of the pancreas and/or peri-ampullary region. These were reported following analysis of the outcome in 233 consecutive cases of PD. It was concluded that small pancreatic ducts 3mm or less in diameter, soft pancreatic parenchyma and ampullary/duodenal/cystic/ islet cell pathology were all associated with an increased risk of developing a clinically relevant pancreatic fistula (Yeh *et al.,* 1997).Soft, non-fibrotic pancreatic parenchyma, a small pancreatic duct and a duct adjacent to the posterior cut edgeare all significantly associated with pancreatic fistula formation. Principal among these is soft pancreatic parenchyma. It may be argued that a soft "fattypancreas" is prone to pancreatic fistula development after DP in the same way as shown for pancreato-duodenectomy (Callery *et al.,* 2009, Ulrich *et al.,* 2010, 2012, Tajima *et al.,* 2009, Kollmar *et al.,* 2007, Mathur *et al.,* 2007, Rosso *et al.,* 2009). In a series of nearly 2000 pancreatico-duodenectomies, it was noted that the fistula rate with a soft pancreas was 22.6%. It was also found that, compared to a hard or intermediate gland; the soft pancreas was associated with a 10-fold increased risk of pancreatic fistula (Lin *et al.,* 2004). Similar high rates of pancreatic fistula formation were also noted in the presence of soft pancreatic parenchyma by several other authors (Shrikande *et al.,* 2006, Callery *et al.,* 2009, Yang *et al.,* 2005, Beger *et al.,* 2009, Van Berge *et al.,* 1997, Yeo *et al.,* 2000). On the contrary, hard pancreatic remnants were not associated with pancreatic leakage (Matsusue *et al.,* 1998, Van Berge *et al.,* 1997). It has been widely accepted that a fibrotic pancreas in patients with chronic pancreatitis facilitates pancreatico-enteric anastomosis, whereas a soft/friable parenchyma increases the technical difficulty. Hence a strong association between pancreatic texture and pancreatic leakage can be made.

Figure 3. MRCP showing dilated common bile duct, intrahepatic duct and the Pancreatic duct

The size of the pancreatic duct is also a major predictor of fistula formation, (Van Berge *et al.,* 1997) as small, non-dilated pancreatic ducts (typically < 3mm in diameter) predispose patients to pancreatic fistulae, compared to 7% of patients with dilated ducts (Shrikande *et al.,* 2008, Callery *et al.,* 2009). (Fig 3) Other disease-related risk factors includeresection of pathologic lesions like ampullary or duodenal carcinoma, intra-ductal papillary mucinous neoplasia, distal cholangiocarcinoma, pancreatic cyst-adenomas, benign islet tumours, duodenal adenomas (Lin *et al.,* 2004, Poon *et al.,* 2002). The presence of a cystic neoplasm has been shown to be associated with PF formation, whereas pancreatic duct adenocarcinoma seems to have a

protective effect. The location of the pancreatic duct close to the posterior margin is also associated with PF formation (Seeliger *et al.,* 2010, Ulrich *et al.,* 2012).

Operative risk factors

Various technical aspects havebeen scrutinized over the past two decades, to identify operative factors associated with increased fistula rates (Schmidt *et al.,* 2004, Bassi *et al.,* 2001, Shrikande *et al.,* 2008, Callery *et al.,* 2009, Yang *et al.,* 2005, Pecorelli *et al.,* 2011, Bassi *et al.,* 2005, Bassi *et al.,* 2005, Cameron *et al.,* 2006, Bassi *et al.,* 2004, Ulrich *et al.,* 2010). Various techniques for managingthe pancreatic remnant have been compared, including:

- Pancreatico-jejunostomy versus pancreatico-gastrostomy
- Theduct mucosa versus invagination pancreatico-jejunal anastomosis
- Stent versus no stent across the pancreatico-entericanastomosis
- Single versus double roux-en-y loop reconstruction
- The use of somatostatin analogues and/or fibrinsealants

The use of an interrupted suture technique was associated with lower rate of fistula formation when compared with transfixing suture (7% vs. 22%, p=0.036), and it was not influenced by pancreatic anatomy (Tajima *et al.,* 2009).Apart from technical consideration, increased intraoperative blood loss is an important contributor to the development of a PF. There are heterogeneous reports on this issue. Several authors proposed that the risk of fistula development increases when blood loss exceeds 1,500mls. Many factors are associated with increased blood loss including patient obesity, advanced stages of disease (i.e. portal or superior mesenteric veininvasion), jaundice-associated coagulopathy and concurrent pancreatitis (Shrikande *et al.,* 2008, Yeh *et al.,* 1997, Lai *et al.,* 2009). Ridolfini *et al.,* in a retrospective series noted that soft pancreatic tissue, spleen preserving procedures, and the non-usage of postoperative prophylactic octreotide were associated with higher rate of PF formation. Age, gender, and technique of pancreatic stump closure in this analysis were not associated with fistula development (Ridolfini *et al.,* 2007). Kollmar *et al.,*, also documented that concomitant surgery and radical lymphadenectomy, high blood loss, prolonged operating time, extensive mobilization of the pancreatic remnant and any involvement of the uncinate process were associated with increased PF formation. Seeliger *et al.,* recently noted no association with blood transfusion or malignancy, butsplenectomy, multi-visceral resection, comorbidity, and stapler use were all associated with PF formation (Seeliger *et al.,* 2010). The experience and technical skill of the surgeonare also important predictors ofpancreatic fistula formation. Apancreatic fistula can develop if meticulous techniques are not utilized.In the case of stapling, if the parenchymal tissue is not sealed properly it can increase the risk of PF formation. Similarly, in cases of suture repair, if these are too loose or so tight that it tearsthrough the parenchyma altogether, there can be increased fistula formation (Seeliger *et al.,* 2010). Therefore, the predominant factors associated with leak are increased weight, higher ASA score, blood loss > 1 L, increased operative time, decreased serum albumin level and suture closure of the stump without the main duct ligation. Similarly, a DP with splenectomy is associated with a higher incidence of grade B or C PF(Ulrich *et al.,* 2010, Goh *et al.,* 2008). (Fig 4a,4b)

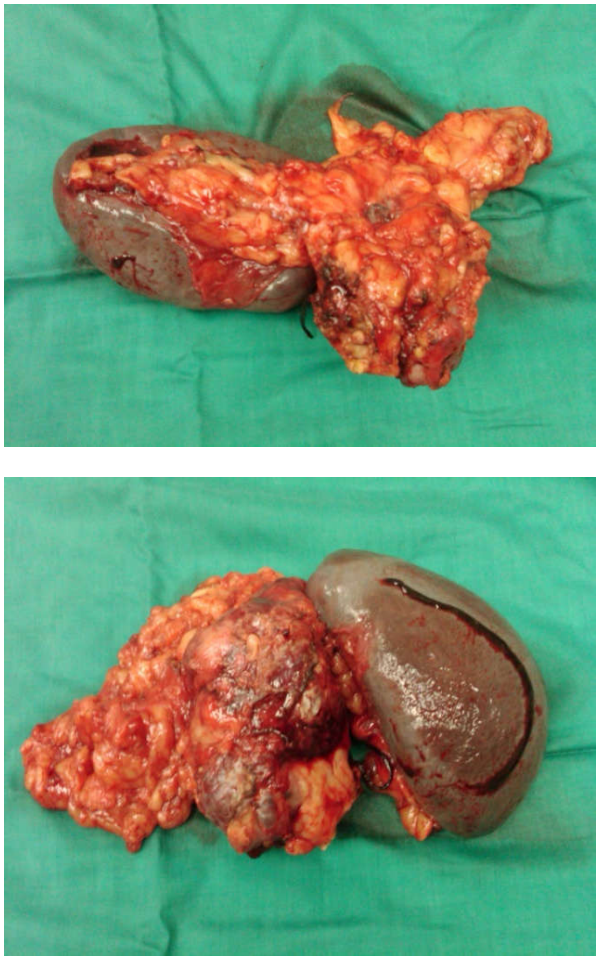


Figure 4(a) & 4(b): En-bloc resection of pancreatic tumour with spleen

Preventative strategies

Certain strategies have been employed in order to decrease the incidence of PF, especially technical modification of the pancreatic anastomosis construction. The correct management of a pancreatic remnant after pancreaticoduodenectomy is a matter of debate. Over the years, a variety of techniques have evolved for the construction of a safe pancreatic anastomosis. These range from pancreatic ductal occlusion to pancreatico-enterostomy with jejunum or stomach. Other innovations include the use of biological adhesives designed to seal the anastomosis, occlusion or ligation of the main pancreatic duct, optimization of the blood supply to the pancreatic remnant, the use of somatostatin and its analogues to inhibit pancreatic secretion, and even total pancreatectomy (Aranha *et al.,* 2006). However, early recognition of PF and prompt institution of appropriate treatment is the cornerstone of management.

Pancreatic duct occlusion vs anastomotic sealants

Pancreatic duct occlusion can be achieved by simple suture ligation of the duct or injection of the duct with non-reabsorbable or reabsorbable glues (Shrikande *et al.,* 2008, Callery *et al.,* 2009, Yang *et al.,* 2005). Simple duct ligation, advocated in the past, has been largely abandoned due to high PF rates, nearing 50% (Goldsmith *et al.,* 1971, Papachristou *et al.,* 1981). However in a recent prospective randomized

controlled trial (RCT) by Tran *et al.,* which compared pancreatico-jejunostomy with duct occlusion alone. The author noted that there were no significant differences in the morbidity or mortality between the groups but in patients with duct occlusion, the incidence of diabetes mellitus was much higher (Tran *et al.,* 2002). The pancreatic fistula rate was significantly higher in the ductal occlusion group (17% versus 5%). However, Di Carlo *et al.,* noted that intra-ductal injection of Neoprene after pancreatico-duodenectomy was a safer procedure compared to pancreatico-jejunal anastomosis, and was not associated with post-surgical diabetes (Di Carlo *et al.,* 1989). In a prospective, multi-centre RCT of 182 patients undergoing either DP or PD, 102 patients received pancreatic ductal occlusion with fibrin glue. Analysis showed that duct occlusion had no effect on the severity or rate of intra-abdominal complications after pancreatic resection (Suc *et al.,* 2003). So far, insufficient evidence exists to show that pancreatico-enterostomy can be replaced by pancreatic ductal occlusion.

Pancreatico-jejunostomy vs pancreatico-gastrostomy- Figure (5a,5b)

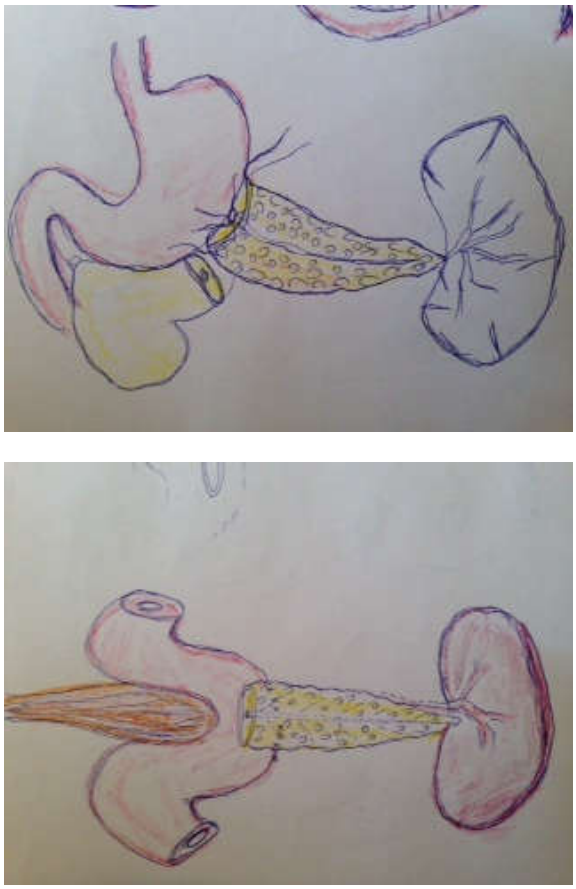


Figure 5(a) Pancreatico-gastrostomy, (b)pancreatico-jejunostomy

The choice of reconstruction after PD, either pancreatico-jejunostomy (PJ) or pancreatico-gastrostomy (PG), the use of pancreatic duct stents, type of anastomosis created, and the use of optical magnification when performing the anastomosis, has recently been under much debate. Regarding the type of reconstruction used, each has its supporters and detractors. PJ is the most commonly used method of pancreatico-entericanastomosis after PD(Schmidt *et al.,* 2004, Shrikande *et al.,* 2008, Callery *et al.,* 2009, Yang *et al.,* 2005, Strasberg *et al.,* 2007, Cameron *et al.,* 2006, Bassi *et al.,* 2001, 2004, 2005). Enteric flow of pancreatic juices after PDis accomplished by uniting the pancreatic remnant with a loop of jejunum. The jejunum has a generous blood supply and mobile mesentery, therefore it is a logical choice for a pancreatico-enteric anastomosis. Over the past 30 years, the reported average fistula rate of this technique is 10% (range 2-19%) (Strasberg *et al* 1997). However, PG has gained favour in recent years as a possible means of reducing the incidence of pancreatic fistula (Sauvanet *et al.,* 2002, Takano *et al.,* 2000, Bassi *et al.,* 2005, Waugh *et al.,* 1946, Aranha *et al.,* 2003, Wente *et al.,* 2007, McKay *et al.,* 2006, Duffas *et al.,* 2005). It was first performed in 1946 by Waugh and Clagett, and proponents of this technique have noticed several potential advantages. These include that pancreatic enzymes are inactivated by an acidic environment, and remain inactive as the stomach does not contain entero-kinase (which is required for conversion of trypsinogen to trypsin and activation of proteolytic enzymes). A lack of enzyme activation may help to prevent auto-digestion of the anastomosis. The proximity of the pancreas to the posterior stomach wall potentially places less tension on the anastomosis line. The excellent blood supply to the stomach wall is favourable for anastomotic healing and the thickness of the stomach holds sutures well. There are three RCTs comparing pancreatico-gastrostomy with pancreatico-jejunostomy (Bassi *et al.,* 2005, Duffas *et al.,* 2005, Fernandez *et al.,* 2008) but they failed to show any significant difference regarding pancreatic fistula rates, postoperative complications, and mortality. Five meta-analyses have been published recently attempted to resolve this controversy (Wente *et al.,* 2007, McKay *et al.,* 2006, Shen *et al.,* 2012, Xiong *et al.,* 2014, Chen *et al.,* 2014). In the firstmeta-analysis of 11 articles along with 1 RCT, 2 prospective non-randomized trials, and 8 cohort studies, it was suggested that PG was safer after PD. The study of Wente *et al.,* analysed 16 articles including 3 RCTs. The results indicated that all cohort studies that reported superiority of PG were most likely influenced by publication bias. A meta-analysis by Shen *et al.,* of 4 RCTs including 276 patients who underwent PG and 277 patients who underwent PJ following PD found a significant difference in the morbidity of intra-abdominal complications ($P < 0.00001$) in patients with PG versus PJ but no significant difference was found for pancreatic fistula, mortality, recovery without complications, biliary fistula or in delayed gastric emptying (Shen *et al.,* 2012). However, Xiong *et al.,* in a recent meta-analysis of 7 RCTs including 1121 patients noted a decreased incidence of POPF rates ($p < 0.001$), intra–abdominal fluid collection ($p < 0.001$) and biliary fistula ($p = 0.03$)in patients undergoing PG than having PJ. Four of these trials applied ISGPF definitions and the remainder used definitions as applied to the individual study. Similar findings were also noted in another recent meta-analysis by Chen-Z *et al.,* 2014. In conclusion, the current evidence suggest that PG is better than PJ for pancreatic reconstruction after PD, although earlier RCTs had failed to show an advantage of a particular technique over other suggesting that both techniques were equally good.

Apart from the different positions of the jejunal loop (ante-colic, retro-colic, or retro-mesenteric) and other variations, such as isolated Roux-loop PJ, the anastomosis can be performed as an end-to-side anastomosis with/without duct-to-mucosa suturing or end-to-end anastomosis with invagination of the pancreaticstump in the jejunum (Strasberg *et al.,* 1997). Isolated Roux-loop reconstruction was advocated to minimize the incidence and severity of anastomotic erosion, which may

occur when pancreatic juice is activated by bile (Khan *et al.,* 2002). Several cohort studies have reported a low pancreatic fistula rate and mortality rate (Khan *et al.,* 2002, Sutton *et al.,* 2004). However, Kaman *et al.,*. in the only non-randomized study, failed to show any significant difference in the pancreatic fistula rates (10% versus 12) following the isolated Roux loop pancreatico-jejunal reconstruction or conventional single loop pancreatico-jejunal reconstruction after PD (Kaman *et al.,* 2008). Based on the limited evidence, the use of isolated Roux loop pancreatico-jejunostomy does not prevent pancreatic fistula formation (Yang *et al.,* 2005).

Duct to mucosa pancreatico-jejunostomy-figure 6(a &b)

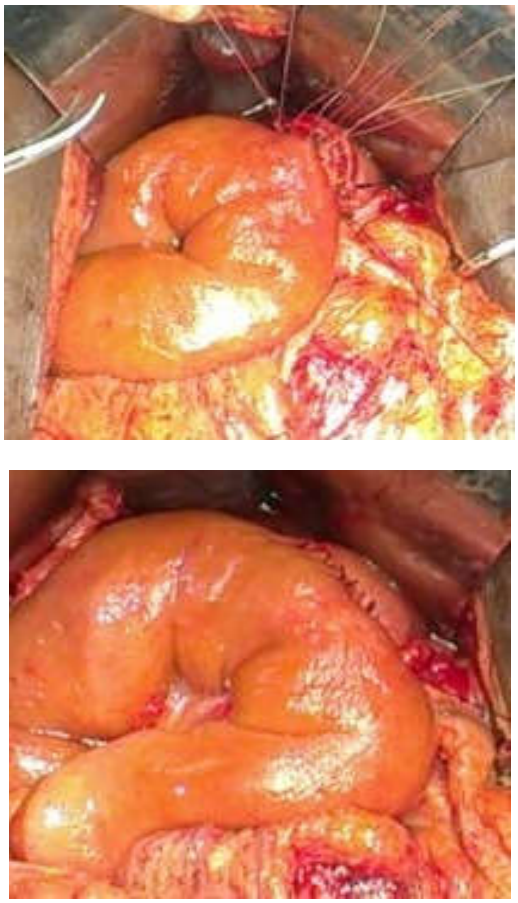


Figure 6(a&b): Duct to mucosa pancreatico-jejunostomy

Duct-to-mucosa pancreatico-jejunal anastomosis allows excellent approximation of the pancreatic duct with jejunal mucosa. This prevents direct contact of the pancreatic juices with the cut end of the pancreas. This aids inmucosal healing and protection of the anastomosis by embedding thepancreatic remnant under jejunal serosa (Schmidt *et al.,* 2004, Bassi *et al.,* 2001, Callery *et al.,* 2009, Yang *et al.,* 2005, Poon *et al.,* 2002). Therefore, duct-to-mucosa anastomosis is theoretically a superior technique to avoid pancreatic fistulae. Since it istechnically difficult to perform, duct-to-mucosa pancreatico-jejunalanastomosis was previously recommended forpatients with a dilated pancreatic duct. However, in recentyears regardless of the diameter of the pancreatic duct, this technique has been preferred.After reviewing various techniques published over the last decade, Poon *et al.,* in 2002 found that the duct-to-mucosa anastomosis was a safer technique than invagination technique. In 1995, Marcus *et al.,* found that duct-to-mucosa anastomosiswas associated with a low pancreatic fistula rate especially, in low-riskpatients with a dilated pancreatic duct or a fibrotic pancreas. On the contrary, the end-to-end invagination technique was a safer option inhigh-risk patients with small ducts or a soft friable pancreas. In 2002, Suzuki *et al.,* in his review of various pancreatico-jejunostomy techniques according to the pancreatic texture and ductsize found that the overall pancreatic leakage rate of 8%. The patients who developed pancreatic fistulae all had a small duct and soft pancreas. In that series, the incidence of pancreatic leakage rate was 6.25% inpatients who underwent a duct tomucosa pancreatico-jejunalanastomosis, compared to 19.6% in invagination group.

However a prospective RCT by Bassi *et al.,* found that there was nostatistically significant difference in PF rate and the morbidity rate between duct-to-mucosa anastomosis and single-layer end-to-sidepancreatico-jejunostomy (Sutton *et al.,* 2004). In a dual-institutional prospective randomized trial, 197 patients were stratified by pancreatic texture and randomized to an end-to-side invagination (n =5100) or a duct-to-mucosa (n =597) PJ anastomosis. There was a 24% PFrate in the duct-to-mucosa cohort and a 12% pancreatic fistula rate in the invaginationcohort ($p < 0.05$) (Beger *et al.,* 2009).

Role of magnification in pancreatic anastomosis

A meticulous approximation is of paramount importance for good outcome, especially for aduct-to-mucosa anastomosis. Operatingloupes have been used by many experts for this procedure. It allows precise reconstruction of the pancreatic anastomosis. Technical errors that may occur during anastomosis include:

- Crossing of the sutures
- Taking unequal or inadequate amounts of pancreatic duct and jejunalmucosa
- Incorrect knot placement, resulting in air knots
- Including both sides of the pancreatic duct while passing the suture

All of these events can be avoided by use of adequate magnification. Some have reported markedly reduced incidence of PF with use of an operating microscope compared to operating loupes (Wada *et al.,* 2006).

Blood supply based technique of pancreatico-duodenectomy

The concept of a vascular watershed in the pancreaticneck and its role in ischemia of the cut surface of the pancreatic remnant has been proposed by Strasberg *et al.,* in 2002. Based on this concept, the blood supply at the cut surface of the pancreas is evaluated intraoperatively, and if necessary the pancreasis cut back by 1.5 - 2 cm to improve the blood supply(n = 47, 38%).

Total pancreatectomy

Total pancreatectom yallows for a more extensive lymphadenectomy, removes wholly the risk of a leak from a pancreatic anastomosisand decreases the chance of a positive resection margin. Obligatory diabetes mellitus, decreased immunity secondary to splenectomy, and loss of pancreatic exocrine function are unfortunately part of the morbidity from this procedure. Unsurprisingly, most studies reported either worse survival or no survival difference between total pancreatectomy and standard PD. The indications for total

pancreatectomy would include serial positive resection margins obtained on frozen section, a very soft pancreas with a potentially increased risk of PF, and in patients withdocumented family history of multi-centric disease (Sarr *et al.,* 1993, Karpoff *et al.,* 2001).

Pancreatic duct stenting -Figure (7)

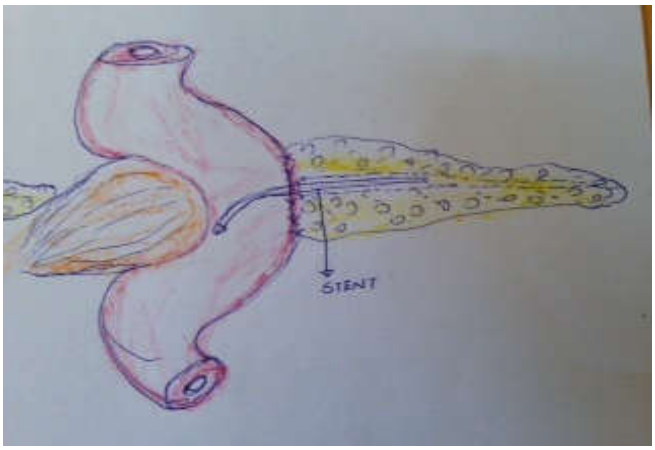


Figure 7. Trans-anastomotic stent for internal drainage of pancreatic secretions

The use of atrans-anastomotic stent for internal and external drainage of pancreatic secretions is a matter of debate (Yoshimi *et al.,* 1996, Roder *et al.,* 1999, Imaizumi *et al.,* 2006, Winter *et al.,* 2006, Ohwada *et al.,* 2002, Poon *et al.,* 2007). The potential advantages of a pancreatic stent include:

- Diversion of pancreatic secretionsfrom the anastomosis
- Facilitation for more precise placement of sutures during the anastomosis
  - Protecting thepancreatic duct from suture injury
  - Reducing the risk of iatrogenic pancreatic duct occlusion

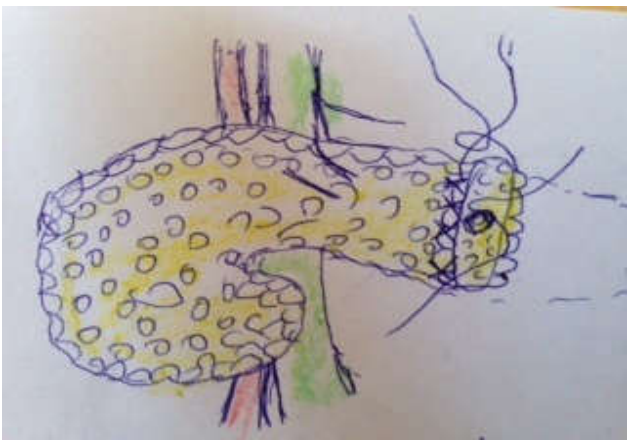
Stent obstruction leading to pancreatic fistula, and stent migration are drawbacks with this adjunct to therapy. Limited studies are available, and the results are conflicting, but internal trans-anastomotic stenting has been reported to reduce the PF rate of pancreatico-jejunal anastomosisin a single cohort study (Yoshimi *et al.,* 1996). However, in a non-randomized study by Imaizumi *et al.,* in 2006 with 168 patients, there was no significantdifference in pancreatic fistula rates between end-to-sidepancreatico-jejunostomy of a normal soft pancreas usingstented (internal or external) method versus non-stented methods (5.7% versus 6.7%).The internal pancreaticstent was evaluated by Winter *et al.,* in a RCT in 2006, among 234patients. This study showed that internal pancreatic ductstenting did not decrease the frequency or severity of postoperative PF. The pancreatic fistula rates in patients under going PD with/without an internal pancreatic stent were 11.3 and 7.6%, respectively.A non-randomized study by Ohwada *et al.* showed equivalent outcomes for external and internal pancreatic stenting of duct-to-mucosa pancreatico-jejunostomy after pancreatico-duodenectomy. However, a RCT byPoon *et al.,* in 2007 showed that among 120 patients who were externally stented, PF rate was significantly lower compared to the non-stented group (6.7%versus 20%). A recent study of 158 patients who underwent PD and were randomized to receive an externalstent versus no stent revealed that the stented group had asignificantly lower rate of PF (26% vs42%, p= 0.034), morbidity (41.5% vs 61.7%, p=0.01), and delayed gastric emptying (7.8% vs 27.2%, p= 0.001).

Similar findings were also noted in another meta-analysis by Wong *et al.,* Seven studies were included, with a total of 793patients. The results showed that use of stents during PD was associated with a significant difference in overall POPF rate (p = 0.02), POPF grades B and C (p = 0.003), and hospital stay (p =0.0009) compared with non-use of stents. Subgroup analyses revealed that external stentsin fact had a significant difference in the incidence of overall POPF (p = 0.0009), POPF grades B and C (p = 0.003), postoperative morbidity (p = 0.03), as well as hospital stay (Wong *et al.,* 2013). Based on the current evidence, it is not clear whether drainage of the pancreatic duct with a stent canreduce the pancreatic fistula rate after PD (evidence levels 2and 3 b). Though some studies have demonstrated that the external stenting technique is superior, as long as a tension-free anastomosis between well-perfused tissues is performed, employing finesutures with meticulous technique, any type of pancreaticanastomosis should result in a good outcome.

Technical modifications after distal pancreatectomy

Despite the experience gained since the technique for distal pancreas resection was outlined by Mayo in 1913, the management of the remaining pancreatic tissue is still a considerable clinical problem (Knaebel *et al.,* 2005, Shrikande *et al.,* 2005). Efforts were made to minimize the complication rate with suitable techniques including end-to-side pancreatico-jejunostomy (Cattell *et al.,* 1948) and staple/suture closure of the pancreatic remnant have been the standard techniques preferred by most (Fahy *et al.,* 2002, Sheehan *et al.,* 2002, Kajiyama *et al.,* 1996, Takeuichi *et al.,* 2003). Several other strategies, such as fibrin glue sealing of the stump or anastomosis, patching the pancreatic stump with the falciform ligament or an omental plug, radio frequency sealing of the pancreatic stump parenchyma, and tissue dissection with the use of an ultrasonic or harmonic scalpel, have been advocated as successful (Ohwada *et al.,* 1998, Suc *et al.,* 2003, Kuroki *et al.,* 2005, Suzuki *et al.,* 1999).Furthermore, the development of techniques does not remain stagnant, and recently a novel method of covering the pancreatic stump has been described. In this method the serosal surface of the first loop of jejunum is used to cover the remnant pancreatic stump (Issekutz *et al.,* 2006). However, no single technique has proven to be satisfactory for all patients.

Suture closure versus staple closure- figure (8a&8b)



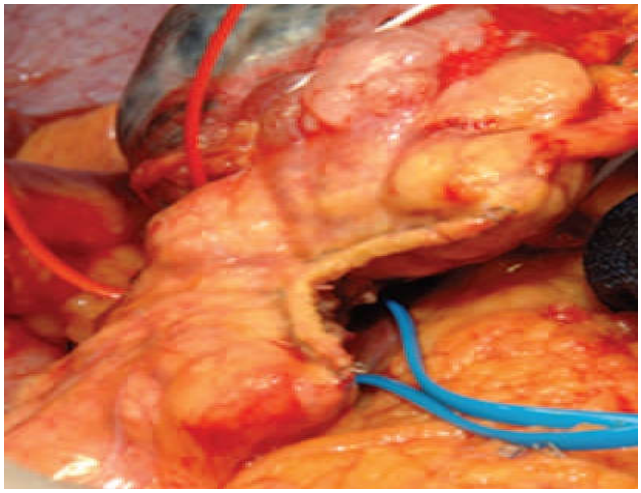


Figure 8. (a) Simple suture closure of distal pancreatic stump(b)Staple closure of distal pancreatic stump

Suture closure and stapler closure of the pancreatic remnant after DP are the techniques used most often. The ideal choice remains a matter of debate, and the surgeon should be guided by individual experience when dealing with the pancreatic remnant after DP. The guiding principle in hand-sewn closure is to make every effort to identify the pancreatic duct first; close it with fine non absorbable sutures and then close the entire stump with non-absorbable suturesas well (Knaebel *et al.,* 2005). In a recent meta-analysis from 2010, of sixteen studies involving 2,286 patients (671-staple closure and 1,615-suture closure) Zhou *et al.,* noted no statistically significant differences between suture and stapler closure with respect to PF formation (22.1% vs. 31.2%) or intra-abdominal abscess formation after distal pancreatectomy, although there is a trend favouring stapler closure [94].The very well-known multicentre RCT (DISPACT), involved450 patients who were randomly assigned to treatment groups (221 staplers, 229 hand-sewn closures), of whom 352 patients (177 staplers, 175 hand-sewn closures) were analysed. There was no statistically significant difference between stapler (32%) and hand-sewn closure (28%) in terms of PF rate or mortality. Stapler closure did not reduce the rate of PF compared with hand-sewn closure for distal pancreatectomy (Diener *et al.,* 2011). Innovative surgical techniques need to be identified, in order to reduce this adverse outcome.

Suture versus staple closure, with/without mesh-figure (9a &9b)

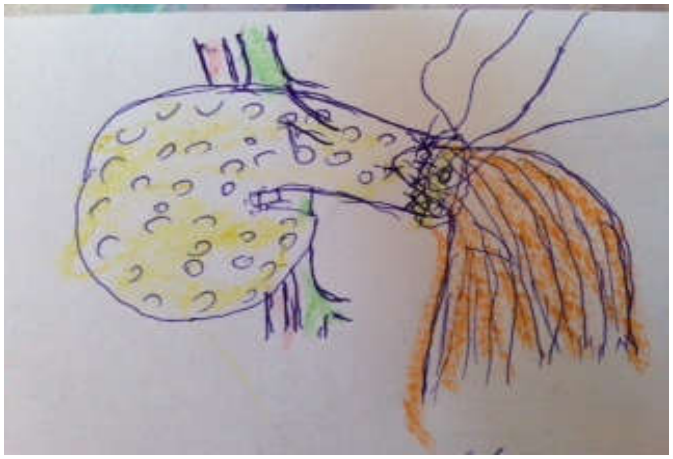


Figure 9. Closure of the distal pancreatic stump with suture plus (a) mesh (b) omentum

Recent evidence has shown that mesh reinforcement after staple or suture closure can reduce the incidence of pancreatic fistula formation. In a recent study, one hundred patients were randomized to either mesh (54) or no-mesh (46) reinforcement of their pancreatic transection. It was noted that there was a statistically significant decrease in the rate of ISGPF grade B and C leaks 1.9% (1/53) with mesh reinforcement, compared to 20% (11/45) without mesh reinforcement (P = .0007) (Hamilton *et al.,* 2012). Similarly, Ramon *et al,* in 2012 concluded that stapler transection with mesh reinforcement is the best available method of pancreatic remnant closure.Finally, in arecent systematic review and meta-analysis of all past and present strategies after DP postulated that stapler transection with mesh reinforcement is the best currently available method of pancreatic remnant closure. Results of ongoing trials using energy sealing devices are eagerly awaited, and further research into this area is necessary to make progress in this field (Jiminez *et al.,* 2012).

Biological adhesives- Figure 10

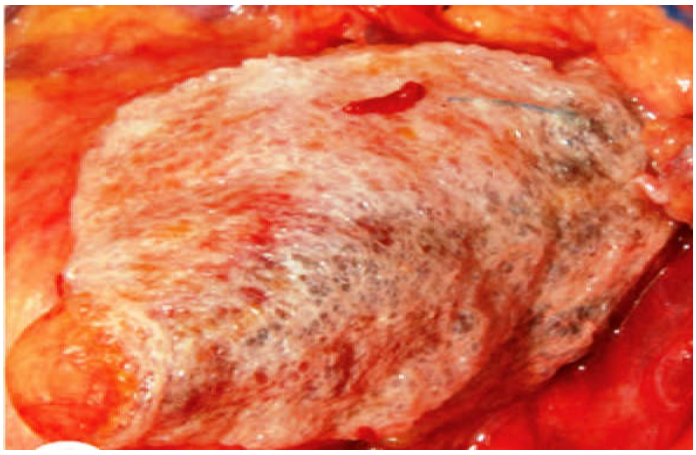


Figure10.Fibrinogen/thrombin-coated collagen patch covering of the pancreatic stump

The use of biological adhesive (Bioglue) fibrin sealant has also been shown to decrease the incidence of POPF rate in several series. Cavallini *et al.,* noted a decreased incidence of POPF after use of the biological adhesive Bioglue to coat the pancreatic resection surface after distal pancreatectomy (DP, N=5) and pancreatico-jejunostomy (PJ) after PD (N=18). However, this experience warrants further larger controlled

studies of the potential value of Bioglue in reducing the incidence of PF after major pancreatic surgery. Fibrin sealant has alsobeen associated with a decreased rate of POPF after both PD and DP. There are no randomized control studies and only three non-randomized studies- two of which reported no fistulas and the other reported no effect. The only prospective, randomized, single-blinded, multicenter study by Suc *et al.*,, (2003), involving 182 consecutive patients undergoing PD with anastomosis or DP, had failed to show any decrease in fistula rate or the severity of intra-abdominal complications after pancreatic resection. Ochiai *et al.,* in 2010, in a non-randomized retrospective study of 54 and 63 patients who underwent PD and DP respectively, compared the occurrence rates for severe postoperative pancreatic fistula (POPF), both with and without application of polyethylene glycolic acid felt with fibrin sealant. Decreased POPF rates after PD (from 39% to 6%) or DP (from 27% to 4%) were noted.

Sero-muscular patching- figure (11a & 11b)

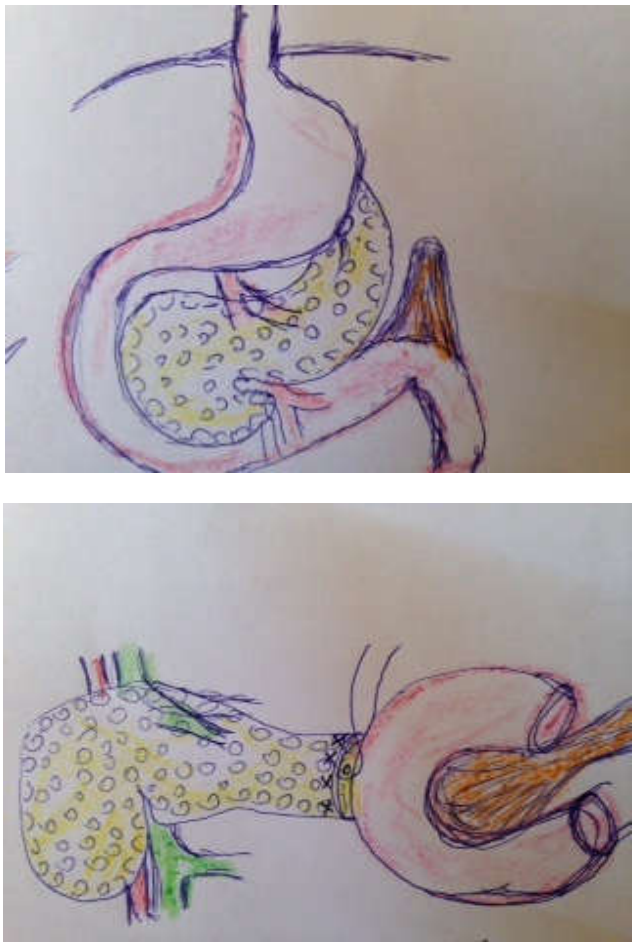


Figure 11.Sero-muscular patching to (a) stomach and (b) jejunum

Applications of a sero-muscular patch or duct-to-mucosa pancreatico-gastrostomy have also shown to be effective in reducing POPF rate. The sero-muscular patch technique was first described by Moriura *et al.,* in 1995, and it was created between the pancreas and posterior wall of the stomach or small bowel. It is quick to perform, technically feasible, and cost-effective when compared with various sealants that are currently available. It has been associated with delayed gastric emptying therefore it is not recommended. Contrary to this, Tani *et al.,* 2006, documented improved gastric emptying in a RCT employing pylorus-preserving PD (13.9% vs. 3.4%).

Pancreatico-gastrostomy-(figure 5a)

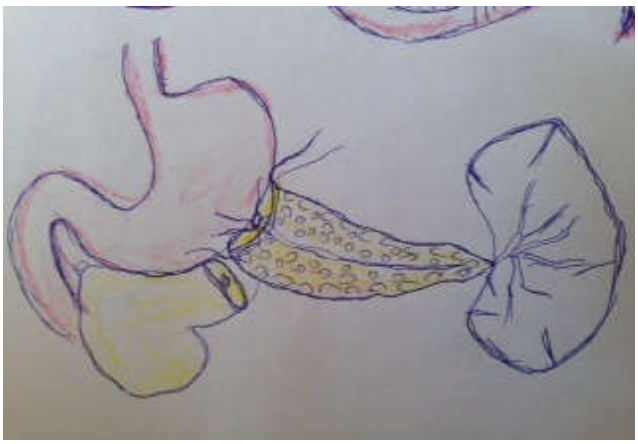


Figure 5a. Pancreatico-gastrostomy

Several authors have documented that duct-to-mucosa pancreatico-gastrostomy after distal pancreatectomy can effectively reduce the POPF. In 2011, Takeshi *et al.,* in their study of twenty-one patients who underwent distal pancreatectomy using the duct-to-mucosa pancreatico-gastrostomy noted 0% grade B or C fistula rate, although the biochemical grade A fistula rate was 29%. Delayed gastric emptying developed in only one patient (5%). The author concluded that duct-to-mucosa pancreatico-gastrostomy may be a safe and effective technique forpreventing PF development after DP when performed by experienced surgeons who are skilled in this technique.

Use of drains versus no drains

This is an on-going debate. Prophylactic, closed abdominal drain placement after pancreatic surgery was recommended to evacuate postoperative intra-peritonealfluid collections. The aim was to prevent infections, allow for early diagnosis of haemorrhage and fistulae if they are externalized, and to avoid reoperation of fistulae or abscesses that could be externally drained (Mutter *et al.,* 1999). Dr Jeekel *et al.,* in 1992, first reported 22 patients underwent PD without the need for an intra-operatively placed drain. Since then several randomized control trials have failed to demonstrate any benefit of prophylactic drains after cholecystectomy (Monson *et al.,* 1991), colorectal surgery (Sagar *et al.,* 1993) or hepatectomy (Fong *et al.,* 1996). Investigators from the Memorial Sloan-Kettering Cancer Centre, in a prospective randomized trial of 179 patients who underwent partial pancreatectomy were randomized to having either a drain or no drain at the end of the procedure. They found statistically similar rates of overall morbidity and mortality between the groups, but the drain group experienced a higher rate of intra-abdominal abscesses and pancreatic fistulas ($p < 0.02$) (Conlon *et al.,* 2001). Despite existing data from this trial that failed to support routine peritoneal drainage, many surgeons continue to place drains at the end of these operations to control any potential POPF.

Findings from recent prospective studies continue to report similar results as the above RCT. Adham *et al.,* in a recent prospective study of 242 patients(130-drain and 112-no drain) noted no statistically significant difference between the drain and no drain groups with respect to post-op complications, fistula formation, requirement of interventional procedures, duration of hospital stay and 90-day mortality rate (Adham *et*

al., 2013). Similarly in 2013,Vishes *et al.,* in a recent retrospective study of 709 patients, noted that placement of closed-suction drains during pancreatic surgery does not appear to decrease the rate of reoperation or secondary drainage procedures, and may be associated with increased pancreatic fistula formation and overall morbidity. At this point, there is no level 1 evidence to support routine use of primary drain placement at the time of pancreatic surgery. A recent systematic review and meta-analysis by Paul *et al.,* (2013) supported a strategy of selective drainage(patients with soft pancreatic texture, prolonged operative times, and increased blood loss) and early drainremoval after pancreatic resection in low-risk patients with drain amylase values <5000 U/L on postoperative day 1(Molinari *et al.,* 2007, Sutcliffe *et al.,* 2012, Bassi *et al.,* 2010, Paul *et al.,* 2013).

Laparoscopic procedures-figure (12)

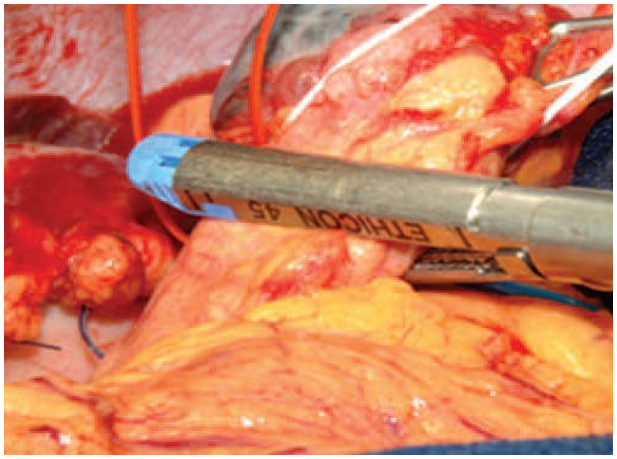


Figure 12. Laparoscopic transection of pancreas with 45 mm Endo GI stapler

In recent years, an increasing number of pancreatic procedures have been performed laparoscopically. Laparoscopic distal pancreatectomy (LDP) has gained worldwide acceptance, because it does not require anastomosis or other reconstruction. LDP has the advantages of shorter hospital stay and operative time, more rapid recovery and a higher spleen-preservation rate as compared with open DP. It may be a safe and feasible option for patients with lesions in the tail and body of the pancreas (Iacobone *et al.,* 2012). To date, English literature reports more than 300 papers published on LDP, but only 6% included more than 30 patients. Two recent meta-analyses, one by Xie (9 articles,1341patients) and another by Jin (15 articles, 1456 patients) comparing open versus laparoscopic distal pancreatectomy (Xie *et al.,* 2012, Jin *et al.,* 2012), noted no difference between the two groups in pancreatic fistula rate and overall morbidity rate. However, Nakamura *et al.,* in 2011 documented that prolonged peri-firing compression (PFC) with a linear stapler can reduce the risk of PF after LDP. Further RCT should be performed to confirm the relevance of these findings.Currently robotic pancreatic surgery is gaining popularity in developed countries.

Management approaches

Management depends on the grades of PF, resources and expertise available in the institute. Numerous novel strategies have been proposed to reduce the POPF rate. But the cornerstone of minimizing the devastating effect of PF is early recognition and institution of appropriate treatment. The suspicion of PF begins whenever there is deviation in the normal clinical course of a patient who has just undergone a majorpancreatic surgery (Shrikande *et al.,* 2008, Callery *et al.,* 2009). Routine radiological investigation of all post-operative patients is generally not recommended.Once the diagnosis of PF is established, appropriate conservative management is the key to successful outcome in majority of the patients. However, interventional radiological assistance is sometimes required, but repeat surgery is rarely indicated (Callery *et al.,* 2009, Cameron *et al.,* 2006).

Conservative management

Non-operative management of pancreatic fistula includes treatment for intra-abdominal collections and postoperative ileus, and is successful in about 90% of cases (Kazanjian *et al.,* 2005, Munoz *et al.,* 2004). Clinical evaluation of the patient at short intervals is ofutmost importance. Patients are kept NPO and well-hydrated. Patients, who have not yet tolerated oral feeds, or those who are presenting with complications on/after the 10th postoperative day, would require total parenteral nutritional support.Enteral nutrition may be used in less severe cases, via nasojejunal tube or feeding jejunostomy. Empiric antibiotics are given if signs of infection (i.e.,purulent discharge, fever, warmth, erythema, tenderness and leucocytosis) are present and adjusted depending on information received from gram stains or cultures. Intra-abdominal drains are left in-situ until daily drainage volumes approach 50mL per day. The patients can be discharged home once the character of the drainage is not purulent or particulate. Carful management of the in-situ drainage is indicated in patients with high drainage output >200mL per day and high drainage fluid amylase level greater than 1000 IU/L (Bassi *et al.,* 2001, Shrikande *et al.,* 2008, Callery *et al.,* 2009, Yang *et al.,* 2005).

Interventional radiology

The role of interventional Radiologist in the management of these patients is evolving. The Manipulation of operatively-placed drains and percutaneous catheters are now routinely placed under ultrasound or CT scan guided by the radiologists to drain any localized collection (Munoz *et al.,* 2004, Halloran *et al.,* 2002). Delayed haemorrhage following PF is a major concern, with angiography and embolization of the bleeding vessel being suitable options. This treatment is successful in stopping the bleeding in 80% of patients (Yekebas *et al.,* 2007, Castro *et al.,* 1997). The prognosis of patients with post-pancreatectomy haemorrhage depends on whether or not PF is present. However, the decision-making should be guided by certain factors such as presence of PF, the time of onset of bleeding, vascular pathology, and the underlying disease process. The failure to successfully control haemorrhage by conservative measures like angiographic embolization may necessitate repeat surgery. Intra-abdominal collections can be dealt by CT or ultrasound- guided percutaneous drainage and is considered to be at the discretion of the surgeon. Some employ this modality in the presence of large fluid collections that have not responded to conservative therapies, but which are amenable to drainage. Surgical exploration is seldom required, but indicated when anastomotic dehiscence is suspected and for patients who deteriorate clinically - often in the setting of sepsis, multipleorgan dysfunctionor a non-

drainable abscess. Options include wide peri-pancreatic drainage of an abscess or fluid collection, revision of the initial pancreatico-enteric anastomosis, conversion to an alternative pancreatico-enteric anastomosis, or completion pancreatectomy (i.e. total pancreatectomy).

Surgical peri-pancreatic drainage, deemed to be a safer alternative to completion pancreatectomy, may be suitable for less severe POPF. However, in patients who have severe POPF with disruption of the pancreatico-jejunostomy, simple peri-pancreatic drainage might not be effective (Bachellier *et al.,* 2008). Completion pancreatectomy, which is often used as a salvage procedure in such instances, is associated with high perioperative mortality ranging from 75% to 100% with severe morbidity of brittle diabetes (Smith *et al.,* 1992). The associated lifelong morbidity of type 1diabetes and exocrine insufficiency created by this procedure requires frequent hospitalization. Hence to avoid these complications, some have recommended salvage pancreatico-gastrostomy (Bachellier *et al.,* 2008).

The use of somatostatin analogues

Somatostatin is a potent inhibitor of both exocrine and endocrine functions. The rationale usingsomatostatin after PD is that it decreases the volume of pancreatic secretions. Therefore, the pancreatic fistula rate would be reduced and also will allow better healing of the pancreatico-enteric anastomosis. There are 11 RCTs involving 2023 patients in whom the somatostatin analogue was examined. Five RCTs from Europe (Montorsi *et al.,* 1995, Buchler *et al.,* 1992, Pederzoli *et al.,* 1994, Friess *et al.,* 1995, Gouillat *et al.,* 2001, Sarr *et al.,* 2003, Shan *et al.,* 2003, Suc *et al.,* 2004, Hesse *et al.,* 2005, Connor *et al.,* 2005, Alghamdi *et al.,* 2007) and one RCT from Asia showedthat the use of somatostatin analogues decreased the postoperative complication rates. Conversely, two recent RCTs from Europe and three RCTs from USA failed to show benefit (Lowy *et al.,* 1997, Yeo *et al.,* 2000, Sarr *et al.,* 2003). Two meta-analyses have been published. Connor *et al.,* in their analysis of 10 studies in 2005 showed that somatostatin and its analogues reduced the rate of pancreatic fistula, but not the incidence of anastomotic disruption. Similar findings were also noted in another report involving seven studies (Alghamdi *et al.,* 2007). Despite this notable reduction in fistula rate, therewas no significant difference in postoperative mortality. In a recent Cochrane review and meta-analysis of 17 RCTs involving 2143 patients Rahul *et al.,* 2010, noted that somatostatin analogues significantly reduced perioperative complications, but not perioperative mortality. However, it is evident that they do shorten hospital stay in patients undergoing pancreatic surgery for malignancy. Therefore, further adequately powered trials of low risk of bias are deemed necessary. The conclusions drawn from these meta-analyses are cautionary, as pooling of data from the RCTs was very difficult due to considerable heterogeneity in these studies, from the end point measures, pathologic findings, definitions of outcome measurements, treatment regimens, type of pancreatic surgery, and anastomotic techniques. Hence the use of somatostatin and its analogues prophylactically during the perioperative period to prevent complications after pancreatic surgery remains controversial. It does not result in a reduction of mortality. However, it is noted that the efficacy of prophylactic octreotide is reported to be improved by their selective administration in the high risk glands, including patients with either a small pancreatic duct or a soft glands, in those harbouring ampullary, duodenal cystic or islet lesions, or in cases where intraoperative blood loss is excessive. Prophylactic octreotide did not influence clinically relevant fistula rates among low-risk glands (Callery *et al.,* 2009). Further RCTs are needed to document its efficacy on low risk glands.

Conclusion

Pancreatic fistula is a common and serious problem after pancreatic resection. Management of this entity can still prove to be a great difficulty to the surgeons. Adequate pre-operative and intra-operative assessment is of paramount importance to identify high risk patients. The management of postoperative fistula remains a therapeutic challenge. Surgeon experience is key to achieving a successful outcome. Meticulous surgical techniques along with the use of an operative microscope and anastomotic modifications, particularly the employment of duct-to-mucosa anastomosis can effectively reduce the PF rate in patients who undergo PD. The use of stents should be restricted to patients with a smaller pancreatic duct (< 3 mm). Similarly, meticulous intra-op technique is required to close the resected stump and duct effectivelyafter distal pancreatectomy. Separate ligation of the main pancreatic duct along with meticulous suturing of the remnant stump, as well as covering the stump with either mesh, omentum or a sero-muscular patch can effectively reduce the PF rate after DP. Although, pancreatico-jejunostomy or pancreatico-gastrostomy has been advocated in several retrospective series, further RCTs are needed before it can be safely applied to these groups of patients. Emerging laparoscopic techniques with vascular stapling & harmonic devices look promising. Stapler transection with prolonged pre-firing compression and mesh reinforcement is the best currently available method of pancreatic remnant closure. Prompt and appropriate conservative management is vital to having a successful outcome in the majority of these patients. When utilized correctly, prompt radiological and surgical intervention can effectively reduce the morbidity and mortality in patients with higher grades of PF. The use of prophylactic octreotide is found to be beneficial in select groups of patients, like those at high risk for developing PF. Robotic surgery can bridge the gap between complex pancreatic surgery and minimally invasive surgery, but further RCTs are required to determine the best closure technique.

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