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Post-operative pancreatic fistula: Analysis of suture materials and detailed review

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Abstract

Pancreatic resection is the preferred treatment for pancreatic malignancy and some benign pancreatic disorders. However, pancreatic resection is a technically challenging operation and whereas death after pancreaticoduodenectomy in skilled high-volume facilities is presently <3%-5%, post-operative morbidity is substantial, around 30%-50%. The growth of pancreatic leakage and fistula (PF) is currently the third most important source of morbidity and mortality after pancreatectomy. The incidence of a Post-operative fistula raises hospital duration and therapy costs, involves extra inquiries and processes, and can lead to life-threatening problems. This report reviews the evolution of the pancreatic fistula post-resection as a concept and discusses evolving definitions, current preventive strategies, suitable suture material analysis and the management of this problem.

Keyword: POPF, Pancreatic resection, Sutures and Surgery

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INTRODUCTION

Pancreatic resection is the normal therapy for pancreatic malignancy and some benign pancreatic illnesses. Pancreatic resection, however, is a technically challenging operation. At treatment, more than 85% of pancreatic cancers are at a developed level. Potentially curative resections are therefore only feasible in 10 percent -15 percent of patients. The normal surgical procedure for a lesion in the pancreatic head is pancreaticoduodenectomy (PD), whereas distal pancreatectomy (DP) with or without splenectomy is conducted for tumours in the neck and tail. At experienced high-volume facilities, death after PD is presently 3%-5%. However, there is significant post-operative morbidity, about 30 percent-50 percent.

At current, the single most important cause of morbidity and death after PD is the growth of pancreatic infection and fistula (PF) and levels of up to 20% are recorded from facilities specializing in pancreatic surgery. Despite countless studies depicting novel techniques to reduce the danger of POPF creation, the recorded POPF levels have not substantially enhanced over the past three decades. This is mainly due to the reality that the fundamental structure of POPF is poorly known, with only latest research starting to disclose the function of postoperative pancreatitis (POP) in the growth of POPF rather than a mere failure of mechanical integrity of pancreatoenteric anastomosis

The formation of PF improves the duration of hospital stay and therapy costs, requires the use of extra inquiries and processes, and can trigger life-threatening complications. Various methods were used to reduce the incidence of PF, including pharmacological manipulation, and surgical technique changes and refinements.

AIM OF THESIS

This paper reviews the evolution of post-resection pancreatic fistula and explores the changing meanings and current preventive policies, management methods, Suitable suture materials analysis in order to reduce fistula formation.

1. STATE OF ART

1.1 What is the pancreas?

The pancreas is often described as having a head, body and tail (

Figure 1). It is surrounded by several large and important organs and blood vessels. The head of the pancreas is next to the duodenum (the first part of the small intestines). The common bile duct carries a fluid called bile from the liver. It passes through the head of the pancreas and empties into the duodenum. The blood vessels that carry blood to the liver, intestines, kidneys and lower part of the body are very close to the pancreas and may touch it [1].

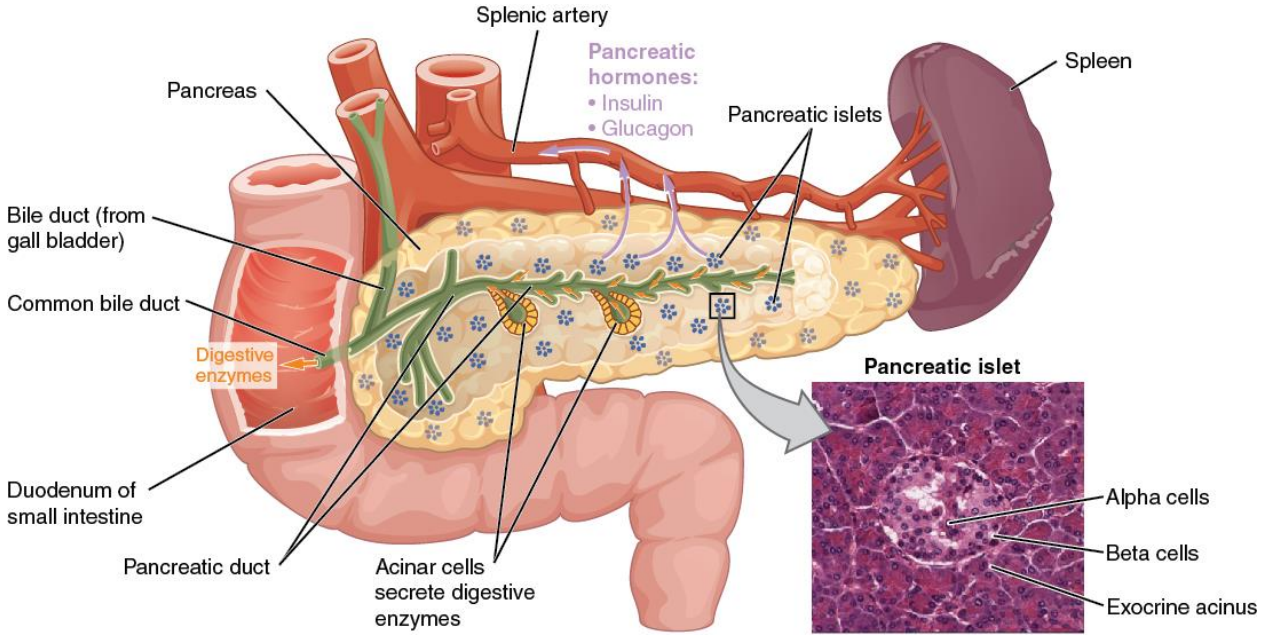

Figure 1 : Anatomy of the Pancreas

1.2 The Main Functions.

The main functions of the pancreas are:

- It makes pancreatic juices containing enzymes. These enzymes help to break down food so the body can absorb it. The digestive juices flow down a tube called the pancreatic duct, which runs the length of the pancreas and empties into the duodenum.
- It makes hormones, including insulin, which control sugar levels in the blood. Both functions can be affected if the pancreas isn't working properly [2].

2. Pancreatic Cancer

2.1 What is pancreatic cancer?

Normal healthy cells grow in a carefully controlled way. Pancreatic cancer develops when cells in the pancreas grow out of control, forming a lump (tumour). This can happen in the head, body or tail of the pancreas (

Figure 2).

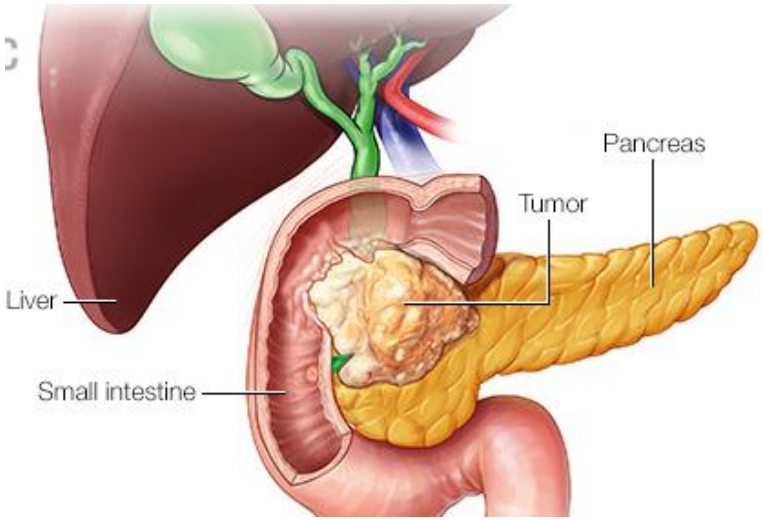

Figure 2 :Graphical view of Pancreatic Tumour

2.2 Main groups of pancreatic cancer

There are two main group of pancreatic cancer.

- Exocrine tumours start in the exocrine cells. These cells make enzymes. About ninety-five out of a hundred pancreatic cancers (95%) are exocrine tumours. The most common type is pancreatic ductal adenocarcinoma – about eighty out of a hundred of all pancreatic cancers (80%).
- Endocrine tumours (also called neuroendocrine tumours) starting the cells that produce hormones. Less than five in a hundred (5%) of all pancreatic cancers are endocrine tumours. Exocrine and endocrine tumours behave differently and are treated differently.

One type of staging uses numbers to describe the stage of the cancer [3].

2.3 Different Stages of Pancreatic Cancer

Stage 1

The earliest stage – the cancer is contained inside the pancreas. This is known as early, localized or resectable pancreatic cancer. It may be possible to operate to remove the cancer (resectable).

• Stage 1A means that the cancer is smaller than 2cm.

• Stage 1B means that the cancer is larger than 2cm

Stage 2

The cancer has started to grow into the duodenum (first part of the small intestines), bile duct or tissues around the pancreas, or there may be cancer in the lymph nodes near the pancreas. Lymph nodes are small glands found around the body, which are part of the immune system. This may be resectable pancreatic cancer – it may be possible to operate to remove the cancer, depending on how far it has grown.

• Stage 2A means that the cancer is larger than 4cm and has started to grow outside the pancreas but has not spread to the lymph nodes.

• Stage 2B means the cancer has spread to nearby lymph nodes.

Stage 3

The cancer has spread into the stomach, spleen, large bowel or into large blood vessels near the pancreas. This is usually locally advanced or unresectable pancreatic cancer, which means it is not possible to remove the cancer with surgery (unresectable). However, it may very occasionally be borderline resectable cancer, which means it may be possible to remove the cancer, but it depends which blood vessels are affected.

Stage 4

The cancer has spread to other parts of the body such as the lungs, liver or peritoneum (the lining inside the tummy wall). This is known as advanced or metastatic pancreatic cancer. It is not possible to remove the cancer with surgery (unresectable), as surgery can't remove all the cancer cells once they have spread to other parts of the body [4].

2.4 Pancreatic Cancer Risk Factors

A risk factor is anything that increases your chance of getting a disease such as cancer. Different cancers have different risk factors. Some risk factors, like smoking, can be changed. Others, like a person's age or family history, can't be changed.

In some cases, there might be a factor that may decrease your risk of developing cancer or has an unclear effect. That is not considered a risk factor, but you may see them noted clearly on this page as well.

Having a risk factor, or even many, does not mean that you will get cancer. And some people who get cancer may have few or no known risk factors. Here are some of the risk factors known to increase your risk for pancreatic cancer

- Smoking (20% of pancreatic cancers are caused by smoking)
- Age older than 55 years old
- Diabetes

- Obesity
- Chronic pancreatitis
- Cirrhosis of the liver
- *Helicobacter pylori* infection
- Work exposure to chemicals in the dry cleaning and metalworking industry
- Family history

Possible risk factors include heavy alcohol consumption, coffee consumption, physical inactivity, high red meat consumption, and two or more soft drinks per day.

2.5 Epidemiology

Analysis of the epidemiology of pancreatic cancer may be the key to understanding the etiology of pancreatic cancer and therefore the cornerstone of creating an efficient policy of avoidance.

2.6 Statistics of Pancreatic Cancer

The incidence of pancreatic cancer varies across regions and populations (Figure 3). In 2018, 458,918 new cases of pancreatic cancer were registered worldwide, representing 2.5% of all cancers. The age-standardized rate (ASR) incidence was highest in Europe (7.7 per 100,000 people) and North America (7.6 per 100,000 people), followed by Oceania (6.4 per 100,000 people). The lowest rate was observed in Africa with an estimated incidence of 2.2 per 100,000 people. Differences in incidence rates were 30-fold between the populations at the highest rate (Hungary: 10.8), and the populations with the lowest rate (Guinea: 0.35).

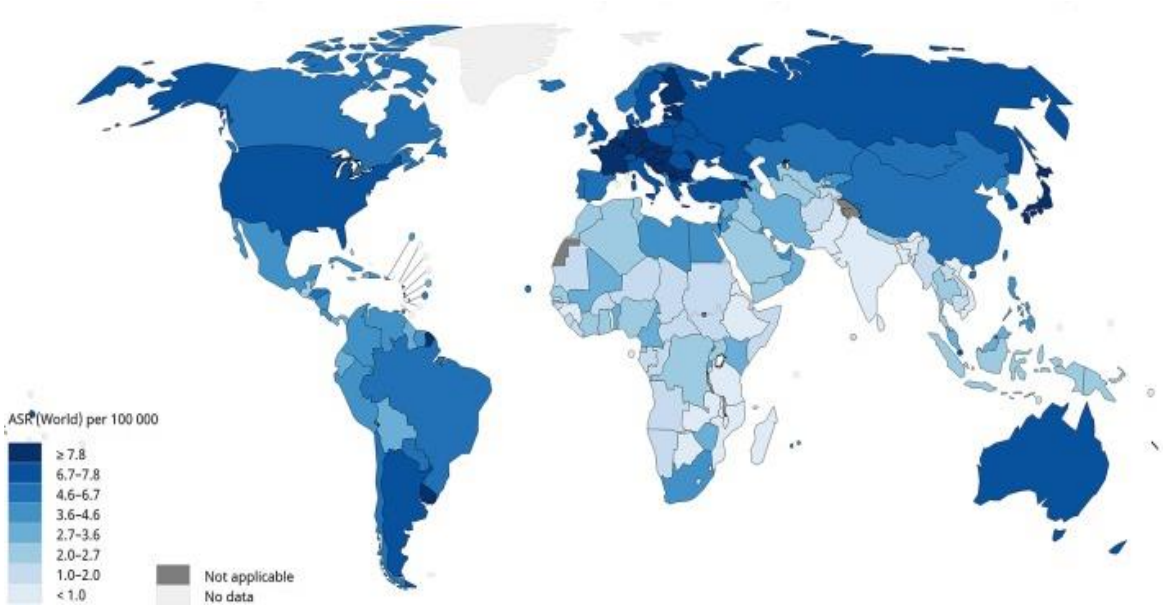

Figure 3: Map shows estimated age-standardized incidence rates (ASR) for pancreatic cancer worldwide in 2018, including both sexes and all ages

Slight difference in pancreatic cancer incidence among genders as well as a significant different geographic distribution was observed. It is more common in men (5.5 per 100,000; 243,033 cases) than in women (4.0 per 100,000; 215,885 cases). In men, the risk of developing pancreatic cancer is high in Central and Eastern Europe. Particularly Latvia and Republic of Moldova (15.3), Estonia (14.2) and Hungary (12.9). Followed by Uruguay (12.0) and Japan (11.7), while the lowest rates are recorded in Guinea (0.23) and Malawi (0.30). The regions with the highest incidence of pancreatic cancer in women are Western Europe (7.2), North America (6.5), and Northern Europe and Australia/New Zealand (equally: 6.4). The regions with the lowest risk (less than 1.0 per 100,000) of contracting pancreatic cancer in women are Eastern Africa and South-Eastern Asia. There is no recorded case of pancreatic cancer for both sexes in the African regions of Comoros and Sao Tome and Principe [5].

2.7 Diagnosis

Pancreatic cancer is mostly diagnosed in an advanced stage, and 80-90% of patients have unresectable tumors now of diagnosis. There are several reasons because this occurs.

First, early-stage pancreatic cancer is usually clinically silent, and most people who present with symptoms attributable to pancreatic cancer have advanced disease. Symptoms are non-specific and include abdominal pain, jaundice, pruritus, dark urine and acholic stools, which may be presenting

symptoms as a result of an obstruction within the biliary tree. Furthermore, anorexia, weight loss (which can arise from anorexia), early satiety, dyspepsia and nausea occur too, while less common manifestations include panniculitis and depression.

Given the wide range of non-specific symptoms, there are a broad number of diseases that need to be differentiated, which include but are not limited to: cholangitis, cholecystitis, cholelithiasis, choledocholithiasis, choledochal cysts, duodenal or gastric ulcers, gastritis, pancreatitis, abdominal aortic aneurysm, lymphomas, and primary or secondary cancers of the biliary tree, liver, pancreas, stomach or intestine. Therefore, diagnosis can be delayed or missed, which makes pancreatic cancer the most common tumor detected at the autopsy studies. To date, there are several diagnostic tools available, such as abdominal ultrasonography, tri-phasic pancreatic-protocol CT (which is the standard for diagnosis and staging), magnetic resonance imaging (MRI) and endoscopic ultrasound-guided fine-needle aspiration for cytological diagnosis (which sensitivity is reported to be about 80%). Additionally, in symptomatic patients, measurement of blood levels of cancer antigen 19-9 can help to confirm the diagnosis and predict prognosis and recurrence after resection; however, it cannot stand as an individual screening tool for asymptomatic patients because it is not tumor specific [6]. Many options are available to treat pancreatic cancer and depending on the stage of cancer, possible side effects and health of the patient. A multidisciplinary team of different types of doctors work out a plan which combines various options and present the best one for the patient.

2.8 Measurement of pancreas stiffness

The surgeon who performed the operation subjectively evaluated the pancreatic hardness by palpation during the operation before resection of the pancreas. The pancreatic hardness was classified into the following four categories: very hard, hard, soft or very soft. Objective measurement of the pancreatic hardness was performed by the same surgeon during the operation using a durometer.

An enlarged pancreas can occur for many reasons. The pancreas is a gland that sits behind your stomach in the upper abdomen and helps with digestion. It produces enzymes that are secreted into the small intestine, digesting protein, fat, and carbohydrates.

Causes of an Enlarged Pancreas, an enlarged pancreas may mean nothing. You may simply have a pancreas that is larger than normal. Or, it can be because of an anatomic abnormality. But other causes of an enlarged pancreas may include the following:

- Pancreatitis occurs when digestive enzymes become active inside the pancreas, attacking and damaging its tissues. This can cause an enlarged pancreas.
- **Acute pancreatitis** is inflammation that occurs suddenly in the pancreas. It can be very serious, even life-threatening. But it usually goes away within a few days of treatment. Gallstones and alcohol are common causes of acute pancreatitis. Other causes include high levels of fats in the blood, certain drugs, certain medical procedures, and some infections[6].
- **Chronic pancreatitis** is inflammation that gets worse over time and leads to permanent damage in the pancreas. Heavy alcohol use is the most common cause. Other causes include heredity, cystic fibrosis, high levels of calcium or fats in the blood, certain medications, and some autoimmune conditions.
- **Pancreatic pseudocyst** is an accumulation of fluid and tissue debris in the pancreas, which can occur after a case of pancreatitis.

3.Type of surgeries

3.1 The Whipple's operation

The Whipple's operation is one of the most common types of surgery for pancreatic cancer. It's usually used for tumors in the head of the pancreas that haven't spread beyond the pancreas. The surgeon will remove the head of the pancreas. They also remove:

- The lower end of the stomach
- The duodenum (first part of the small intestines)
- The gall bladder (which stores a fluid called bile which helps digestion)
- Part of the bile duct (which carries bile from the liver to the duodenum)
- Surrounding lymph nodes (part of the immune system).

They then attach the remaining part of the stomach and bile duct to the small intestines. The pancreas is attached to the small intestines or to the stomach (Figure 4).

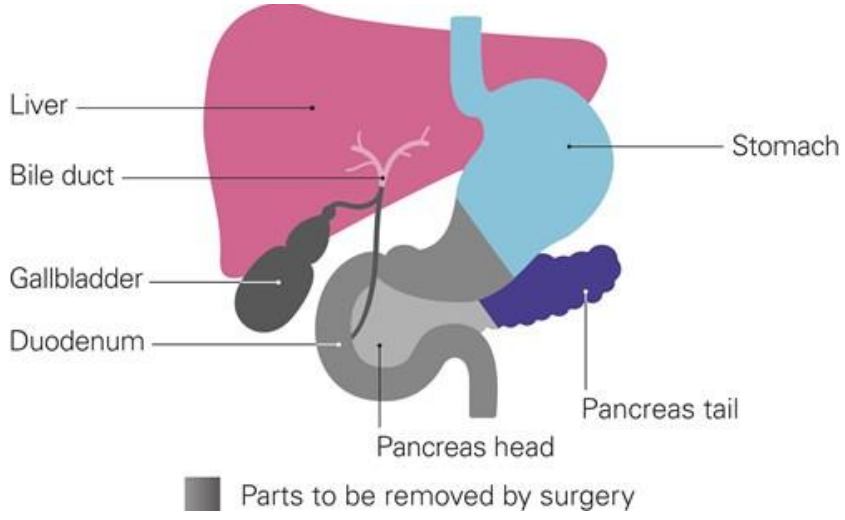

Figure 4 : Parts of the body to be removed by a Whipple's operation

As part of pancreas is removed during a Whipple's operation (Figure 5), the digestion will be affected, and patient will probably need to take pancreatic enzyme supplements. There is also a risk of getting diabetes [7].

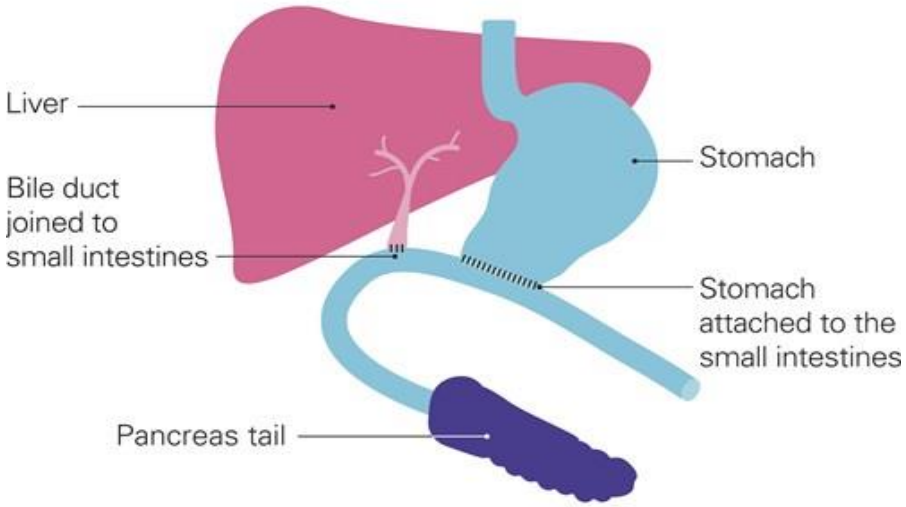

Figure 5 :The pancreas and surrounding organs after a Whipple's operation

3.2 Pylorus-preserving pancreaticoduodenectomy (PPPD)

This operation is like the Whipple's operation, but none of the stomach is removed. The stomach valve (the pylorus), which controls the flow of food into the duodenum, isn't removed either. The tail of the pancreas is joined to the small intestines or stomach [8].

The digestion may be affected, and patient will probably need to take pancreatic enzyme supplements. There is also a risk of getting diabetes.

3.3 Distal pancreatectomy

A distal pancreatectomy involves removing the body and tail of the pancreas (Figure 6). The spleen is also often removed. The spleen helps the body to fight infections, so if it's removed, the patient will be more at risk of infections. Usually before surgery, the patient will be given vaccinations against some infections, and the patient will need to take antibiotics for the rest of life.

The digestion may be affected, and patient will probably need to take pancreatic enzyme supplements. There is also a risk of getting diabetes [9].

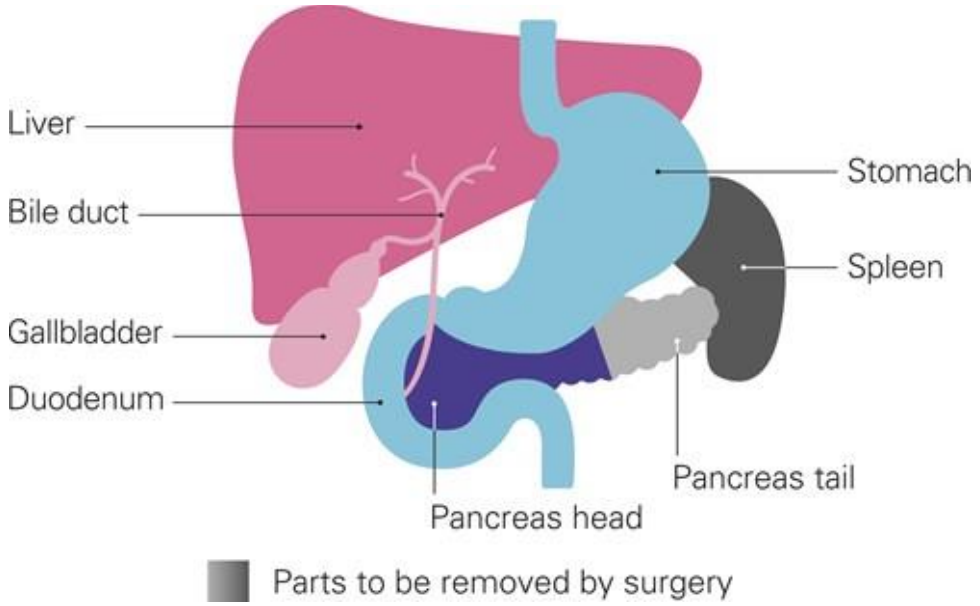

Figure 6 : Schema of a distal pancreatectomy

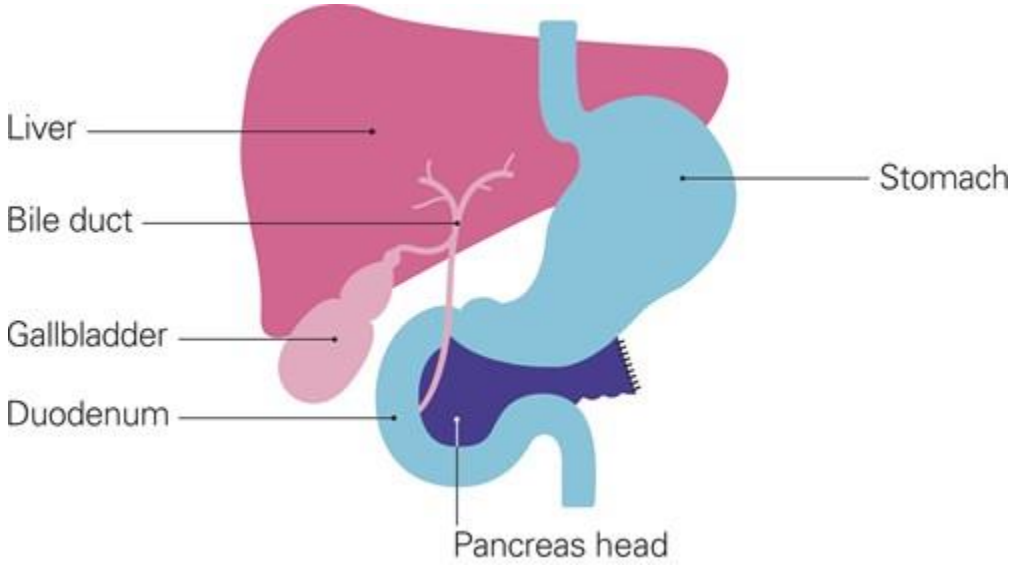

Figure 7: Pancreas and areas around it after a distal pancreatectomy

3.4 Total pancreatectomy

A total pancreatectomy involves removing the whole pancreas, the duodenum, the gall bladder, part of the bile duct and sometimes part of the stomach (Figure 8). Exactly what is removed will depend on where the cancer is located. It is done when there is a large tumor, or more than one tumor in the pancreas. As the whole pancreas is removed (Figure 9), the patient will need to take pancreatic enzyme supplements. There is also a risk of getting diabetes.

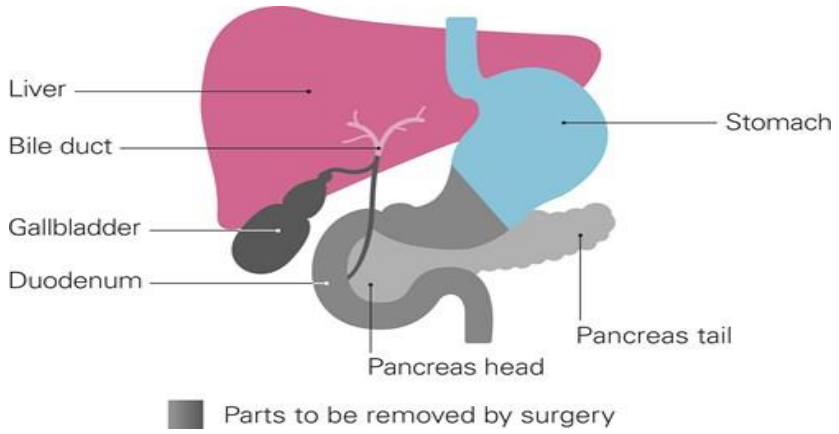

Figure 8 : Schema of a total pancreatectomy

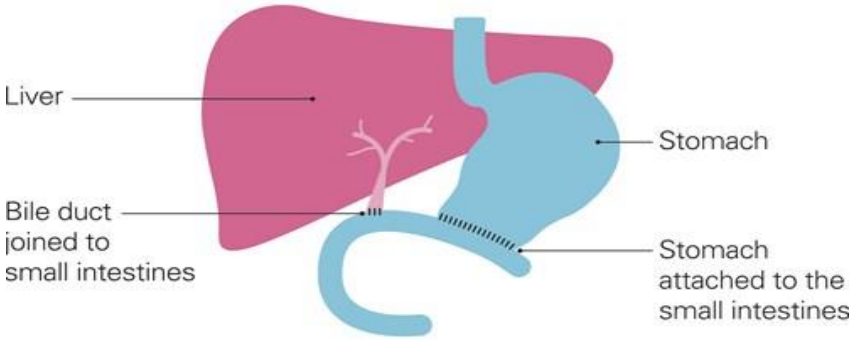

Figure 9: Pancreas and areas around it after a total pancreatectomy

Descriptions of the common types of treatments used for pancreatic cancer are listed below, followed by an outline of treatments by stage. The current treatment options for pancreatic cancer are surgery, radiation therapy, chemotherapy, targeted therapy, and immunotherapy etc. The care plan also includes treatment for symptoms and side effects, an important part of cancer care.

Palliative – Performed if the cancer cannot be removed and only the symptoms can be relieved and the quality of life of the patient can be improved

Biliary bypass- If the tumour blocks the small intestine, it leads to bile build up in the gall bladder. Then a biliary bypass can be done wherein the doctor cuts the gall bladder or bile duct and connects it to the small intestine.

Stent placement- Followed if the tumour is blocking, he bile duct. A stent is placed and help drain the bile build up. The stent can be placed through a catheter which drain the bile outside the body or redirects the bile to the small intestine

.

Gastric bypass- When the tumour blocks the stomach, it is sewn directly to the small intestine to help the patient eat normally.

Ablative techniques – When the tumour has metastasized, the following techniques can be used:
Radiofrequency Ablation (RFA) – A probe is inserted into the tumour through which radiofrequency waves travel, heat up the tissue and destroy it.
Microwave therapy- Microwaves are used in similar method to destroy tumour cells.
Cryosurgery or cryoablation- A probe is introduced which uses liquid nitrogen or carbon dioxide to freeze and destroy the tumour cells.

Embolization- Introduction of small emboli (A clot, bubble, etc.) in the blood vessel feeding the tumour cuts of blood supply to the tumour and kills it.

Radiation therapy- Usage of high energy rays or particles to kill cancer cells. X rays and gamma rays are some examples of types of radiation used.

Chemoradiation- It is the combination of chemotherapy with radiation ans is used to treat widely spread cancer cells.
Radiation therapy has numerous side effects as these high energy rays can kills normal cells as well. Low blood cell count leads to a higher risk of infection.

Chemotherapy and other anti-cancer drugs- Usage of drugs (chemicals) like cytotoxic anti neoplastic substances to kill the cancer cells. These drugs can kill the cells or prevent them from dividing any further. The drugs can be injected orally or intra- venously. Chemo can be used at any stage of cancer usually during the advanced stages when surgery will not be helpful. It can be combined with surgery

Systemic chemotherapy- When the drugs are taken orally or injected into a vein or muscle, they enter the bloodstream and reach cancer cells throughout the body.

Regional chemotherapy- When the drugs are introduced into the cerebrospinal fluid, body cavity like the abdomen, only the regional cells are killed.
Combination chemotherapy- It uses more than one chemotherapeutic drug.
Common chemotherapeutic drugs: gemcitabine, fluorouracil, capecitabine, cisplatin and oxaliplatin.

Targeted therapy- Drugs and other substances are used to attack only the tumour cells. In this way the normal cells will not be affected. Cell signalling pathway proteins are one of the main targets of this therapy. One example of such a drug is Erlotinib which is a type of tyrosine kinase inhibitor which blocks the cell signals for tumour growth. Others can induce direct apoptosis.

4.Pancreatic Fistula

4.1 Definition

The term ' fistula ' is used to define an unusual transition from one epithelialized layer to another. A comprehensive search for literature does not give POPF a universal concept. The problem is further complicated using concepts such as leakage, leakage, collection, anastomotic inability and anastomotic insufficiency. Worldwide, pancreatologists have used the following different terms to define POPF. Drainage fluid exceeding 50 mL in 24 hours with amylase content exceeding 3 times the normal serum amylase activity for more than 10 days after operation. Drainage of more than 10 mL of amylase fluid in 24 hours at least three times the normal serum activity, 3 or 4 days after surgery. Post-operative fluid drainage comprising amylase activity more than 3 times serum exercise for more than 7 days.

It has been suggested that the notion of clinically important leakage involves fever (> 38° C), leukocyte counts higher than 10,000 cells/mm^3, sepsis and/or water requirements. The literature was studied by an International Study Group on Pancreatic Fistula (ISGPF), created by an international consortium of 37 major pancreatic surgeons from 15 nations, addressed their clinical experiences with POPFs and suggested description and classification. ISGPF has defined POPF as ‘an abnormal communication between pancreatic ductal epithelium and another epithelial surface, containing pancreas derived enzyme rich fluid.’ Interestingly, this definition also includes clinically asymptomatic patients and for the same reason a grading system (Grade A, B and C) has been proposed to assess the severity of POPF [10].

4.2 CLASSIFICATION

4.2.1 High or Low Output Fistula

A fistula is called a high output fistula when output in 24 hours is greater than 200 mL and output is lower when output in 24 hours is less than 200 mL. However, for both groups the incidence of spontaneous resolution is similar.

4.2.2 Pure or Mixed Fistula

A fistula that drains only pancreatic juice is called a pure fistula, while a mixed fistula is a fistula that drains pancreatic juice mixed with entry content. The production of a pure POPF includes and is comparatively inert, inactive pancreatic enzymes. A mixed POPF's output contains activated proteases that can cause additional complications such as necrosis and hemorrhage.

4.2.3 End or Side Fistula

An end fistula results from disruption of main pancreatic duct. The two portions of pancreas are not continuous and tend to heal separately. This condition is termed “disconnected duct syndrome”. End fistulae are unlikely to heal on conservative management because of discontinuity from the gastrointestinal tract and the remaining pancreatic duct. In addition, end fistulae are not suitable for transpupillary stent positioning. On the contrary, the continuity of the pancreatic duct was preserved in a side fistula. The likelihood of side fistula healing with conservative leadership is greater. Side fistulae may be inflammatory or postoperative, the latter may react faster to medical therapy than inflammatory fistulae [11].

4.3 Fistulae after PD

The incidence ranges from 0-24% with an average fistula rate of 12.9% following PD .The mortality rate from a major pancreatic fistula is up to 28% and the usual cause of death is retroperitoneal sepsis and hemorrhage [12].

Grading system to assess the severity of Post-operative pancreatic Fistula are given below (Table 1) Henegouwen et al [12].

Table 1: Grading system to assess the severity of POPF			
Grade	**A**	**B**	**C**
Clinical conditions	Well	Often well	Ill appearing/Bad
Specific treatment	No	Yes/No	Yes
Ultrasonography/Computed tomography	Negative	Negative/Positive	Positive
Persistent drainage	No	Usually yes	Yes
Reoperation	No	No	Yes
Death related to POPF	No	No	Possibly yes
Signs of infections	No	Yes	Yes
Sepsis	No	No	Yes
Readmission	No	Yes/No	Yes/No

4.4 Fistulae after DP

POPF is a common complication after DP with an incidence of 5-28% (Table 2).

Classification scheme for grading complications arising after PD applicable to all complications arising from PD and not just postoperative pancreatic fistula (POPF).

Grading complications arising after PD are given below (Table 2) Henegouwen et al [12].

Table 2 : Classification scheme for grading complications arising after PD applicable to all complications arising from PD and not just postoperative pancreatic fistula (POPF).

Grade	**Definition**
I	Any definition from the normal post-operative course without pharmacologic treatment or surgical, endoscopic and radiological interventions. Allowed therapeutic regimens are drugs such as antiemetics, antipyretics, analgesics, diuretics, electrolytes and physiotherapy. This grade also includes wound infections opened at the bed side.
II	Requiring pharmacologic treatment with drugs other than ones allowed for grade I complications. Blood transfusion and total parenteral nutrition are also included
III - IIIa - IIIb	Requiring surgical, endoscopic or radiologic intervention. - Intervention not under general anesthesia. - Intervention under general anesthesia.
IV - IVa - IVb	Life threatening complication requiring Intermediate care/ Intensive care unit management. - Single-organ dysfunction - Multiorgan dysfunction
V	Death of a patient
Suffix "d"	If the patient suffers from a complication at the time of the discharge, the suffix "d" (for disability) is added to the respective grade of complication (including resection of pancreatic remnant). This label indicates the need for a full follow-up to fully evaluate the complication.

5.Risk Factors for POPF

Risk factors for pancreatic leakage include general patient-related risk factors (age, gender, jaundice, and malnutrition), disease-related risk factors (pancreatic pathology, pancreatic texture, pancreatic duct size, pancreatic juice output), and procedure related factors (operative time, resection type, anastomotic technique, intraoperative blood loss). In addition, surgeons experience has been shown to correlate with pancreatic anastomotic leakage rate and in some reported cases the prophylactic use of somatostatin

Risk factors can be classified as

- Patient factors
- Disease related factors

5.1 Patient Factors

Though male sex is seen to be associated with increased risk for POPF, no specific reason has been found for this phenomenon. Similarly age greater than 70 years is associated with increased risk for POPF. Other risk factors for POPF that have been evaluated in various studies include duration of jaundice, creatinine clearance and intraoperative blood loss. But none of these are found to have a definitive relation with POPF [13].

5.2 Disease Related Factors

Pancreatic texture, pancreatic pathology, high pancreatic juice output, pancreatic duct size and biochemical parameters are factors seen to contribute towards POPF.

5.2.1 Pancreatic Texture

The texture of the pancreas is generally associated with the fundamental disease mechanism. It is commonly recognized that a fibrotic pancreatic residue in chronic pancreatitis maintains the pancreatic anastomosis well, while a smooth friable pancreas observed in pancreatic or periampullary cancer generally betrays. Several studies have justified this concept. A study of 2644 physicians who had experienced PD prior to 1991 revealed a fistula level of 5% in acute pancreatitis, 12% in pancreatic cancer, 15% in ampullary disease, and 33% in bile duct cancer. Yeo et al [14] discovered a powerful connection between pancreatic texture and pancreatic fistula rate. In their study, none of the 53 patients with hard pancreatic remnants developed pancreatic

fistula, whereas 19 of 75 patients (25%) with soft pancreatic texture developed POPF. Other studies too show similar results regarding POPF and pancreatic texture [14].

5.2.2 High Pancreatic Juice Output

A high pancreatic juice output was considered an important factor contributing to POPF in setting a nondilated duct in a soft textured pancreas. Ishikaw et al.[15] reported significantly reduced POPF rates after PD among patients who received preoperative radiation therapy compared with patients who did not, and they have even suggested that preoperative radiation therapy might reduce the risk of POPF by decreasing pancreatic secretion.

5.2.3 Size of the Pancreatic Duct

A small sized pancreatic duct has been suggested as a risk factor for POPF. In a study[15], which included 62 patients who underwent PD, the incidence of POPF was 4.88% among patients with a pancreatic duct size greater than or equal to 3 mm and was 38.1% in those with ducts smaller than 3 mm.

5.2.4 Biochemical Parameters

Various biochemical parameters like serum bilirubin, serum albumin, blood urea nitrogen (BUN), serum amylase and N-benzoyl-L-tyrosyl-p-aminobenzoic acid (BT-PABA) excretion test values have been evaluated as risk factors for POPF. A normal preoperative BT-PABA test value has been suggested as a risk factor for POPF [15].

6. Technical Aspects

Appropriate management of the pancreatic remnant has been one of the core issues regarding prevention of POPF. Some of the recommended methods for the management of pancreatic remnant include

1. Pancreatic duct ligation
2. Pancreatic duct obliteration
3. Pancreatojejunostomy (PJ)
4. Pancreaticogastrostomy (PG)

6.1 Pancreatic Duct Ligation

Ligation of the pancreatic duct of the pancreatic remnant was one of the earliest practices in the management of the pancreatic remnant. However, this procedure is associated with a high incidence of pancreatic fistula, infection and inevitable pancreatic insufficiency. Even though ligation technique was uniformly associated with a high incidence of fistula, the resultant complications were not fatal because of the non-activated enzymes in the fistula output. Bartoli and colleagues in a metanalysis concluded that although ligation was associated with a significantly higher fistula rate compared with anastomosis, the mortality rates were not significant [16].

6.2 Pancreatic Duct Obliteration

Obliteration of the pancreatic duct with fibrin glue or synthetic polymers have shown to result in a low pancreatic fistula rate of 4% to 7%. This technique carries the advantage of being technically easier and less time consuming to perform as compared with pancreatoenteric anastomosis. However, it has the disadvantage of being incomplete and is associated with physiological disturbances.

6.3 Pancreatojejunostomy (PJ)

Jejunum is a good choice for reconstructing the drainage of pancreatic remnant because of its good vascularity and mobility. The anastomosis between pancreatic remnant and jejunum could be:

• End-to-side duct-to-mucosa anastomosis, wherein the pancreatic duct is anastomosed to the mucosa on the antimesenteric border of the jejunum. The cut margin of the pancreas is then circumferentially opposed to the jejunal wall with seromuscular sutures.

• End-to-end invagination technique (dunking method), wherein end-to-end anastomosis between pancreatic remnant and jejunum is achieved in two layers. The inner layer approximates the cut margin of the pancreas to the full thickness of the jejunal wall. The sutures of this layer should incorporate pancreatic duct to splay the duct. The outer layer circumferentially opposes the capsule of the pancreas to the seromuscular coat of the jejunum.

• End-to-side invagination technique, which is like dunking method, except that the anastomosis is between the cut surface of the pancreatic remnant to the antimesenteric aspect of the jejunum [17].

6.4 Comparison of Different Techniques of PJ's

The debate on the technique of PJ having a favorable outcome remains unsettled. Although several studies have compared various techniques of PJ, a consensus is yet to be arrived at. Studies from 1980s did not find any significant difference in the pancreatic fistula rate among different techniques of PJ. A meta-analysis of 2361 patients who underwent PD before 1991 found significantly higher incidence of POPF with end-to-side invagination anastomosis compared with duct-to-mucosa anastomosis[28]. Few non-randomized studies have suggested that duct-to-mucosa anastomosis may be associated with lower POPF rate compared with invagination technique. Studies have also compared continuous and interrupted duct-to-mucosa anastomosis, wherein continuous duct to- mucosa anastomosis was found to have a significantly lower leakage rate.

Retrospective studies comparing duct-to-mucosa and dunking technique for PJ have not found any statistical difference between the two in preventing anastomotic failure. Marcus et al[18] found that duct-to-mucosa anastomosis was associated with a low pancreatic fistula rate in low risk patients with dilated pancreatic duct or firm fibrotic pancreas, whereas end-to-end invagination technique was safer in high risk patients with small ducts or soft friable pancreas and this opinion is shared by other workers as well.

To summarize, there is still no consensus regarding the choice of anastomotic technique for PJ. Different techniques find their application among different group of surgeons. It is preferable for pancreatic surgeons to have more than one technique in their armamentarium for managing the pancreatic remnant. Ultimately a well-designed prospective randomized study will be required to prove the superiority of one technique over the other [18].

6.5 Pancreaticogastrostomy (PG)

PG involves an anastomosis between residual pancreatic stump and posterior wall of stomach. The anastomosis is accompanied by implantation of the pancreatic stump into stomach or by creating a mucosa-to-mucosa anastomosis. PG as a technique for reconstruction after PD was first introduced in 1946. However not much attention was paid to this technique until in 1990s when there was an emergence of renewed interest in PG. Proponents of PG claim the following potential advantages over PJ [19].

The natural close apposition between stomach and pancreas facilitates a tension free anastomosis A long jejunal loop with its retained secretion that may exert a traction effect on anastomosis is avoided. The thick and vascularized gastric wall provides excellent blood supply to the anastomosis. There is incomplete activation of pancreatic enzymes in the stomach because of acidic environment absence of enterokinase. Provision for easy monitoring of duct patency by nasogastric amylase estimation in the early postoperative period and long-term access for radiological and endoscopic evaluation. The major complication with PG is gastrointestinal bleeding presumably from the pancreatic stump [19].

6.6 Pancreatojejunostomy vs Pancreaticogastrostomy

Several studies have compared PJ and PG with respect to the incidence of POPF. Published single institutional studies have favored PG over PJ[27]. A large meta-analysis has shown a significantly lower incidence of pancreatic fistula after PG as compared to end-to-end or end-to-side PJ. In this meta-analysis, there were no significant differences in mortality between the two groups. However, the definition of pancreatic fistula was not uniform among studies included in this meta-analysis.

A prospective, randomized single institution study comparing PG with PJ concluded that the incidence of POPF as well as other postoperative complications and length of postoperative stay were similar among PG and PJ groups. A meta-analysis concludes that PG is the safer method of reconstruction following PD, as PJ is associated with a higher incidence of POPF. However, another recent systematic review and meta-analysis of randomized control trials show no differences in outcomes irrespective of the method of pancreatic anastomosis after PD [20].

6.7 Prevention of POPF

The measures recommended to prevent POPF following PD can be considered under following categories

- Pharmacological measures
- Preoperative irradiation
- Modifications in operative techniques

Pharmacological Measures

A high pancreatic juice output in a soft pancreas is an important risk factor for POPF. Hence it appears rational to hypothesize that inhibition of exocrine pancreatic secretion in the postoperative period may reduce the incidence of POPF. Somatostatin and its octapeptide analogue have been used by various groups to reduce the pancreatic juice secretion and thereby prevent POPF (Figure 10). A German group was the first to report reduced complication rate after PD with

perioperative infusion of somatostatin [21]. Subsequently many other studies have evaluated the effect of somatostatin/octreotide in preventing and lowering the incidence of POPF.

Most European studies which included various pancreatic surgeries for different pancreatic pathologies opined that somatostatin/octreotide reduces the incidence of POPF. On the contrary, American studies did not show any benefit from prophylactic use of octreotide. The exact reasons for the different outcomes between European and American trials are not clear but the suggested reasons were [21]. Difference in the study designs - The European trials were all multi-institutional and thus the surgical techniques were not standardized, while the American studies were conducted in a single institution with a high volume of pancreatic surgery; Inclusion of various pancreatic procedures in the European trials, whereas the American trials concentrated exclusively on PD; Heterogeneity in the pathological diagnosis; Different criteria used for defining pancreatic fistula.

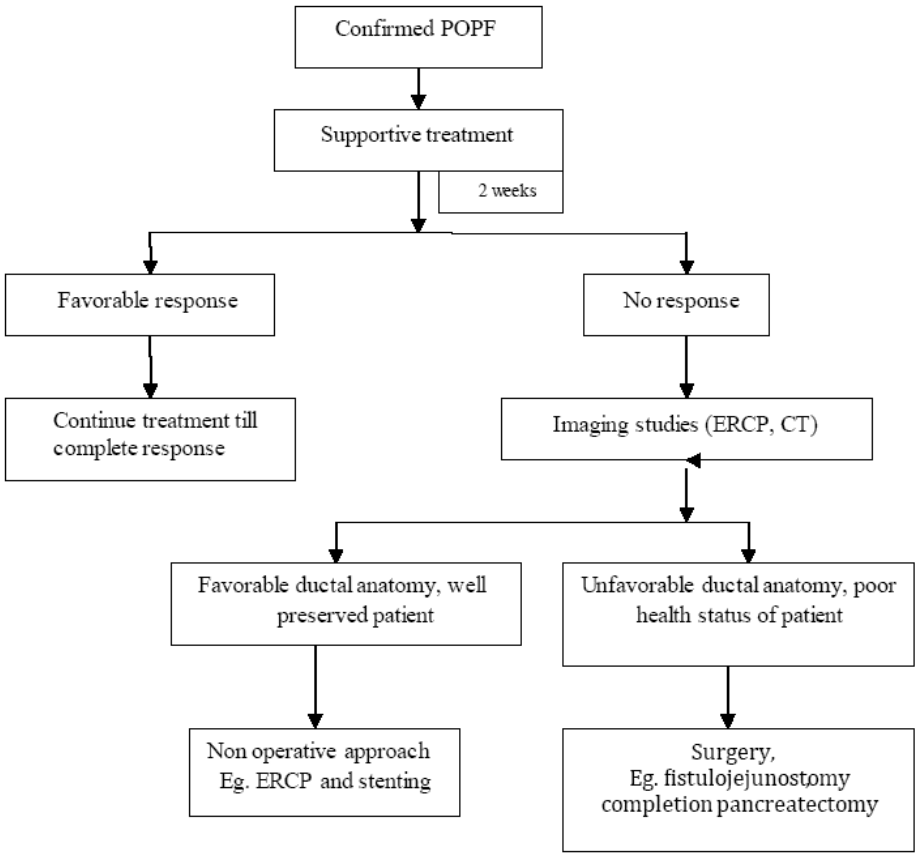

Figure 10: Management of POPF

It has been suggested that for PD's performed by highly specialized units, octreotide may not have a benefit with already low POPF rates, whereas it may have a potential benefit in operations performed by less experienced surgeons. A meta-analysis regarding the prophylactic use of octreotide in pancreatic resections on the fore mentioned randomized control studies concluded that, There were no significant differences between octreotide and control groups in the frequency of local complications, There were no significant differences between octreotide and control groups in the frequency of local or systemic complications which often develop because of pancreatic anastomotic leakage[22].

7. Suture Material and Methods

Data from 270 successive PDs were gathered in a prospectively generated database between March 2013 and September 2014[22]. All surgical procedures were performed at the University of Verona Hospital, General Surgery B-The Pancreas Institute under the direct supervision of three expert surgeons. The study included only PD, both with antrectomy or preservation of Pylorus, with PJ resulting in a total of 130 PDs. Using a single transmesocolic jejunal limb, where PJ is first conducted in an end-to-side manner, the reconstruction can be accomplished after performing PD. Then an end-to-end HJ is performed.

The reconstruction is finished by an end-to-side ante colic duodenojejunostomy (or gastrojejunostomy in the case of Whipple operation). The overall strategy is to carry out a straightforward dunking PJ in dealing with a pancreatic relic with a difficult texture and a dilated duct. In the case of a soft pancreatic impurities with a small duct, a duct-to-mucosa PJ is performed using interrupted stitches (absorbable or non-absorbable) for the anterior and posterior layers and four polypropylene stitches for the Wirsung duct. Each patient received subcutaneous octreotide 0.1 mg three times daily as a remedy for POPF until drains were removed in non-complicated instances or as soon as was essential for POPF [23].

The study population included 65 cases in which PJ was performed using absorbable sutures and 65 cases using non-absorbable sutures (Table 3). In every surgical procedure, the expert surgeon supervisor was responsible for the choice of the type of suture material at the time when PJ was carried out. PJs performed with absorbable sutures were carried out using monofilament polydioxanone (n = 65) (PDS II®, Ethicon). Non-absorbable sutures used for PJ were: braided polyester (n = 42) (TiCron®, Covidien), coated braided silk (n = 15) (Sofsilk®, Covidien), coated monofilament polybutester (n = 8) (Vascufil®, Covidien). Influence of suture material and of other well-known variables in determining POPF was investigated. POPF was defined and classified as reported by ISGPS as well as other complications like DGE and PPH [23].

Patients' demographic data, pre-operative, intra-operative and post-operative characteristics are given below (Table 3) Gurusamy KS et al [22].

Table 3 : Patients characteristics: Absorbable vs. Non-Absorbable sutures.

		Absorbable sutures (n = 65)	**Non absorbable sutures (n = 65)**	***P***
Gender	Male	32 (49.2%)	30 (46.1%)	0.72
	Female	33 (50.8%)	35 (53.9%)	
Age (median, range)		62 (36–80)	65 (18–82)	0.24
BMI (mean, SD range)		24.7 (±3.1; 17.7–30.9)	23.9 (±3.4; 17–30.4)	0.28
Diabetic		10 (15.3%)	10 (15.3%)	0.93
Jaundice		33 (50.8%)	35 (53.8%)	0.86
Biliary drainage		25 (38.4%)	29 (44.6%)	0.57
Type of surgery	WPD	4 (6.1%)	5 (7.7%)	0.56
	PPPD	61 (93.9%)	60 (92.3%)	
Vascular resection		3 (4.6%)	3 (4.6%)	1
Texture	Hard	24 (36.9%)	19 (29.2%)	0.28
	Soft	38 (58.5%)	45 (69.2%)	
MPD diameter (mm, mean, SD, range)		4 (±2.1; 1–12)	4 (±2.1; 2–12)	0.18
Operating Time (min, mean, SD, range)		387 (±76; 210–510)	421 (±64; 275–585)	0.65
LHS (days, median, range)		9 (6–75)	8 (5–50)	0.11
Histology	PDAC	34 (52.4%)	38 (58.5%)	0.77
	IPMN	10 (15.3%)	8 (12.4%)	
	Ampullary cancer	6 (9.3%)	6 (9.2%)	

	NET	1 (1.5%)	2 (3%)	
	Other	14 (21.5%)	11 (16.9%)	
POPF		20 (30.8%)	15 (23.1%)	0.32
	Grade A	4 (20%)	2 (13.3%)	0.05*
	Grade B	10 (50%)	13 (86.7%)	
	Grade C	6 (30%)	0	
PPH		10 (15.3%)	2 (3%)	0.01*
DGE		4 (6.2%)	2 (3%)	0.41
Biliary fistula		6 (9.3%)	1 (1.5%)	0.06
Post-operative hyperamylasemia		15 (24.2%)	17 (26.2%)	0.64
Re-laparotomy		7 (10.8%)	2 (3%)	0.08
Death		2 (3%)	0	0.15

The sub analysis between polydioxanone(absorbable) and Polyester(non-absorbable) are texted in the below (Table 4)

Table 4 : Sub-analysis – patients characteristics: Polydioxanone vs. Polyester.

		Polydioxanone (n = 65)	**Polyester (n = 42)**	***P***
Age (median, range)		62 (36–80)	66 (18–82)	0.21
BMI (mean, SD, range)		24.8 (±3.1; 17.7–30.9)	24 (±3.3; 19–30.4)	0.42
Texture	Hard	23 (36.5%)	17 (40.5%)	0.77
	Soft	38 (60.3%)	25 (59.5%)	
MPD diameter (mm, median, range)		4 (1–12)	4 (2–10)	0.12
Operating time (mean, min, SD, range)		387 (±76; 210–510)	427 (±62; 275–585)	0.21

LHS (days, median, range)		9 (6–75)	8 (5–50)	0.02*
Histology	PDAC	34 (54%)	23 (54.7%)	0.81
	IPMN	9 (14.3%)	7 (16.7%)	
	Ampullary cancer	6 (9.5%)	4 (9.5%)	
	NET	1 (1.5%)	2 (4.8%)	
	Other	13 (20.7%)	6 (14.3%)	
POPF		20 (31.7%)	5 (11.9%)	0.01*
	Grade A	4 (20%)	1 (20%)	0.05*
	Grade B	10 (50%)	4 (80%)	
	Grade C	6 (30%)	0	
PPH		10 (15.8%)	2 (4.7%)	0.08
DGE		4 (6.3%)	1 (2%)	0.35
Biliary fistula		6 (9.5%)	1 (2%)	0.15
Post-operative hyperamylasemia		15 (23.8%)	9 (21.4%)	0.7
Re-laparotomy		7 (11.1%)	2 (4.7%)	0.25
Death		2 (3.1%)	0	0.12

8.Results

There were no important variations in population information and pre-operative variables between the two communities. As anticipated, there was no distinction in the growth of POPF between the two distinct anastomotic methods. No variations in POPF threat variables such as pancreatic remnant texture, primary pancreatic duct (MPD) diameter and histology between the two communities were recognized. There was no distinction in the POPF level (30.8 % remnant vs. 23.1 %; p= 0.32), but PJ with non-absorbable sutures produced less serious fistulae (grade C) (6 % vs. 0 % p= 0.05) and less important incidents of PPH (15.3% vs. 3% p = 0.01). The allocation of other post-operative problems between the two organizations was comparable. The non-absorbable sutures group included PJs conducted with distinct types of synthesized, natural, braided or monofilament sutures, which resulted in a sub-analysis (Table 4) above comparing two more homogeneous groups: PJs performed with polydioxanone (n = 65) and PJs performed with polyester (n = 42).

Results are summarized in (Table 4) above. Also, in this case there were not differences among pre-operative data and POPF related risk factors. POPF rate was significantly lower in cases of PJ carried out with polyester sutures (31.7% vs. 11.9%; p = 0,01) and, consequently, LHS was also shorter (9 vs. 8 days; p = 0.02). Also, the incidence of other post-operative complications was lower using polyester although this difference was not statistically significant. A third analysis was carried out in order to identify factors associated with POPF.

The univariate analysis confirmed the role of well-known factors, such as pancreatic texture and histology, in influencing POPF. Only the diameter of MPD was not confirmed as a risk factor of POPF, probably due to the sample's meagerness [24]. The other two factors associated to POPF were post-operative hyperamylasemia, which led to a higher risk of POPF, and the use of polyester sutures for PJ that was associated to a lower risk of POPF. At multivariate analysis hard pancreatic texture (OR = 0.05; CI 95% 0.006–0.446; p < 0.01), PDAC at final histology (OR = 0.27; CI 95% 0.09–0.79; p < 0.01) and polyester sutures (OR = 0.15; CI 95% 0.04–0.53; p < 0.01) were

confirmed as factors able to reduce the risk of POPF. Post-operative hyperamylasemia, instead, was associated to a higher risk of POPF (OR = 4.09; CI 95% 1.46–11.4; $p < 0.01$).

Discussion

Different variables have been suggested in comparison to POPF variables linked to illness, patient, surgeon knowledge and surgical method. All these variables lead to the creation of POPF in a distinct way. It continues uncertain whether the sort of anastomotic suture material could affect the development of pancreatic fistula. To the finest of our understanding, this is the first research that addresses the position of suture material in the incidence of POPF in clinical exercise. Each sort of suture has its own mechanical characteristics and generates distinct tissue reactions.

Braided sutures are generally less elastic and have less memory than monofilament sutures. Sutures with less memory often provide higher tightness and safety of the knots. Polydioxanone, a synthetic monofilament absorbable suture, is one of the most elastic, powerful and hard sutures at its origin, but after in vitro use only polyester, a synthetic braided non-absorbable suture retains its initial vigor, toughness and strain at rupture. Mechanical characteristics of each suture are described at the beginning or after in the incubation of skin or subcutaneous tissue. Sutures positioned over the PJ layers are often in touch with extremely digestive liquids such as bile and pancreatic juice. Studies that investigate the impact of pancreatic enzymes on distinct suture products in relation to the usual hydrolytic degradation are not accessible. Non-absorbable sutures are considered permanent, but they can be absorbed over the years.

Early findings indicate that polydioxanone is the only form of suture that can maintain its initial tensile strength in pancreatic juice and bile after incubation. Among non-absorbable sutures, silk retains a decent amount of tensile strength, though worse than polydioxanone. Polypropylene, a synthetic monofilament non-absorbable suture, normally ensures an adequate tensile strength for more than two years, but it loses 23% of tensile strength after 7 days of incubation in pancreatic juice. Experienced surgeons detest soft pancreas because they know how the suture can cut soft pancreatic parenchyma when knots are tied. A soft and adipose pancreatic gland has a very low suture holding capacity, because it is friable, bloody and reacts with inflammation. Anastomotic

dehiscence sometimes can be explained by pancreatic stump necrosis that follows acute inflammation or ischemic damage. Pancreatic tissue, in fact, reacts to suturing with an acute inflammatory response that resembles acute pancreatitis. It has been demonstrated that fewer, thinner and less tighten sutures reduce pancreatic tissue damage. In our series, the possible suture induced damage on pancreatic remnant (expressed by post-operative hyperamylasemia) was similar between monofilament polydioxanone and braided polyester (23,8% vs. 21,4%; p = 0,7).

In the present study, post-operative hyperamylasemia was also found as an independent risk factor for POPF. Suture material could influence POPF incidence, but also POPF severity. Complications following PD resolve very slowly, especially high flow rate POPF grade B or C that often requires weeks to achieve an optimal healing after several therapeutic measures. After 6 weeks almost all absorbable sutures loss their initial mechanical characteristics appearing less strong and less tough. Polydioxanone (4–0 and smaller), for example, maintains only 35% of initial tensile strength after 6 weeks as reported by the manufacturer. Only polyester sutures maintain their initial strength and toughness. We can speculate that polyester sutures allow containing PJ dehiscence reducing POPF clinical severity even weeks after the onset of the fistula. In case of POPF from an absorbable suture made PJ, the progressive suture reabsorption could lead to a worsening of pancreatic anastomosis dehiscence as seen in several cases of re-laparotomy for grade C POPF. This consideration could be confirmed by the evidence that, in the present study, there were only grade A and B POPF and no grade C POPF in polyester PJ group (0% vs. 30%; p = 0,05).

9.Conclusion

The causes of pancreatic fistula include pancreaticojejunal anastomotic leak, leak from pancreatic resection, leak associated with damage to the pancreatic capsule, and leak via the puncture channel. Using polyester sutures for PJ after PD for periampullary illness, POPF frequency and seriousness can also be decreased. This consideration may not be a straightforward aspect if we believe that there is presently no agreement on which surgical technique can decrease the incidence of POPF.

Although mortality after pancreatic resection, especially after pancreatoduodenectomy, has decreased to levels below 5% in many centers over the past two decades even in more recent reports itself "Centers of excellence" postoperative morbidity remain high. In most published series is leakage of pancreatic anastomosis was a significant factor in postoperative morbidity and mortality, mortality rates of up to 28% in the presence of pancreatic fistula were reported by larger numbers of patients. Although out in some centers, the incidence of pancreatic fistulas after pancreatic head resection has recently been reported as 5% or less, the incidence of postoperative pancreatic leakage is in most cases even using standard surgical techniques and the application of octreotide newer works still at or above 10%. However, the general benefits of octreotide are still discussed controversially.

The analysis of the postoperative fistula, treatment and outcome of pancreatic fistulas. POPF rates stayed mainly unchanged after pancreatic resection despite decades of studies. This is mainly due to a bad comprehension of this complication's pathophysiology. POP is now emerging in the underlying pathophysiology of POPF as a possible critical factor. To explore approaches to mitigate the impacts of POPF. Meanwhile, POPF remains a complicated issue that requires a multidisciplinary strategy to effectively predict, prevent, and manage.

POPF incidence and severity can be also reduced using polyester sutures for PJ after PD for periampullary disease. This consideration may not be a simple detail if we consider that currently there is no consensus on which surgical technique is able to reduce POPF incidence. Further

randomized studies are needed to confirm this evidence. The reason why polyester sutures reduce the risk of POPF is not clear, additional data could be obtained analysing the effect of pancreatic juice and bile on this type of suture and the effect of polyester and other suture materials on pancreatic tissue. Despite decades of research, rates of POPF have remained largely unchanged after pancreatic resection. This largely relates to a poor understanding of the pathophysiology of this complication. POP is now emerging as a possible critical factor in the underlying pathophysiology of POPF. Further research is required to investigate strategies to mitigate the effects of POP. Meanwhile, POPF remains a complex problem requiring a multidisciplinary approach to achieve effective prediction, prevention, and management.

POPF continues to haunt pancreatic surgeons even despite of all advances in surgical field Use of a common suitable nomenclature facilitates comparability among various studies. Normal BT-PABA test, soft-friable pancreas and a small sized pancreatic duct is well acknowledged risk factors for POPF. There is no difference in surgical outcomes with respect to POPF between PG and PJ None of the methods recommended for preventing POPF have been conclusively proved to be effective.

Pancreatic fistula after pancreaticoduodenectomy is a common and serious complication and the most important cause of subsequent complications and death after this procedure. The dilemma of pancreatic fistula after pancreaticoduodenectomy has not yet been resolved[27]. Currently, researchers believe that the following factors are related to pancreatic fistula: gender, age, preoperative jaundice, intraoperative blood loss, operative time, pancreatic texture, BMI, diameter of the main pancreatic duct, and pancreaticojejunal anastomosis suggested that bundled pancreaticogastrostomy was a safe and effective anastomosis technique to prevent the leakage of pancreatic juice from pancreaticojejunal anastomosis. Further randomized control trails are needed to avoid the fistula complications.

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