

## Original article

### PANCREATIC FIBROSIS AND ITS RELATION WITH POST PANCREATICODUODENECTOMY PANCREATIC FISTULA

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#### **Abstract:**

**Background:** Pancreaticoduodenectomy (Whipple's Procedure and its variants) is the treatment of choice for malignant diseases of periampullary region. Postoperative Pancreatic Fistula (POPF) is the most dreaded complication and contributes substantially to the failure rate. Data regarding the relation of pancreatic fibrosis to pancreatic fistula is limited in the literature.

**Methods:** Patients undergoing Pancreaticoduodenectomy (PD) for malignant etiology were included in the study. POPF was graded according to the International Study Group of Pancreatic Surgery (ISGPS) grading system into 3 Grades (A- mild, B- moderate, C -severe). Pancreatic Fibrosis Scale was used for Classification of pancreatic fibrosis into three types.

**Results:** During the study period 48 patients of periampullary malignancy treated by PD at NHLM Medical College, VS Hospital, Ahmedabad where enrolled. The factors which were significantly associated with POPF in our study were Pancreatic duct size, Pancreatic Fibrosis, Age, DM, low albumin level and intraoperative blood loss. Type 1 fibrosis was found in 14 patients out of which Grade A fistula was found in 3 patients, Grade B fistula in 5 patients and Grade C fistula in 3 patients. Type 2 fibrosis was found in 17 patients of which Grade A fistula was found in 8 patients, Grade B fistula in 1 patient and none of Type 2 fibrosis developed Grade C fistula. Type 3 fibrosis was found in 17 patients out of which only 2 patient developed Grade A fistula and no patient developed grade B or C fistula with clinical relevance. High Grade of pancreatic fibrosis was associated with lower risk of POPF (0.005) compared to Low Grade fibrosis (p value 0.0002)

**Conclusion:** Pancreatic fibrosis correlates well with POPF. The pathological findings of High Grade pancreatic fibrosis has protective effect and is related to the lower rate of pancreatic fistula as compared to Low Grade pancreatic fibrosis.

**Keywords:** Pancreaticoduodenectomy, Pancreatic fistula (POPF), Pancreatic fibrosis

#### **INTRODUCTION**

Pancreatoduodenectomy (PD) has over the years become the treatment of choice for malignant diseases of the periampullary region [1]. Improvement in perioperative management has led to decrease in mortality, around 5% in high volume centers however morbidity has remain close to 50%, as described by large series in the literature [2]. The major complications after this surgery includes pancreatic fistula, intraabdominal abscesses/septic complications, delayed gastric emptying and postoperative bleeding [3,7]. Among the all complications, the POPF, is most dreaded and contributes substantially to the mortality and morbidity [5]. This has an incidence between 8% and 50%, affecting both morbidity and mortality .There are descriptions of several complications with the occurrence of pancreatic fistula, from small surgical wound infections, followed by peritonitis, sepsis and death of

the patient [6]. Clinical studies have identified many risk factors such as gender, diabetes mellitus, cardiovascular disease, obesity, leukocytosis, decreased serum albumin, impaired renal function, underlying pathology, long operative time, concomitant surgery, high intraoperative blood loss, small pancreatic duct diameter and fatty or soft pancreas to predict the development of POPF. The consistency of the remaining pancreatic tissue and the calibre of the main pancreatic duct have been proven to cause pancreatic fistula as highlighted by many authors [8-10]. However pancreatic stump histology which gives objective evidence of fibrosis and its relation with POPF has not been extensively studied. The aim of this study is to evaluate the relationship between the occurrence of pancreatic fistula in patients undergoing pancreaticoduodenectomy for periampullary malignancy with pancreatic fibrosis and the diameter of pancreatic duct.

## **METHODS**

A retrospective review of prospectively maintained database on patients with obstructive jaundice because of periampullary malignancy was done from August 2011 to February 2014.

A total of 48 patients underwent Pancreaticoduodenectomy (PD) by Superior Mesenteric Artery first technique at a tertiary hospital ( N.H.L. Municipal Medical College, Ahmedabad, Gujarat). All surgeries were carried out by surgeon experienced in Hepatobiliarypancreatic surgery at our center which is the one of the first centers in the country to have superspeciality degree course in Surgical Gastroenterology. Reconstruction was performed by end-to-side pancreaticojejunostomy end to side hepaticojejunostomy and gastrojejunostomy. External stent drainage tube was inserted into the pancreatic duct in all patients. All patients were given injection octreotide 100 microgram subcutaneously thrice a day for 5 days starting at time of surgical incision. Fibrosis of the pancreas was evaluated by a pathologist who was unaware of the clinical information and postoperative course of patients. Diameter of the main pancreatic duct was measured by preoperative contrast enhanced CT abdomen and intraoperative findings. Two abdominal drains was kept near anastomotic site in lesser sac and Morrison pouch. Amylase levels were monitored in the intraoperatively placed abdominal drains on 4<sup>th</sup> and 7<sup>th</sup> day after surgery as quoted by [Molinari E et al Ann surg2007 11]. POPF is considered if drain amylase > 3 times serum amylase. Drains were removed after day 7 of surgery if there is no evidence of pancreatic fistula.

Pancreatic fistula was defined according to the criteria by the International Study Group on Pancreatic Fistula (ISGPF)

POPF grade A: This grade of pancreatic fistula is the most common; called transient fistula, it has no clinical impact. Patient is fed orally and remains clinically well, and the use of TPN or somatostatin analogues is not required. Imaging in form of CT\USG shows no evidence of collection. It is not associated with delay in hospital discharge and managed frequent with keeping drain for few more days.

POPF grade B: This requires a change in standard postoperative management. Patient might need nutritional support in form of elemental or TPN. Patient will show signs of infection like abdominal pain, fever and leukocytosis. Antibiotics and prolonged somatostatin analogues might be required. Imaging may show evidence of collection which might require percutaneous drainage or repositioning of drains. Usually associated with delayed discharge but reoperation and mortality are not seen.

POPF grade C: A major deviation in standard clinical management has to be done. Patient need ICU care, nutritional support, intravenous antibiotics. Imaging usually shows peripancreatic fluid collection which requires intervention. Patient may require re exploration and together with sepsis and organ failure mortality can happen.

## **HISTOPATHOLOGY [Table 1]**

Paraffin embedded tissue blocks & histological slides from 39 patients who underwent Whipple's pancreaticoduodenectomy were gathered from the pathology archives of Smt. NHL Municipal Medical College & Sheth V.S. Hospital, Ahmedabad, Gujarat. The cases spanned the period August 2011 to February 2014. All specimens were received in 10% formalin & fixed for 24-48 hours. The grossing was done according to College of American Pathologist Protocol (CAP). In pancreaticoduodenectomy specimen, representative sections were taken from every part of the specimen. After routine

processing of the sections, paraffin blocks were made, at 4 micron & stained with the haematoxylin & eosin stain & studied with Nikon light microscope. Gross & microscopic photographs were taken using a digital camera. The histopathology slides were morphologically assessed for pancreatic fibrosis using pancreatic fibrosis scale [Pereira 12].

**Table 1-PANCREATIC FIBROSIS SCALE -**

Score (Points)	Fibrosis	Lobular Changes	Inflam- mation	Lobule Changes	Duct Changes
1	Little	Focal Perilobular Fibrosis	Focal	Atrophy Of Normal Lobe	Mild Duct Ectasia
2	Moderate	Intralobular Fibrosis With Septa	Moderate	Focal Atrophy Of Lobule	Moderate Duct Ectasia
3	Severe	Generalised Fibrosis, Destruction Of Acini	Extensive	Total Atrophy Of Lobe	Intense Duct Ectasia

**Table 2-CORRELATION OF PANCREATIC FIBROSIS WITH POPF**

	No Fistula	Fistula Type-A	Fistula Type-B	Fistula Type-C	Chi Square	P Value
Fibrosis Grade -1 (N-10)	3	3	5	3	19.951	0.0002
Fibrosis Grade-2 (N-14)	8	8	1	0	6.691	0.0824
Fibrosis Grade-3 (N-15)	15	2	0	0	12.857	0.0050
Total	21	10	5	3	48	

**Classification of fibrosis-**

Grade-I - normal pancreas or with mild fibrosis (0-4 points);

Grade-II - pancreas with moderate fibrosis (5-10 points);

Grade-III - pancreas with severe fibrosis (11- 15 points).

These criteria were assessed with optical microscopy by analyzing the cuts made in the parenchyma related to the resection margin. After histological analysis, the groups were related to the incidence of fistula.

**STATISTICAL ANALYSIS**

Continuous variables, such as age, fluid input, and intraoperative blood transfusion volume, were converted to categorical variables expressed as a mean and standard deviation (SD) and compared using the Chi squared test with Fisher's exact test to evaluate the impact of clinical and operative parameters. Statistical analysis was performed using SPSS 20 statistical software. A P value 00.05 was considered statistically significant.

**RESULTS**

From August 2011 to February 2014 , 48 patients with periampullary tumors underwent Superior Mesentric Artery first Pancreaticoduodenectomy by single Hepatopancreaticobiliary surgeon .

Factors which were significantly associated with POPF in our study were Age, DM, low albumin level (<2.5gm), Pancreatic stump fibrosis, Duct size and Intraoperative blood loss. Out of these we analysed pancreatic stump fibrosis and duct size in detail. Operative time, Pre operative biliary drainage, BMI, Gender, Tumor size were not significantly associated with POPF.

The correlation of pancreatic fistula and fibrosis is shown in the Table 2.

In our study [Table2]

Grade 1 fibrosis were found in 14 patients, out of which Type A fistula developed in 3 patients, Type B fistula in 5 patients and Type C fistula in 3 patients. This suggest that almost all patients in this group had pancreatic leak and 70% developed significant fistula.

Grade 2 fibrosis was found in 17 patients. Type A fistula developed in 8 patients, Type B fistula in 1 patient and none of patients with Grade 2 fibrosis developed Type C fistula.

Grade 3 fibrosis was found in 17 patients and none of these developed Type B and C fistula. Only 1 patient with Grade 3 fibrosis developed Type A fistula .

From these result we can conclude that most of clinically significant fistula develop in patients who had low Grade fibrosis, while the high Grade of fibrosis had a protective effect on fistula development and thus had a lower rate of significant fistula. In patients with small duct size 13 out of 18 patients developed pancreatic fistula. 6 out of these patients developed clinically significant fistula which contributed to 75% of significant fistula, Type B in 3 patients and Type C in 3 patients. In patients with large duct size 5 out of 21 developed pancreatic fistula out of which 2 were Type B fistula. All 3 patients who died had smaller duct.

## **DISCUSSION**

Pancreatic fistula is the major cause of morbidity and mortality, and has been aptly stated as “Achilles’ heel” of pancreaticoduodenectomy. There is an extensive literature illustrating many predictive factors for POPF development, classified as patient-related, operative and gland-related factors [13,14]. In an attempt to predict the development of POPF, clinical studies have identified many risk factors, such as gender, cardiovascular disease, diabetes mellitus, [15,16] obesity, leukocytosis, low serum albumin, impaired renal function, centre effect, underlying pathology, long operative time, concomitant surgery or radical lymphadenectomy, high intraoperative blood loss, small pancreatic duct diameter and fatty or ‘soft’ pancreas. [17-25] Therefore identifying these complications early is key to attaining a good outcome in these patients undergoing pancreaticoduodenectomy. There is an increasing tendency to define the pancreatic fistula as a preventable complication, and the surgeons tend to focus on the consistency of pancreatic parenchyma and ductal caliber as determinants of the onset of anastomotic dehiscence.

Main pancreatic duct diameter of 3 mm or less was an independent risk factor for morbidity and mortality in many studies [26-28]. Soft pancreatic parenchyma is widely recognised risk factor for pancreatic fistula. Soft pancreas is more vulnerable to injury while suturing. Sutures are more vulnerable to tearing through soft parenchyma as well as smaller duct. Smaller duct accommodate fewer sutures and more likely to either occlude or dehisce. Exocrine activity of soft pancreas is well preserved and leads to increased pancreatic secretions rich in proteolytic enzymes. [5] [Pereira et al 12] On transected pancreatic stump there is existence of branch pancreatic ducts that secrete pancreatic juice and can lead to anastomotic leak. Injury to these ducts or main duct can occur while suturing which further predispose to fistula development. [27]

In our study clinically significant fistula POPF (ISGPF grade B & C) developed in 8 (20.51%) patients and insignificant (Grade A) in 10 (25.64%) patients. Of these 3 (7.25%) patients died, all due to multiorgan failure secondary to Type C pancreatic fistula. Factors associated with pancreatic fistula in our study were Age, D.M, serum albumin, intra-operative blood loss, duct size and pancreas texture and pancreatic stump histology.

In 2000 Yeo et al. [29] found that POPF rate was 0% among patients with hardened remaining pancreas and increased to 25% in patients with soft parenchyma. Other investigations confirmed low POPF rates in the presence of firm pancreatic consistency. This result can be easily explained by the technical difficulties of a pancreatoenteric anastomosis in the presence of a soft, friable tissue, which cannot resist the sutures. It has been demonstrated that increased fibrosis of pancreatic tissue is associated with decreased exocrine activity, resulting in a reduction of the pancreatic juice output. [28]. Our experience also shows that hard pancreas has protective effect on POPF. Conversely, all the factors which increases gland fibrosis, like chronic pancreatitis or cancer, had a protective role, allowing for a more secure anastomosis. Soft tissue cannot resist the tearing forces of sutures as reliably as hard tissue. Erkan et al [30] shows Pancreatic stellate cells (PSCs) are the main fibroblastic cells of the pancreas which are responsible for producing the desmoplasia in chronic pancreatitis (CP) and adenocarcinoma. Pancreatic cancer cells activate the PSC around them, and this activation leads to the fibrosis of the tumor. Clinically, the effect of desmoplasia is two-sided; on the negative side it is a

hurdle in the diagnosis of PDAC because the fibrosis in cancer resembles that of CP. It is also believed that PSCs and pancreatic fibrosis are partially responsible for the therapy resistance in pancreatic cancer. On the positive side, a fibrotic pancreas is safer to operate on compared to a fatty and soft pancreas which is prone for postoperative pancreatic fistula.

We also found that patient with soft pancreas had a higher incidence of pancreatic fistula. However to get objective evidence, we opted for pancreatic stump histopathology and correlated it with pancreatic fistula. We classified it into 3 Grades of fibrotic changes depending upon point score of fibrosis, lobular changes, lobule changes, inflammation and duct changes.( Table-2 ) Histopathological analysis of pancreatic stump demonstrated a high degree of fibrosis, elevated inflammatory activity and higher inflammatory infiltrate correlating with a lower incidence of pancreatic fistula and vice versa. We found that Grade 1 fibrotic changes were significantly associated with pancreatic fistula (p-value 0.0002). On the contrary Grade 2 and Grade 3 fibrotic changes were rarely associated with significant fistula (p-value 0.005).

Pereira et al [12] retrospectively analysed 77 patients who underwent Pancreaticoduodenectomy. using fibrosis and inflammation they did pancreatic histological classification and also noted pancreatic fistula rate. They showed Masson trichrome and Immunohistochemistry did not add information to that achieved by hematoxylin and eosin They concluded that fibrosis and duct dilatation usually coexist and is related to lower incidence of pancreatic fistula. Erkan et al. [30] and Felix et [31]al shows similar results by using histological grading system. Ridolfi [28]et al studied 145 consecutive Pancreaticoduodenectomy and intra operative recorded morphological features of pancreatic stump and collected data on postoperative morbidity. They concluded that pancreatic stump features evaluation, including histology, can help the surgeon in fitting postoperative management to patient individual risk after Pancreaticoduodenectomy. If we consider histopathological grade of fibrosis as well as duct size, small duct size is usually associated with soft less fibrotic pancreas and normal pancreatic secretions and thus predisposing to pancreatic fistula. On the contrary, large duct size is associated with hard fibrotic pancreas and decrease pancreatic secretions and less likely to develop pancreatic fistula.

Addition of histopathological data of pancreatic stump has also helped us in postoperative management of patients undergoing PD. There is enough evidence in literature which shows that prolonged drainage can lead to complications and earlier removal of prophylactic drain decrease risk of intraabdominal infections in patients undergoing PD.[Kawai [30] et al ]. In our study we removed the intra abdominal drain after 7th post operative day based on drain fluid amylase level. We have used our histopathological data to alter protocol of drain removal at our institute and removed the drain earlier by postoperative day 4 in patients with high grade fibrosis and normal drain amylase. Thus under proper clinical situation addition of histopathological data can give information about chances of development of POPF and can guide in postoperative management in patients undergoing PD.

**CONCLUSION:** Pancreatic fibrosis correlates well with POPF. The pathological findings of High Grade pancreatic fibrosis has a protective effect and is related to the lower rate of pancreatic fistula as compared to Low Grade pancreatic fibrosis.

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