

Correlation analysis between post-pancreatoduodenectomy pancreatic fistula and pancreatic histology

Fístula pancreática após duodenopancreatectomia: correlação dos aspectos intra-operatórios e histológicos do pâncreas

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A B S T R A C T

Objective: To evaluate the relationship between the occurrence of pancreatic fistula after pancreatojejunal anastomosis in patients undergoing pancreaticoduodenectomy for periampullary malignancy and the histological fibrosis and inflammation found in pancreatic tissue and the caliber of the main pancreatic duct. **Methods:** We conducted a retrospective study with patients that were treated with surgical resection. The rate of pancreatic fistulae was recorded. Histology classification was performed according to fibrosis and pancreatic inflammation. **Results:** We identified 77 patients, mean age was 57.6 years; 62.4% were male. As for the type of operation performed, 66.3% were gastroduodenopancreatectomies and 33.7% pancreatoduodenectomies with pylorus preservation. Regarding the number of fistulas diagnosed, it was found that 23.4% patients displayed this postoperative complication and in 66.7% the cause was cancer of the papilla. As for intraoperative macroscopic findings, we identified the classification of pancreatic texture, seen as normal in 85.8%, and the caliber of the main pancreatic duct, finding an average of 4.9 mm. There was a significant relationship between the hardened pancreatic stump and the absence of fistula. In patients with normal or soft tissue, the rate of fistula was 25.4%. Regarding ductal diameter, we identified a higher number of pancreatic anastomotic dehiscences in the absence of ductal dilation ($p < 0.05$). We noticed that patients with an average ductal diameter of 5.4 mm (76.7%) did not show this complication. **Conclusion:** The presence of fibrosis and ductal dilation usually coexist and is related to a lower percentage of pancreatic fistulae.

Key words: Pancreatic fistula. Pancreaticoduodenectomy. Pancreatic ducts. Pancreas. Pancreas/anatomy & histology.

INTRODUCTION

According to the American Cancer Society ¹, it was estimated that approximately 33,500 new diagnoses of pancreatic cancer occurred in the United States in 2007 and there were approximately 28,800 deaths from the disease in the same year. It was found a five-year survival index of 5% in any stadium; of 15.2% with local commitment, ie, confined entirely to the organ; 6.8% for regional commitment, when it extends beyond the limits of organ, involving regional lymph nodes or both; and 1.8% with distant metastasis ².

In our country, according to a study from the National Cancer Institute (INCA) in 2005, it was anticipated for 2006 a total of 472,050 new cases of cancer, the percentage of 4% for pancreatic cancer, or approximately 18,882 new cases of the disease in the country ³. Still in

our country, another study in 2004, also by the National Cancer Institute, showed that the mortality rate for pancreatic cancer per 100,000 men was between 0.45 and 5.4%, and the rate per 100,000 women between 0.39 and 4.91% in the states between 1995 and 1999 ⁴.

It is an alarming incidence, even more so if one considers that the diagnosis of periampullary malignancy remains a challenge the digestive surgeon, as healing, basically, resides in surgical resection ⁵.

Gastroduodenopancreatectomy (GDP) or pylorus preserving pancreatoduodenectomy (PPPD) has become over the years the operation of choice in the treatment of periampullary neoplasms. However, and for a few decades, high mortality was noted. As a result, this operation was not recommended by the medical community of the time ⁶.

Spread worldwide Today, the first Pancreatoduodenectomy was described by Kausch in

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Germany, in 1912⁷. Other groups in Europe also performed this operation in the next 20 years, but only after the procedure described by Whipple et al. In 1935, it became famous and accepted. Unfortunately, during the first 50 successive years of experience with the procedure, its morbidity and postoperative mortality were unacceptably high. Furthermore, survival rates for patients with pancreatic cancer were disappointing, with a rate less than 5% in five years postoperatively⁸.

Despite technological development of the period, in the late 60's and during the 70's the poor results in relation to survival of patients undergoing the procedure were so many, that some authors have even suggested the abandonment of pancreatoduodenectomy for pancreatic cancer treatment^{9,10}.

Nevertheless, the results of pancreatoduodenectomy have improved gradually since the mid-80s, mainly due to more accurate understanding of pancreatic diseases, advances in surgical techniques and care before, during and after surgery. This was due Especially to intensive care, anesthesia, as well as greater understanding of the management of the use of prophylactic and therapeutic antibiotics and due to the emergence of centers with a significant number of patients ("centers of excellence"). Thus, there was considerable and progressive decrease in mortality, keeping, in majority, rates of 5%, although high rates of morbidity, by 50%, are still observed¹¹.

Despite all the security that the procedure is currently offering, the pancreatic fistula, among the complications of the postoperative period, is frequently observed and contributes substantially to the failure rate¹². This is a frequent and troublesome complication, with an incidence between 8% and 25%, affecting both morbidity and mortality in the first post-operative results. 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 patient¹³.

Some factors are related to the genesis of pancreatic fistula. Amongst them, the consistency of the remaining pancreatic tissue and the caliber of the main pancreatic duct has been highlighted by some authors¹⁴⁻¹⁷.

There is the assumption that macroscopically normal pancreatic tissues, with soft consistency, associated with small-caliber or normal-size pancreatic ducts, predispose to the occurrence of enteropancreatic anastomotic fistula, mainly due to technical difficulties, preserved exocrine reserve and increased pancreatic juice flow^{2,17}. On the other hand, the hypothesis that the anastomosis held in a pancreas with fibrous tissue, characteristic of chronic pancreatitis, has a significantly reduced incidence of complications related to anastomosis is sustained².

Pancreatic Consistency can be studied subjectively, through intraoperative macroscopic findings by the surgeon or with histological quantification,

determination and classification of various degrees of fibrosis and inflammation, which may change the consistency of pancreatic tissue in different patterns of stiffness¹⁸.

Few studies have analyzed the histology of the pancreas after enteropancreatic anastomosis and its relation to the development of pancreatic fistulas¹⁷.

Knowledge of the flow of pancreatic secretion further supports studies that show the direct relationship of this low value in milliliters with the hardened remnant pancreatic stump and its lower incidence of pancreatic anastomotic dehiscence¹⁴. However, despite the value of surgery in the treatment of periampullary pancreatic cancer, the literature shows no representative number of studies with statistical significance that examined the caliber of the Wirsung duct, pancreatic histology and correlated them with the number of enteropancreatic fistulas¹⁹.

The objective of this study is to evaluate the relationship between the occurrence of pancreatic fistula after pancreatojejunal anastomosis in patients undergoing pancreatoduodenectomy for periampullary malignancy, with intraoperative aspects of glandular consistency and of the caliber of the main pancreatic duct, in association with histological fibrosis and inflammation found in the optical microscopy of pancreatic tissue.

METHODS

Through a retrospective study using secondary data obtained through information from medical records of the Department of Statistics and Medical File (SAME), Central Hospital of the Santa Casa de Misericórdia de São Paulo (ISCMSP) from 1990 to 2005, we analyzed patients with a diagnosis of periampullary malignancy who underwent surgical resection.

We identified patients who underwent GDP or PPPD for periampullary malignancy admitted to the Department of Surgery.

All charts were included in the protocol, according to the following inclusion criteria: similar type of end-to-side pancreatojejunal reconstruction with or without cannulation of the main pancreatic duct; length of stay greater than four days after surgery; resection margin free of cancer; identification of the corresponding paraffin blocks. As already established, treatment with resection of periampullary neoplasia, either GDP or PPPD, has a single bowel loop as the defined type of reconstruction. However, there is a variation represented by a linear stapling (usually with linear stapler Ethicon TLC 75 mm ®) followed by a manual enteroenteric anastomosis in two planes with Vicryl ® 4-0, so as to prevent contact of biliopancreatic secretions. The biliodigestive anastomosis was usually end-to-side, made with 4-0 Caprofil® running sutures. The enteropancreatic anastomosis was also performed in an end-to-side fashion, duct-mucosa type, with separate

braided synthetic absorbable sutures (Vicryl®) 4-0 or 5-0 till the year 1997 and thereafter until the end of the study the pancreatic anastomoses were performed with separated absorbable synthetic monofilament (Caprofil®) 4-0 or 5-0 sutures.

Also in the intraoperative period, the measurement of main pancreatic duct caliber was performed. Should the presence of a small pancreatic duct, namely, smaller than two millimeters, be detected, which would bring difficulty for the anastomosis, there was the standardization of placement of a silicone tube in the anastomosis to guide the suture line. There are also routine systematic draining of the abdominal cavity with a tubulo-laminar drain placed near the anastomosis and exteriorized from the right flank.

Once the operation terminated, the surgical specimen was macroscopically classified as for pancreatic texture in: softened; normal; hardened.

The rate of pancreatic fistula found was then characterized, according to the study's data leak of Verona, in 2005, as any amount of drainage of amylase-rich abdominal secretion from the tubulo-laminar drain placed near the anastomosis and exteriorized on the right flank, from the third postoperative day. The level of abdominal secretion amylase was determined by usual laboratory and the reference values adopted were up to 115U/L for serum amylase, stipulated by the Central Laboratory of ISCMSP, and the abdominal fluid amylase presenting a value at least three times higher than the serum^{19,20}.

Histological analysis was performed by a single pathologist, Laboratory of Pathology and Cytopathology of Presidente Prudente (Anthony Placido Pereira), stipulating three different times.

At first, there was a classification with hematoxylin-eosin. In the second, the same cuts previously analyzed underwent coloration of Masson trichomic and, finally, there was inclusion of such slides in an immunohistochemistry study with actin for smooth muscle alpha (1A4), muscle actin (HHF-35) and vimentin (V9 Vim 3B4).

Before the special stains, a control slide was confectioned and all others were stained simultaneously, so as to keep the pattern of staining intensity. The pathologist had no prior knowledge of which patient was being studied, the identities, as well as the individual postoperative results, being concealed.

We determined criteria for quantification of fibrosis and pancreatic inflammation adapted by Giulio Cesare Santo²¹, as follows: - perilobular fibrosis: fibrosis involving the lobes, but no penetrating them, being focal or extensive; - periacinar fibrosis: fibrosis within the lobes, respecting the acini, but forming septa; - cirrhosis: complete replacement of acini by fibrosis; - mild ductal ectasia: when the pancreatic duct dilatation presented no change in gross morphology; - intense ductal ectasia: gross morphology alterations of the ducts; - glandular atrophy,

being restricted to acini or lobules, focal or generalized; - infiltration by inflammatory cells, being focal or generalized.

These criteria were assessed with optical microscopy by analyzing the cuts made in the parenchyma related to the resection margin. The values found resulting from the sum of the valid points for each criterion were divided into three groups thus classified: I - normal pancreas or with mild fibrosis (0-4 points); II - pancreas with moderate fibrosis (5-10 points); III - pancreas with severe fibrosis (11-15 points).

Group I was represented by histologically normal pancreas or with little fibrosis: focal perilobular fibrosis; focal inflammatory infiltrates; atrophy in normal lobe; mild ductal ectasia (Figure 1).

Group II was characterized by moderate degree of pancreatic fibrosis: intralobular fibrosis with septa; extensive inflammatory infiltration; focal atrophy of lobules; intense ductal ectasia (Figure 2).

Group III was characterized by pancreas with increased degree of fibrosis: generalized fibrosis and destruction of acini; extensive inflammatory infiltrate; total atrophy of lobes; intense ductal ectasia (Figure 3).

After histological analysis, the groups were related to the incidence of fistula and compared to the different staining techniques applied.

It was adopted a significance level of 5% ($p = 0.05$) for the application of statistical tests in this study. We used the chi-square technique and the ROC curve, establishing associations between two quantitative variables in order to verify possible association.

It was Then possible to identify, within groups, which of the subgroups produced differences in the Mann-Whitney test. And finally, this result was associated with the Spearman correlation test, to prove the relationship between several variables.

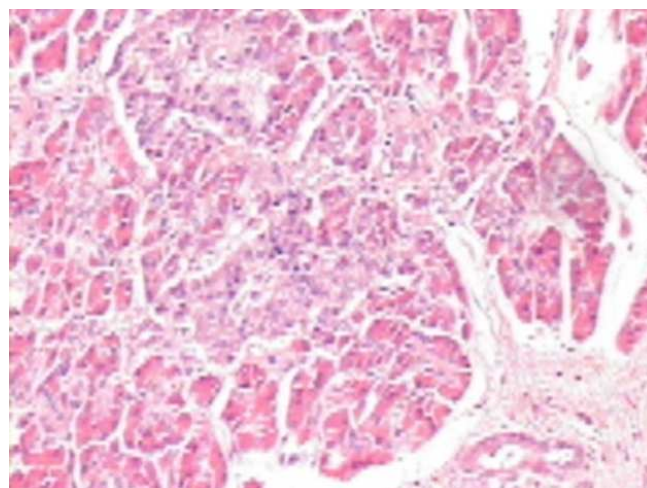


Figure 1 - Group I - Pancreas histologically normal and with little fibrosis (HE, 40x).

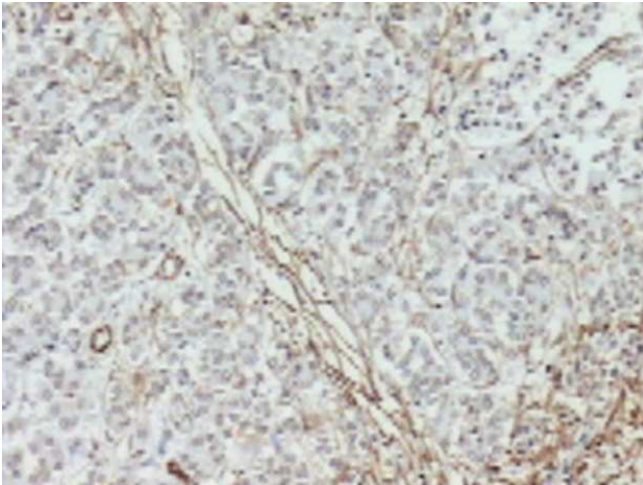


Figure 2 - Group II - Pancreas with moderate fibrosis and displaying some septa (1A4-40x).

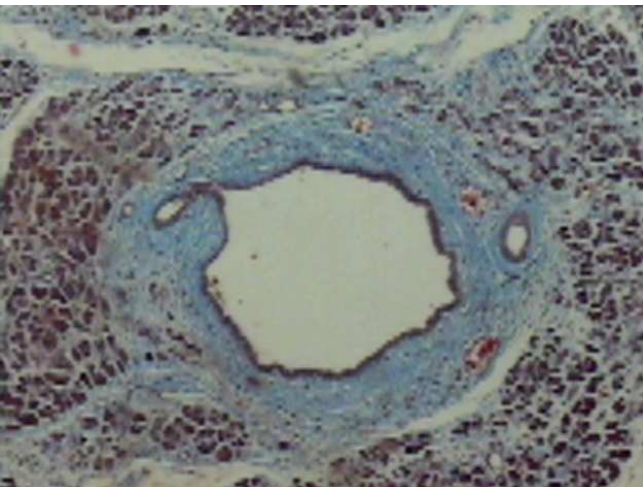


Figure 3 - Group III - Pancreas with widespread fibrosis and intense ductal ectasia (TM-40x).

RESULTS

From 255 patients who underwent surgical treatment, 77 were identified who met all inclusion criteria, with a mean age of 57.6 years and mostly male, a total of 48 patients (62.4%). Regarding the type of operation performed, 51 of them (66.3%) were constituted in GDP and 26 (33.7%) PPPD. The average length of stay was 20 days and mean postoperative hospital stay was 15.5 days.

According to the cause, we found that both pancreas and papilla malignant neoplasms were present, in 34 patients, totaling 44.2% each.

Regarding the number of fistulas diagnosed, we found that 18 patients (23.4%) presented this postoperative complication, 12 (66.7%) with cancer of the duodenal papilla and six (33.3%) with pancreatic cancer. There were no pancreatic fistulas in patients with cancer of the bile duct or duodenum. According to the type of operation, we identified a higher incidence of enteropancreatic

anastomotic dehiscence in patients submitted to GDP (66%).

Regarding intraoperative macroscopic findings, normal pancreatic texture was identified in 66 patients (85.8%). As for the size of the main pancreatic duct, it ranged from two to 15 mm in diameter, with an average of 4.9 mm.

There were 12 deaths (15.6%), and of these, three (25%) were result of sepsis after peritonitis caused by pancreatojejunal anastomotic fistula.

Regarding the presence of fistula and its relationship to the macroscopic classification of pancreatic texture, there was a statistically significant association ($p = 0.004$) between the hardened texture and no anastomotic fistula.

As for the association of fistula and the caliber of the pancreatic duct, we observed not only a statistically significant difference ($p < 0.001$) but also that the cutoff point for anastomotic pancreatic fistula in a duct caliber smaller than 0.35 cm.

Regarding the presence of fistula and histopathology assessment, there was a statistically significant similarity between the pathological analysis, so that there is an equivalence between the values found for scores analysis with hematoxylin-eosin, Masson trichrome, as immunohistochemistry. Thus, we considered the mean of the values found in the scores of all analyzes, observing each individual patient. We found a statistically significant association ($p = 0.019$) between the scoring categories and the presence or absence of fistula have. On the other hand, considering not the score categories, but their pointed out value, the lowest score proved to demonstrate the presence of pancreatic fistula.

As for the caliber of the pancreatic duct and histopathology, we noted a relation with statistical significance ($p = 0.002$) between the score values and the caliber of the duct up to 0.34 cm.

DISCUSSION

GDP and PPPD have been widely used in recent years as safe procedures that offer appropriate resection for patients with malignant or benign diseases of the pancreas and periampullary region¹¹. Postoperative mortality is, in many reference centers, less than 4%^{12,13,22}.

Despite the low surgical mortality observed, the incidence of postoperative morbidity approaches 50%. From the reported Complications, the most common include delayed gastric emptying, anastomotic dehiscence enteropancreatic fistula, wound infection and bleeding^{12,22,23}.

As a result of the identification of pancreatic fistula as a very common complication after GDP, numerous techniques for reconstruction and anastomosis of the

pancreatic stump remnant have been studied and proposed in the last decades²⁴.

There is extensive literature regarding risk factors that influence the development of pancreatic fistula, among them the texture of the remnant pancreas and pancreatic duct diameter^{15,16,25}.

Although studies demonstrating the lack of correlation between enteropancreatic anastomotic dehiscence and texture of the pancreas²⁶, there are reports that the subjective assessment of greater consistency associated with pancreatic ductal dilatation contributes to the lower occurrence of enteropancreatic fistulas. Nevertheless, the correlation of the macroscopic findings with the quantitative histological analysis of ductal dilatation and consequent fibrosis has not been studied¹⁹. Based upon this important variability of the consistency of pancreatic parenchyma, along with the diameter of the pancreatic duct, we opted for histology and quantification of fibrosis and inflammation to point out the relationship between its analysis and the macroscopic identification of the difference in texture made of routine pathological examination.

The choice of using markers for immunohistochemistry was due to attempt to establish greater visualization of tissues rich in fibrosis and inflammation.

At macroscopic analysis it was found an important relationship between the hard consistency of the pancreatic stump and the absence of anastomotic fistula, since no patient with intraoperative verification of a more fibrotic texture of the parenchyma showed anastomotic dehiscence. Yeo also showed that none of the 53 patients with hardened remaining pancreas had pancreatic fistula. However, 25% (19/75) with soft pancreatic texture displayed this complication²⁷. As in our sample, no patient with hardened pancreatic texture had anastomotic fistula. The explanation for the increased rates of pancreatic fistula with softened pancreatic texture seems obvious, since the normal pancreatic tissue, usually friable, is more difficult to keep the suture line, but the histological evidence of this subjective evaluation of the pancreas texture was not found in this literature review.

In this study, as for the diameter of the main duct, we observed a higher number of pancreatic anastomotic dehiscence and fistula in patients who had no ductal dilation. It was evident that patients with average diameter of 5.4 mm duct (76.7%) showed no complications, while others, with average values of 3.3 mm, had

pancreatic fistula.

Regarding histological grade, it was identified that 55.9% of patients without pancreatic fistula had higher score values, i.e., intense degree of fibrosis and glandular inflammation. On the other hand, considering the absolute values of histopathological score, we identified lower mean values of these, i.e., associated with a less consistent demonstration of pancreatic anastomotic fistula.

It was shown that the more intense the quantification of fibrosis and inflammation and increased the diameter of the pancreatic duct, the lower the rate of pancreatic fistula.

A prospective randomized study showed association between less consistent (softer) glands and the presence of a fistula²⁷.

Another study, which relates the pathologic findings of the pancreatic gland in 510 pancreatoduodenectomies, cites the pancreatic inflammatory process in corroborating the occurrence of anastomotic fistula of the pancreas and also relates it to the size and tumor differentiation²⁸.

Dong *et al.*, in 2011, based on the classification of the International Study Group on Pancreatic Fistula, reaffirmed that the technique of reconstruction, made with an invaginating continuous suture may influence in reducing the incidence of fistulas²⁹.

The analysis of the subgroup from the sum of cases of pancreas with normal and softened texture, based on the quantification of fibrosis, allowed to identify the maintenance of the result, i.e., the group without pancreatic fistula presents with intense graduation in its majority (54.7%).

Despite the wide variety of studies, there is practically a nonexistent discussion about the cause and clinical significance of the pancreatoduodenectomy in the postoperative period. There is an increasing global tendency to define the pancreatic fistula as a preventable complication, and the surgeon himself tends to focus on the consistency of pancreatic parenchyma and ductal caliber as determinants of the onset of anastomotic dehiscence.

The three methods we used on pathological assessment were appropriate and returned expected results. However, Masson trichrome and immunohistochemistry did not add information to that already achieved by hematoxylin and eosin. So they can be dispensed in medical practice.

In conclusion, fibrosis and ductal dilation usually coexist and are related to a lower percentage of enteropancreatic fistulas.

R E S U M O

Objetivo: Avaliar a relação entre a ocorrência de fistula pancreática pós-anastomose pancreatojejunal, em doentes submetidos à duodenopancreatectomia por neoplasia maligna periampolar, com aspectos histológicos de fibrose e inflamação encontrados no tecido pancreático e com o calibre do ducto pancreático principal. **Métodos:** Estudo retrospectivo interessando doentes que foram submetidos ao tratamento com ressecção cirúrgica. Verificou-se o índice de fistulas pancreáticas encontradas. Classificou-se de acordo com a histologia da fibrose e da inflamação pancreática. **Resultados:** Identificaram-se 77 doentes, com média de idade de 57,6 anos, sendo 62,4% do sexo masculino. De acordo com o tipo de operação realizada, 66,3% constituíram-se em gastroduodenopancreatectomia e 33,7% em duodenopancreatectomia com preservação do piloro. Em relação ao número de fistulas diagnosticadas, identificou-se que 23,4% doentes apresentaram tal complicação pós-operatória, sendo que em 66,7% a causa era neoplasia de papila. Achados macroscópicos intraoperatórios, identificou-se classificação da textura pancreática, tida como normal, em 85,8% e, quanto ao calibre do ducto principal pancreático, foi encontrada média de 4,9mm. Houve relação importante entre a consistência endurecida do coto pancreático e a ausência da fistula. Nos doentes com tecido normal ou amolecido, o índice de fistula foi 25,4%. Quanto ao diâmetro ductal, identificou-se ($p < 0,05$) maior número de deiscências da anastomose pancreática na ausência de dilatação ductal. Evidenciou-se que doentes com valores médios do diâmetro de ducto de 5,4mm (76,7%) não mostraram esta complicação. **Conclusão:** A presença de fibrose e de dilatação ductal habitualmente coexistem e estão relacionadas à menor porcentagem de fistulas enteropancreáticas.

Descritores: *Fistula pancreática. Pancreaticoduodenectomia. Ductos pancreáticos. Pâncreas. Pâncreas/anatomia & histologia.*

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