

The effect of duct width and pancreatic gland structure on pancreatic fistula rates in patients who underwent pancreaticoduodenectomy for pancreatic cancer

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ABSTRACT

Introduction: One of the most important causes of morbidity in pancreaticoduodenectomy (PD) surgery is pancreatic anastomosis leakage. There is a possibility of pancreatic fistula even in the most experienced hands. After PD, pancreatic fistula occurs between 10% and 20% in various series. This study aims to evaluate the effects of pancreatic duct size and pancreatic tissue on the development of pancreatic fistula after PD is performed in our center.

Material and Method: Pancreatic duct size was categorized as small <3 mm and large >3 mm. Pancreatic gland tissue was categorized as a soft, medium, and hard. These variables were calculated preoperatively with the help of computed tomography (CT), ultrasonography(USG), and Endoscopic ultrasound (EUS), and postoperative pathology results. It was accepted that the 24-hour flow rate of the drain behind the pancreatic anastomosis was more than 50 ml during 3 days after PD and/or the amylase concentration of the drain content measured at 3 different times was 3 times higher than the serum amylase concentration.

Results: A total of 90 patients were included in the study, anastomotic leakage was not observed in 63 (70%) of 90 patients, and leakage was observed in 27 (30%) patients. The mean age was 71.22±10.78 years (p=0.615). There was no statistically significant difference between the ductus diameters between the two groups (p=0.240). There was no statistical difference between the groups formed according to pancreatic duct width. (p=0.059). It was observed that 60.3% of the patients in the non-leakage group had a hard appearance, and this rate was statistically significantly reduced to 29.6% in the patients with leakage (p=0.008).

Conclusion: In summary, our study showed that pancreatic fistula after PD is associated with soft pancreatic parenchyma. The surgeon should consider this risk factor when performing a PD and be more careful to reduce the rate of pancreatic fistula.

Keywords: Pancreaticoduodenectomy, fistula, duct width, pancreatic gland structure

INTRODUCTION

Although pancreaticoduodenectomy (PD) was first performed by Kausch, it was popularized by Whipple in 1935 (1,2). It was considered an operation that should not be performed for a period because it causes high morbidity and mortality, but it could not be abandoned because it is the only potentially curative treatment option for pancreatic head and periampullary tumors. The most important step of PD surgery is pancreaticojejunostomy anastomosis.

Many different methods have been tried to be developed to reduce this morbidity and mortality. These include ligation of the pancreatic stump and occlusion of the duct

with prolamin or fibrin adhesives, pancreaticogastrostomy anastomosis, prophylactic pharmacological agents such as octreotide, and external drainage of the pancreatic duct, internal drainage of the pancreatic duct, and many different pancreaticojejunostomy anastomosis techniques (3-6). Despite this, the pancreatic fistula rate is inevitable even in the most experienced hands.

After PD, the most prevalent cause of prolonged hospitalization and morbidity is pancreatic fistula formation, which is seen in postoperative patients between 10% and 20% in various series (7-9).

Several research reportson the fistula risk score after PD Both small pancreatic duct size and soft glandular tissue were identified as factors impacting fistula formation following PD (10-15). This study aims to evaluate the effects of pancreatic duct size and pancreatic tissue on the development of pancreatic fistula after PD is performed in our center.

MATERIAL AND METHOD

The study was carried out with the permission of Hitit University Erol Olçok Training and Research Hospital Non-Invasive Research Ethics Committee (Date: 10/01/2022, Decision No: 2021-88). All procedures were carried out in accordance with the ethical rules and the principles of the Declaration of Helsinki.

Study Population

Between January 2014 and March 2022, patients over the age of 18 who underwent PD due to pancreatic cancer, underwent duct mucosa anastomosis, were not considered inoperable and did not undergo vascular anastomosis were included in the study. Patients under the age of 18 who underwent PD for non-cancer reasons, who developed intraoperative complications, who could not undergo ductomucosal anastomosis, and who had different anastomosis techniques were excluded from the study.

PD anastomosis was performed by all surgeons with the same surgical technique.

Two independent variables were tested in our study. The first of these was the pancreatic duct size. Pancreatic duct size was categorized as small <3 mm and large >3 mm. The second variable was pancreatic gland tissue. It was categorized as a soft, medium, and hard. These variables were calculated preoperatively with the help of computed tomography (CT), ultrasonography (USG), and Endoscopic ultrasound (EUS), and postoperative pathology results. Other demographic and clinical variables included age, gender, preoperative Bilirubin, aspartate aminotransferase (AST), alanine transaminase (ALT), alkaline phosphatase (ALP), gamma-glutamyl transferase (GGT), carbohydrate antigen (CA) 19-9, and carcinoembryonic antigen (CEA) levels, and postoperative amylase level (units/liter).

Postoperative morbidity was determined as surgery-related or systemic complications. As pancreatic fistula definition, as defined in ISGPF (international study group for pancreatic fistula definition), the 24-hour flow rate of the drain behind the pancreatic anastomosis for 3 days after PD is more than 50 ml and/or the amylase concentration of the drain content measured at 3 different times, serum 3 times higher than amylase concentration was accepted as Pancreatic fistula grading was classified according to ISGPF (16).

Normal values of serum albumin levels between 3.5-5.2 g/dl and serum bilirubin between 0.2-1.1 mg/dl were accepted. The length of stay in the hospital was recorded as the number of days between the day of surgery and discharge.

Surgical Technique

Between the posterior capsule of the pancreatic stump parenchyma and the seromuscular layer of the jejunum, posterior sutures were created using 4/0 nonabsorbable sutures in the duct-to-mucosal pancreaticojejunostomy anastomosis approach. For pancreatic duct anastomosis, the antimesenteric wall of the jejunum was opened to match the duct diameter. The pancreatic duct and all layers of the jejunum were then sewn together one by one using 5/0 nonabsorbable sutures, with the nodes on the outside. Subsequently, the anterior capsule of the residual parenchyma of the pancreas and the seromuscular layer of the jejunum were closed using the same technique to form the anterior wall of the anastomosis. Duct-to-mucosal PJ anastomosis was performed without stenting in the pancreatic duct.

Statistical Analysis

Data analysis was evaluated with SPSS 22.0 for the Windows data analysis program. Numbers and percentages for categorical variables, the mean and standard deviation for numerical variables, and the median in parenthesis were provided as descriptive statistics. The Shapiro Wilks test was used to assess the data's normal distribution. The data distribution looked into relationships between variables using the Pearson or Spearman correlation coefficient. Comparison of numerical measurements for two independent groups according to research groups, using two-sample t-tests for MPV and Albumin by the data distribution, age, duration of operation, duration of postoperative hospitalization, monocytes (MO), platelet distribution width (PDW), lymphocyte (LY), platelet (PLT), C-reactive protein (CRP), CA 19-9, albumin, amylase values, pancreatic duct width and time to mortality were evaluated with Mann Whitney U test. Chi-square and Fisher exact tests were performed to compare the categorical variables such as gender, ASA, duct groups, pancreatic morphology, mortality rates at the same hospitalization and during the whole follow-up, and the rate comparisons between the study groups separated according to the presence of an anastomotic leak. The Kaplan-Meier Survival Analysis was used to compute the patients' predicted survival, and the Log-Rank test was used to determine statistical significance between the two groups. P<0.05 was considered statistically significant.

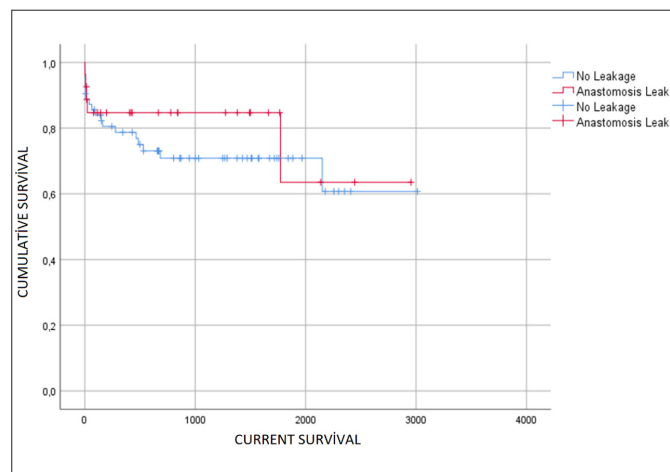


Figure 1. Kaplan-Meier curve showing no difference was observed between the groups with and without anastomotic leakage

Kolmogorov-Smirnov test was performed and it was shown that the parameters fit the normal distribution. Descriptive statistics (frequency, percentage distribution, etc.) were used as statistical analysis. In the comparison of the two groups; the Chi-square test was used for qualitative values and the Student-t-test was used for quantitative data. $P < 0.05$ was considered statistically significant.

RESULTS

The study included 90 patients; anastomotic leakage was not seen in 63 (70%) of the 90 patients, while leakage was observed in 27 (30%) of the 90 patients. An additional intervention was required in only 1 (3.7%) of the patients with leakage.

When the mean ages of the two groups were compared, no statistically significant difference was observed, and the mean age of the whole group was 71.22 ± 10.78 (73.5) years ($p = 0.615$). The rate of female patients in the whole group was found to be 40%, this rate was 39.7% in the group without anastomotic leakage and 40.7% in the group with leakage, However, the difference was not statistically significant ($p = 0.925$).

There was no significant difference between the operation times of both groups, the mean duration of all operations was found to be 308.63 ± 71.8 minutes ($p = 0.784$). However, when the post-operative hospitalizations of these patients were compared, it was observed that patients with anastomotic leakage were hospitalized for approximately 6 days longer, with a statistically significant difference of 14.73 ± 9.28 vs 20.63 ± 14.46 , as expected ($p = 0.029$). There was no significant difference between the two groups when the distribution of ASA scores was compared. In the whole group, 20 patients were ASA2 (22.2%), 53 patients were ASA3 (58.9%), 15 patients were ASA4 (16.7%), and 2 patients were ASA5. (2.2%) was evaluated.

When the patients' monocyte, MPV, PDW, LY, and PLT were examined, there was no discernible difference between the two groups. The mean monocyte of the whole group was 0.62 ± 0.25 , the mean of MPV was 10.29 ± 1.16 . The mean PDW was found to be 13.9 ± 2.6 , lymphocyte mean 1.74 ± 0.76 and platelet mean 263.88 ± 103.21 ($p = 0.940$; $p = 0.262$; $p = 0.191$; $p = 0.567$; $p = 0.860$, respectively).

When the albumin values of the patients were compared, the mean of the group without anastomotic leakage was 3.37 ± 0.61 , and the mean of the group with leakage was 3.37 ± 0.51 , no statistical significance was observed ($p = 0.975$). When the CRP values were examined, the mean of Group 1 was 21.18 ± 27.93 , the mean of Group 2 was 37.95 ± 65.52 , and no significant difference was found ($p = 0.715$).

The mean pre-operative CA19-9 level of the group without anastomotic leakage was 882.77 ± 2662.23 and the mean of the patients with leakage was 229.23 ± 455.1 , although the average of the patients with leakage was lower. this difference was not statistically significant ($p = 0.122$). There was no significant difference in amylase values between the groups. The mean amylase value of all patients was observed as 62.78 ± 68.3 ($p = 0.476$).

When the relationship between the ductus diameters between the two groups was evaluated numerically, the duct width of the patients without leakage was 4.13 ± 2.26 mm (3.4) and that of the patients with leakage was 3.91 ± 3.03 mm. Although a difference of 1 mm was observed between the median values, no statistically significant difference was found in the Mann-Whitney U test ($p = 0.240$). When the relationship between the groups formed according to the pancreatic duct width being less than 3 mm and 3 mm and above and the anastomotic leakage relationship is examined, the rate of duct width of 3 mm and above in the group without leakage was 41.27%, while this rate was significantly higher with 62.96% in the group with leakage, but it was statistically significant. no difference could be found, which was thought to be related to the low number of patients ($p = 0.059$).

When the appearance of the patients on CT was evaluated, it was seen that 60.3% of the patients in the non-leakage group had a rigid appearance, and this rate was statistically significantly reduced to 29.6% in the patients with leakage ($p = 0.008$).

The mean duration of observation of all patients was found to be 922.84 ± 809.155 days. When the observation times of the two groups were evaluated, no significant difference was observed between the two groups ($p = 0.570$). When the patients were examined in terms of mortality, there were 12 (13.3%) patients with mortality at the same hospitalization in the whole group, no statistical difference was observed between the two groups ($p = 0.787$). Disease-

related mortality was observed during the postoperative period in 25.6% of the patients who were followed up, and no statistically significant difference was observed between the two groups (p=0.316).

The mean time to mortality in patients with mortality was 302.22±564.42, and no difference was observed between the groups with and without anastomotic leakage (p=0.628). As a result of the Kaplan Meier analysis performed to determine the estimated average survival time, the estimated average survival time of the patients in the whole group was determined as 2151.437 days (±155.468). The estimated survival time of the group without anastomotic leakage was 2103,849 days (±180.75) and the estimated survival of the group with anastomotic leakage was 2253,698 days (±286.06). (p=0.473).

DISCUSSION

It is a general opinion that the quality of pancreatic tissue and the width of the pancreatic duct may be related to the rates of postoperative pancreatic fistula (POPF). Pancreatic anastomosis, which is included in a complex surgery such as PD, is an issue that needs to be emphasized, both in terms of its location and the tissue it contains.

Pancreatic tissue evaluated preoperatively, perioperatively, and postoperatively is an important risk factor for anastomotic leakage. In a study by Yeo et al.(17), they showed that the softness of the pancreatic tissue statistically increased the risk of pancreatic anastomotic leakage. Lin et al. (18) found that soft pancreatic parenchyma is the most frequently accepted risk factor for pancreatic fistula in a study of

Table 1. Comparison of variables between groups

Variable	All Patients (n=90)	No Leakage (n=63)	Anastomosis Leak (n=27)	Statistical Significance
Age	71.22±10.78	71.43±11.38	70.74±9.4	0.615
Gender				0.925
Male	54 (60.0%)	38 (60.3%)	16 (59.3%)	
Female	36 (40.0%)	25 (39.7%)	11 (40.7%)	
Post-operative hospitalization time	16.5±11.34	14.73±9.28	20.63±14.46	0.029
Operation duration	308.63±71.8	305.35±68.67	316.3±79.48	0.784
ASA				0.285
ASA 2	20 (22.2%)	11 (17.5%)	9 (33.3%)	
ASA 3	53 (58.9%)	38 (60.3%)	15 (55.6%)	
ASA 4	15 (16.7%)	12 (19%)	3 (11.1%)	
ASA 5	2 (2.2%)	2 (3.2%)	0 (0%)	
MO	0.62±0.25	0.61±0.23	0.64±0.3	0.940
MPV	10.29±1.16	10.38±1.24	10.08±0.96	0.262
PDW	13.9±2.6	14.1±2.57	13.43±2.66	0.191
LY	1.74±0.76	1.73±0.65	1.77±0.99	0.567
PLT	263.88±103.21	266.98±109.12	256.63±89.39	0.860
ALB	3.37±0.58	3.37±0.61	3.37±0.51	0.975
CRP	26.21±43.1	21.18±27.93	37.95±65.52	0.715
CA 19-9	686.71±2255.78	882.77±2662.23	229.23±455.1	0.122
Amylase	62.78±68.3	62.23±70.76	64.07±63.47	0.476
Ductus diameter (mm)	4.07±2.5	4.13±2.26	3.91±3.03	0.240
Ductus diameter groups				0.059
<3 mm	47 (52.22%)	37 (58.73%)	10 (37.04%)	
≥3 mm	43 (47.78%)	26 (41.27%)	17 (62.96%)	
Pancreas morphology				0.008
Soft	44 (48.9%)	25 (39.7%)	19 (70.4%)	
Hardened	46 (51.1%)	38 (60.3%)	8 (29.6%)	
Anastomosis leak incidence	27 (30.0%)			
Leak Type (n=27)				
Leak w/o Intervention	26 (96.3%)			
Leak w/ Intervention	1 (3.7%)			
Same admission mortality	12 (13.3%)	8 (12.7%)	4 (14.8%)	0.787
Overall survey duration	922.84±809.155	944.21±793.209	873±858.579	0.570
Overall mortality	23 (25.6%)	18 (28.6%)	5 (18.5%)	0.316
Overall days to mortality	302.22±564.42	285±514.86	364.2±787.03	0.628
Estimated survival duration (SE)	2151.437 (155.468)	2103.849 (180.75)	2253.698 (286.06)	0.473

1891 patients. This demonstrated that patients with a soft pancreas were much more likely to develop a POPF following PD than those with a hard pancreas. The data on the increased risk of anastomosis in patients with soft pancreatic tissue was found in our study in line with the literature.

We discuss many possible explanations for the link between soft pancreatic tissue and the probability of fistula formation. First, a soft pancreas is more easily injured, either directly or as a result of ischemia caused by sutures placed between the pancreatic parenchyma and the seromuscular layer of the jejunum; second, and perhaps most importantly, the soft pancreas has a better exocrine function, secreting more pancreatic juice rich in proteolytic enzymes (18-20).

Mazzafero et al. (21), Van Berge et al. (22) and Yang et al. (23) stated that the size of the pancreatic duct is effective in pancreatic leakage, and the risk of pancreatic leakage increases in ducts with a size of ≤ 3 mm, as a result of their large-scale studies. In a study, it was shown that each 1 mm shrinkage of the pancreatic duct increases the risk of anastomotic leakage by 68% (24). In this study, when the relationship between the ductus diameters between the two groups was evaluated numerically, the canal width was 4.13 ± 2.26 mm (3.4) in patients without leakage and 3.91 ± 3.03 mm (2.5) in patients with leakage. Although a difference of 1 mm was observed between the median values, no statistically significant difference was found in the Mann-Whitney U test ($p=0.240$). We believe that the limited number of our patients is to blame for this condition, which differs from the literature.

There are certain limitations to our research. Our research was a retrospective one with a small number of participants. In addition, Therefore, there were patients that we could not include in the study.

CONCLUSION

In summary, our study showed that pancreatic fistula after PD is associated with soft pancreatic parenchyma. The surgeon should consider this risk factor when performing a PD and be more careful to reduce the rate of pancreatic fistula.

ETHICAL DECLARATIONS

Ethics Committee Approval: The study was carried out with the permission of Hitit University Erol Olçok Training and Research Hospital Non-Invasive Research Ethics Committee (Date: 10/01/2022, Decision No: 2021-88).

Informed Consent: Because the study was designed retrospectively, no written informed consent form was obtained from patients.

Referee Evaluation Process: Externally peer-reviewed.

Conflict of Interest Statement: The author has no conflicts of interest to declare.

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Author Contributions: The author declare that they have all participated in the design, execution, and analysis of the paper, and that they have approved the final version.

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