Clinical Analysis of Pancreaticoduodenectomies for Benign Pathologies

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ABSTRACT

Objective: To evaluate the clinical, laboratory and imaging data of patients who underwent pancreatoduodenectomy (PD) for proven benign pathologies.

Study Design: Descriptive study.

Place and Duration of Study: Department of General Surgery, İzmir Katip Celebi University, School of Medicine, Turkey between January 2015 and June 2020.

Methodology: All patients who underwent PD, and were found to be benign histopathologically, were included in the study. Patients who had to undergo PD due to trauma during operations performed for other reasons, were also included in the study. The data was collected as per objective.

Results: Diagnosis of benign pathologies was made histopathologically in 27 of the 248 patients (10.89%). It was found that 8 of 17 patients, who had biopsy in the preoperative period, were operated with a pre-diagnosis of malignancy, nine were performed PD due to accompanying clinical findings despite the detection of non-diagnostic cytology, and ten patients were taken into surgery; because of the malignancy risk could not be ruled out.

Conclusion: Patients with benign pathology were found to have better parameters of CRP and total bilirubin. PD was performed in patients with mass in the pancreas; and whose cancer risk could not be ruled out. To reduce PD due to benign causes, patients with undiagnosed lesions should be evaluated with a multidisciplinary approach, and diagnostic tools should be cross-checked. PET/CT may also be useful in the differential diagnosis.

Key Words: *Benign, Diagnosis, Pancreas, Pancreaticoduodenectomy, Pathology.*

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INTRODUCTION

Pancreatic cancer is the seventh leading cause of cancer-related deaths worldwide.[1] Despite improvements in treatment modalities, surgical resection is the only curative treatment today.[2] Despite improvements in current cross-sectional imaging and invasive diagnostic modalities, it has been reported in the literature that benign disease was postoperatively detected in 6.5-15.6% of pancreatoduodenectomy specimens.[3-7] Due to the aggressive course and poor-survival of pancreatic cancer, surgical excision is recommended in patients with suspicious lesions; even biopsies do not support malignancy diagnosis.

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Morbidity and mortality after PD are not negligible, and it is controversial whether it is the only way to exclude malignancy.[2,8] Five-year survival of pancreatic cancer following margin negative (R0) pancreaticoduodenectomy (PD) is reported to be 30% in those without lymph node involvement and 10% in those with lymph node involvement.[9] Standard lymphadenectomy for pancreatoduodenectomy should strive to resect lymph node stations No. 5, 6, 8, 12, 13, 14 and 17. Extended lymphadenectomy cannot be recommended.[9]

The main purpose of this study was to examine the indications of patients who underwent PD due to benign periampullary lesions and find the predictive factors that will reduce the amount of patients who undergo PD for benign reasons.

METHODOLOGY

This is a descriptive study, retrospective analysing the data from a database. Patients who underwent PD between 2015 and 2020 in the Department of General Surgery were evaluated. All patients, who underwent PD and were found to have benign histopathology, were included in the study. Patients, who had to undergo PD due to trauma during operations performed for other reasons, were also included in the study.

The study was carried out in accordance with the principles of the Helsinki Declaration. As a routine procedure, written, signed informed consent form was obtained from all patients for treatment modalities and publication, before the procedures. İzmir Katip Celebi University, Atatürk Training and Research Hospital, Human Research Ethics Committee approved this study: 2020--GOKAE-0238.

The parameters analysed for all patients included: Age, comorbidities, preoperative levels of total bilirubin (TB), cancer antigen 19-9 (Ca 19-9), Ca 19-9/ TB ratio, radiological imaging results, histopathological examination of preoperative tissue sampling, postoperative outcomes, and final histopathological evaluation.

The operation decision was made at the multidisciplinary Hepatobiliary Council, which included a surgeon, a gastroenterologist, a radiologist, oncologist, and a pathologist experienced in gastrointestinal and hepatopancreatobiliary pathology. Tissue sampling was performed preoperatively by biopsy, EUS-FNA, brush cytology, and papillectomy. Pathological results were categorized as; benign, suspicious, malignant, and non-diagnostic.

Data were evaluated in the statistical package programme of IBM SPSS Statistics version 25.0. Data are presented as number of observations (n, %), mean ± standard deviation, Q1-Q3 and range. The results of homogeneity (Levene's test) and normality (Shapiro-Wilk test) were used to decide the statistical methods for comparing the study groups. Among normally distributed groups with homogeneous variances, dependent groups were compared using the Student's t-test. According to the test results, parametric test assumptions were not available for some variables; therefore, the independent groups were compared using the Mann-Whitney U-test. Categorical data were analysed, using Fischer's Exact test and the Chi-square test. A p-value <0.05 was considered statistically significant

RESULTS

Diagnosis of benign pathologies were made histopathologically in 27 of the 248 patients included in the study. The frequency of benign pathologies was 10.89% (Table I). Of the 27 patients, 15 (55.56%) were male and the median age was 63 (52-69) year.

The most common complaints in the benign pathology group were abdominal pain (10 patients; 37.04%). The clinical findings predicting benign pathologies were primarily found as diagnostic criteria. The most common finding in CT, MRCP, and EUS was the periampullary mass (Table II). Preoperative tissue sampling was performed by biopsy, EUS-FNA, brush cytology, and papillectomy (Table III).

Preoperative tissue sampling was performed in 17 (62.96%) patients with a final diagnosis of benign or premalignant pathologies. In the preoperative period, eight patients were taken to surgery with a pre-diagnosis of malignancy, nine patients could not be biopsied, and ten patients were taken to surgery with suspected malignancy.

Patients with benign pathology were found to have a better condition for inflammation parameter (CRP, Table I). The total bilirubin level was found significantly higher in the malignant pathologies group than the benign pathologies group.

Three patients, who underwent papillectomy, were diagnosed with malignant (adenocarcinoma) disease. PD was performed in these three patients due to positive excisional margins.

Early mortality (first thirty days postoperatively) in the benign pathologies group was observed in two patients. During long-term follow-up, there was mortality in two patients.

Table I: Details of the criteria analysed between benign and malignant groups.

	Benign (n=27)	Malign (n=221)	p-value
Age[f] (years)	63 (52-69)	63 (56-70)	0.499
Gender† (Male)	15 (55.56)	126 (57.01)	0.885
ASA score† ASA I-II ASA III-IV	 17 (62.96) 10 (37.04)	 142 (64.25) 79 (35.75)	0.895
Leukocyte[f] (10^9/L)	7.6 (6.5-9.7)	7.5 (6.1-9.4)	0.842
Hemoglobin[f] (g/dL)	12.85±1.41 (10.4-15.7)	12.02±1.75 (8.3-16.7)	0.02
Total protein[f] (g/dL)	6.72±0.86 (4.7-7.9)	6.56±0.80 (4.2-8.9)	0.44
CRP[f] (mg/L)	0.5 (0.3-2.3)	1.7 (0.45-3.3)	0.038
TB[f] (mg/dL)	0.9 (0.6-3.6)	3.2 (0.9-7.6)	0.001
Ca 19-9[f] (U/mL)	20 (7.5-35.5)	45 (15.75-213.25)	0.008
Ca 19-9/ TB ratio[f]	18.46 (9.42-41.71)	24.32 (6.67-89.94)	0.418
Surgical technique† Classical PD Pylorus-preserving PD	 14 (51.85) 13 (48.15)	 150 (67.87) 71 (32.13)	0.097
Vascular intervention† (Yes)	2 (7.41)	26 (11.76)	0.749
Peroperative blood transfusion† (Yes)	10 (37.04)	124 (56.11)	0.061
Duration of surgery[f] (min.)	310 (253-346)	323 (267.5-365)	0.328
Duration of hospital stay[f] (days)	10 (7-17)	10 (7-15)	0.869
Morbidity† (Yes)	16 (59.26)	164 (74.21)	0.1
SSI† (Yes)	9 (33.33)	93 (42.08)	0.383
DGE† (Yes)	8 (29.63)	53 (23.98)	0.52
CR-POPF† (Yes)	6 (22.22)	39 (17.65)	0.597
PPH† (Yes)	3 (11.11)	30 (13.57)	>0.999
Mortality† (Yes)	2 (7.41)	22 (9.95)	>0.999

[f]: Median (IQR) or mean ± standard deviation (min-max), †: numbers (%), ASA: physical status classification system by the American Society of Anesthesiologists, CRP: C reactive protein, TB: Total bilirubin, Ca 19-9: cancer antigen 19-9, PD: Pancreaticoduodenectomy, SSI: surgical site infection, DGE: delayed gastric emptying, CR-POPF: Clinically related postoperative pancreatic fistula, PPH: post-pancreaticoduodenectomy hemorrhage.

DISCUSSION

The prognosis of pancreatic cancer is poor, and advances in adjuvant therapy have lagged behind other common cancers.[9] It causes doctors to prefer PD as a risk-reducing method in the decision-making process. As a result, 6.5-15.6% benign disease is ultimately detected.[3-7] In this study, the frequency of benign pathologies was 10.89%.

Some clinical series reported that weight loss, jaundice/hyperbilirubinemia, and high levels of Ca 19-9 were high predictive factors in terms of malignancy.[3-7] In this study, it was found that total bilirubin and Ca 19-9 levels were higher in the malignant group, and the difference between the groups was statistically significant.

Molina *et al.* reported that benign disease in 27% of patients with a height of Ca 19-9.[10] There are studies in the literature on whether the Ca 19-9/TB ratio is a prognostic factor for pancreatic cancer.[11]

Table II: Preoperative clinical findings, diagnostic tools and predictive values in benign group.

Findings (n)	Total	US (n=13)	CT (n=15)	MRCP (n=13)	PET-CT (n=2)	EUS (n=22)	ERCP (n=6)	Endoscopy (n=2)	PPV (%)
Normal	3	3	2	-	-	-	-	-	11.11
Mass	16	2	11	9	2	16	-	-	59.25
Biliary dilation	9	9	6	3	-	5	-	-	33.33
Biliary stenosis	6	-	-	-	-	-	6	-	22.22
Biliary duct irregularity	2	-	-	-	-	2	-	-	3.7
Double duct sign	4	-	4	2	-	3	-	-	14.82
Honeycomb pattern	3	-	-	-	-	3	-	-	11.11
Cholecystitis	2	2	-	-	-	-	-	-	7.4
Cholelithiasis	2	2	-	-	-	-	-	-	7.4
Pancreatic duct dilation	3	-	1	2	-	3	-	-	11.11
Target mark in duodenum part 2	1	-	1	-	-	-	-	-	3.7
Lymphadenopathy	1	-	1	-	-	1	-	-	3.7
Pancreas divisum	1	-	-	1	-	-	-	-	3.7
Portal vein invasion	1	-	-	-	-	1	-	-	3.7
Duodenal polyp	2	-	-	-	-	-	-	2	7.4
NPV (%)		84.62	36.36	30.77	0	27.27	0	0	

In some patients, more than one finding was detected and examined with a diagnostic tool.
NPV: negative predictive value, PPV: positive predictive value, US: abdominal ultrasography, CT: computed tomography, MRCP: magnetic resonance cholangiopancreatography, EUS: endoscopic ultrasonography, ERCP: endoscopic retrograde cholangiopancreatography, PET-CT: positron emission tomography, FDG: fluoro-2-deoxy-glucose.

Table III: Positive predictive values of preoperative sampling techniques.

Procedure	Preoperative pathology	Final pathology		Positive predictive value (%)
		Malign	Benign	
Biopsy (65)	Malign	32	3	91.43
	Benign	6	0	
	Non-diagnostics or suspicious	20	4	
EUS FNA (38)	Malign	16	0	100
	Benign	3	1	
	Non-diagnostics or suspicious	14	4	
Brush cytology (22)	Malign	9	1	90
	Benign	2	1	
	Non-diagnostics or suspicious	9	0	
Papillectomy (13)	Malign	8	3	72.73
	Non-diagnostics or suspicious	2	0	

There is no study analysing its place in distinguishing pancreatic benign and malignant diseases. Ca 19-9 /TB ratio was higher in the malignant group. However, no statistical significance was found due to the sample size in this study.

The sensitivity of USG is insufficient in detecting of pancreatic cancer. The sensitivity varies between 48% and 89% with lower specificity and accuracy, with variation in these rates with the size of the tumor and operator's level of experience.[12]

The most frequently used method in the diagnosis of pancreatic mass is CT. Despite current developments in pancreatic imaging, there is still overlap in the imaging findings of benign and malign pathologies, and these similarities are a trap for radiologists.[13,14]

In a study on 344 patients, Gerritsen *et al*. and two expert radiologists retrospectively evaluated pancreatic CT scans. The sensitivity, specificity, positive and negative predictive value of masses identified in the original CT-report were 68%, 42%, 79%, and 7%, respectively. For masses identified in expert-consensus, these values were 54%, 87%, 98%, and 12%.[14]

MRCP is better than CT in revealing the anatomy of the biliary tract and pancreatic duct. It is at least as sensitive as ERCP to detect pancreatic cancers. Today, ERCP's role in patients with suspected pancreatic cancer has turned into a mainly therapeutic modality.[2]

In patients who are thought to have a benign disease, it may be beneficial to undergo PET CT before performing interventional procedures. In a retrospective study involving 87 patients, Santhosh *et al.* concluded that it might be useful in the differential diagnosis of benign and malign pathologies. This study found that the cut-off value for SUVmax was 2.8.[15] In this study, two patients in the benign group were evaluated with PET CT, and SUVmax values of these patients were determined as 10.3 and 8.64.

Combinations of several imaging findings are recommended to increase the probability of correct diagnosis.[16] A study involving 589 patients by Ghaneh *et al.* reported that sensitivity and specificity of CT on the diagnosis of pancreatic cancer were 88.5% and 70.6%, respectively, and these

values of PET-CT were 92.7% and 75.8%, respectively. In addition, the combination of monocarboxylate carriers with PET-CT promises to distinguish benign and malign pathologies.[17]

As the study centre is a tertiary-care Oncology centre, the most frequently used imaging method in the benign group was EUS. EUS may be useful in detecting masses that cannot be demonstrated on CT.[12]

It is reported that the specificity rate of EUS FNA is 96%, and brush cytology is 48%.[18] In the present study, it was found that brush cytology and EUS FNA positive predictive values were similar in literature. In a study by Aslam *et al.*, thick needle biopsy was associated with less repetition, higher quality histopathological sample, and shorter processing time for sampling.[19] In this study, a thick needle biopsy was used most frequently for preoperative tissue sampling.

Studies report that sampling errors of pancreatobiliary malignancies as well as abnormalities leading to inadequate cytological evaluation.[7,18] In some cases, it should come to the agenda to get opinions from different pathologists and to repeat the sampling, if necessary.

Papillectomy is a widely accepted treatment for benign papilla diseases, but there is controversy about the treatment of early-stage malignant lesions (tumors limited by mucosa or Oddi sphincter). Some studies reported that early-stage T1 adenocarcinomas without lymphovascular invasion can be successfully treated with papillectomy. In a study by Alvarez-Sanchez *et al.*, 32% of patients staged as N0 in EUS and CT showed nodal metastasis after surgery.[20] For this reason, its use as a current treatment modality in malignant patients is limited.

Future research should focus on reliable tumor markers, molecular markers (K-ras, p53, etc.), and effective diagnostic strategies that confirm the malignancy diagnosis with high precision.[7]

In this study, unlike other studies in the literature, all steps in the diagnostic stages were considered. Besides, almost all of the studies in the literature were conducted before 2015, and the chronology of this study is between 2015-2020, and all current diagnostic modalities have been used in the diagnosis phase. The most important limitation is that the study is based on retrospective data collection. The fact that premalignant and benign patients are in the same group can be considered as another limitation.

CONCLUSION

Patients with benign pathology were found to have a better parameters for CRP and total bilirubin. Surgeons tended to perform PD in patients with mass in the pancreas and whose cancer risk could not be ruled out. To reduce PD due to benign causes, patients with undiagnosed lesions should be evaluated with a multidisciplinary approach, and diagnostic tools should be cross-checked. PET/CT may also be useful in the differential diagnosis.

ETHICAL APPROVAL:
Ethical approval was obtained from the İzmir Katip Celebi University, Atatürk Training and Research Hospital, Human Research Ethics Committee, prior to the initiation of the research work.

PATIENTS' CONSENT:
All participants signed the informed consent before enrollment in the study.

CONFLICT OF INTEREST:
The authors declared no potential conflicts of interest with respect to the research, authorship, and/or publication of this article.

AUTHORS' CONTRIBUTION:
AA: Collected and analysed data, wrote manuscript.
FG: Analysis and interpretation, materials, data collection.
NA: Searched literatüre, data collection.
YS: Analysis and interpretation, materials, data collection.
FHD: Drafted and reviewed the paper, advices and final approval
OND: Conception and design, critical reviews, approval of the final version.

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