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Partial Atrophy of The Pancreas in Endoscopic Ultrasonography may be a Sign of Pancreatic Cancer

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ABSTRACT

Introduction: Solid and/or cystic lesions of the pancreas can range from benign to malignant, and the differential diagnosis of pancreatic carcinoma (PC) is of uttermost importance. Endoscopic ultrasonography (EUS) is frequently used and is helpful in detecting small (<2 cm) lesions and provides information about the extralesional pancreas. EUS also facilitates tissue diagnosis and allows the cyst fluid examination. Our aim was to evaluate the role of EUS findings and cyst characteristics of pancreatic lesions in predicting PC.

Methods: Records of patients with pancreatic lesions were retrospectively assessed. EUS findings, serum C19-9 levels, CEA levels, and cyst biochemistry of the patients were noted. The relationship between PC, mucinous pathologies, EUS findings, cyst characteristics, and serum biochemistry was evaluated.

Results: Two-hundred-four patients had EUS-guided biopsy for a pancreatic lesion (48% solid). Eighty-nine patients had PC. The serum CA19-9 cut-off value for PC was 37 U/mL (AUC: 0.81). In multivariate analysis, solid lesions, age, CA19-9>37 U/mL, and partial atrophy in the pancreas were independently associated with PC. For solid lesions, age and size >24 mm; and for cystic lesions, male gender and mucinous pathology were independently associated with PC. Thirty-six of the cystic lesions had mucinous pathology. Cyst and serum CEA, string sign, wesung connection, and tail location was associated with mucinous pathology. Cyst CEA cut-off for mucinous pathology was 80 ng/mL (AUC: 0.89). CEA >80 ng/mL was found to be associated with mucinous pathology in multivariate analysis.

Conclusion: High CA19-9, solid lesion, and lesion-related partial atrophy of the pancreas are associated with PC, and these should be alarming for clinicians in practice. The mucinous character, which is a significant risk of PC for cystic lesions, can be optimally defined with the CEA cut-off value of 80 ng/mL.

Keywords: Endoscopic ultrasonography, fine needle aspiration biopsy, pancreatic carcinoma, mucinous pathology, CEA

Introduction

Solid and/or cystic lesions can be detected in the pancreas, either symptomatic or incidentally and are generally more common with advancing age. These include benign inflammatory/post-inflammatory lesions, benign neoplastic lesions, and pre- or low/high-grade malignant lesions (1). Although the probability of solid lesions being neoplastic is higher than cystic ones, there is a premalign-malignant neoplastic potential also for cystic lesions, especially for those with mucinosis features (2). Among these lesions of the pancreas, the most feared in the differential diagnosis is pancreatic adenocarcinoma (PC), which is mostly diagnosed at an advanced stage when surgical treatment is no longer an option. Advanced PC is associated with very low survival rates and is still an important cause of cancer-related deaths worldwide (3). Recognizing PC and distinguishing them from other pathologies should be the aim of evaluation due to the potential aggressive clinical course.

Endoscopic ultrasonography (EUS) is frequently used in the examination of pancreatic lesions because it is superior to cross-sectional imaging methods in detecting small (<2 cm) and solid lesions of the pancreas (4). EUS also provides information about extralesional pancreas and adjacent tissues. Another advantage is that EUS facilitates tissue diagnosis by allowing fine-needle aspiration (FNA) biopsy in solid lesions during the examination and may also help the classification of cystic lesions by providing an opportunity for cyst fluid aspiration and biochemical examination.

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Sampling the cyst content allows biochemical analyses such as amylase, CEA, and glucose levels in the cyst fluid, as well as advanced genetic and molecular examination (5).

The aim of our study was to evaluate the role of EUS findings and cyst fluid characteristics in predicting PC and/or mucinous pathologies in solid and cystic lesions of the pancreas.

Methods

The records of patients who underwent EUS examination of the pancreas between January 2017 and 2022 were retrospectively assessed. The location, size, and characteristics (cystic or solid) of the lesions were evaluated and FNA and/or biopsy if performed was noted. Other parameters accompanying the lesion detected in EUS and evaluated were as follows: ductal dilatation (common bile duct and/or Wirsung), lymphadenopathy, presence of ascites, solid lesion in the liver suggesting metastasis, appearance compatible with vascular invasion (portal vein, splenic vein, splenic artery, superior mesenteric vein, artery, hepatic artery and celiac trunk), presence of chronic pancreatitis, and partial/local pancreatic atrophy that does not meet the criteria for chronic pancreatitis. Chronic pancreatitis was defined as having 5 or more of the 9 EUS criteria put forward by the International Working Group (6).

In cystic lesions, the presence of septation or mural nodule (solid component), the relationship of the cyst with Wirsung, the presence of a string sign if aspiration was performed, and the cyst CEA levels were also examined. If available, serum CA19-9 and CEA levels of the patients, which were measured within 2 weeks before the EUS procedure, were also included in the analysis.

All EUS examinations were performed by the same physician, and lesion biopsies were performed using a 22 G needle. Among the reported FNA biopsy results, categories 5 and 6 defined by the Pancreatic Cytopathology Study group were considered malignant (7,8). Lesions that were category 4b and showed mucinous components cytologically or lesions that underwent pancreatic resection and whose surgical pathology was reported as mucinous were considered as mucinous pathology. Clinical, radiological, and treatment (oncological) data of the patients were obtained from electronic medical records. Patients with malignant FNA results and/or patients who received oncological treatment for PC and/or patients with radiological evidence of metastatic disease with a primary origin of the pancreas (taking into account radiological work-up, FDG - positron emission tomography) were regarded as having PC. The relationship between PC, mucinous pathologies, and EUS findings, cyst characteristics, and serum biochemistry was evaluated.

This study was approved by the local ethics committee. The procedures used in this study comply with the principles of the Declaration of Helsinki.

Statistical Analysis

Mean and standard deviation were used for normally distributed data, median and IQR for non-normal distribution, and frequency for categorical data. Cut-off values and sensitivity specificity for CEA and CA19-9 were calculated using ROC analysis. Significant parameters related to pancreatic carcinoma (PC) and/or mucinous pathology were evaluated further by logistic regression analysis. IBM-SPSS v.29 Was used for statistical calculations.

Results

A total of 319 EUS procedures for the pancreas was evaluated. Of these, 204 (64%) patients had EUS-guided biopsy for a pancreatic lesion, and 78 of those who underwent biopsy also had cystic fluid aspiration available for biochemical analysis. Fifty-five percent (n=113) of the patients who underwent the procedure were women. The mean age was 58 years (±13.7). Forty-eight percent (n=98) of the cases were solid and the rest were cystic lesions. While 81% of cystic lesions were pure cystic, the rest had a solid component/mural nodule accompanying the cystic lesion (n=20). The lesion and demographic characteristics of the study group is summarized at Table 1.

The size of solid and cystic lesions was similar, and the median size for both was 30 mm (solid: minimum-maximum: 5-120; IQR: 19; cystic: 8-115; 21; p=0.85). Among cystic ones, lesions including the solid component were larger in size numerically than isolated cystic lesions [34 mm (8-115;19) vs 30 mm (19-80;23), respectively] but the difference between them was not significant (p=0.119).

The distribution of the lesions in the pancreas was evaluated; the most common site for the lesions was the head of the pancreas, while the least common site was the uncinate. Table 2 summarizes the distribution and solid-cystic features of the lesions. Cystic lesions were significantly more common in the tail than in other parts of the pancreas (p=0.007). There

Table 1. Lesion and demographic characteristics of the study group

Patient demographics	
Sex (F)	55% (113)
Age	58±13.7
Lesion characteristics	
Solid	48% (98)
Cystic	52% (106)
Pure cystic	81% (86)
Cystic with solid component	19% (20)
Cases with biopsy	100% (204)
Cases with aspiration	38% (78)

Table 2. Distribution of lesions by anatomical parts of the pancreas, and cystic-solid features

	Anatomic parts of the pancreas				
	Uncinate	**Head**	**Neck**	**Body**	**Tail**
Total, % (n)	9.3% (19)	39.7% (81)	15.2% (31)	23.5% (48)	12% (25)
Solid, % (n)	52% (10)	53% (43)	51% (16)	50% (24)	24% (6)
Cystic, % (n)	48% (9)	47% (38)	49% (15)	50% (24)	76% (19)

was no relationship between the localization of cystic lesions in the pancreas and the presence of solid component/mural nodules (p=0.702). No correlation was found between the location and size of cystic or solid lesions and between location and patient age (p=0.803 and p=0.744 for cystic lesions and p=0.554 for solid lesions, respectively).

In patients undergoing biopsy and/or aspiration, findings reported in EUS that may be related to the lesion and cyst features are summarized in Table 3.

Thirty-six of the cystic lesions had mucinous pathology. When the lesion characteristics were evaluated, in terms of predicting mucinous pathology, aspiration CEA value (p<0.001), string sign positivity (p=0.009), cyst connected to wesung (p=0.033), cyst located at body or tail of pancreas (<0.028), and serum levels of CEA >3.1 (p=0.020) were found to be associated with mucinous pathology. The cut-off value for cyst CEA level in predicting mucinous pathology by ROC analysis was calculated as 80 ng/mL (AUC: 0.89; Figure 1). For this value, the sensitivity was 82% and the specificity was 90%. When the cut-off value for CEA was taken as 192 ng/mL, which is reported in the literature, the sensitivity decreased to 76%, while the specificity increased to 97%. In the multivariate regression analysis of mucinous pathology-related factors, aspiration CEA >80 ng/mL was found to be associated with mucinous pathology [p=0.002; 81 (5.1-1290)].

In 133 patients, the final diagnosis was clinically and/or histopathologically confirmed, and 89 of these patients were followed up and/or treated with a diagnosis of PC. While the final diagnosis was benign in 31 patients, neuro-endocrine tumor was detected in 13 patients. In the ROC analysis, the cut-off value for serum CA19-9 in distinguishing PC was 37 U/mL, and the AUC value was calculated as 0.81 (Figure 1). For this value, the sensitivity of CA19-9 in terms of PC was 79% and the specificity was 78%. Also, ROC analysis was performed (AUC: 0.76; Figure 1) for serum CEA, and pointed a cut-off level of 3.1 ng/mL could predict PK with 70% sensitivity and 65% specificity. Univariate and multivariate analysis associated with PC are summarized in Table 4. In multivariate analyzes, the solid character of the lesion, increasing age, a CA19-9 value >37 U/mL, and presence of local atrophy in pancreas (without chronic pancreatitis) were found to be independently associated with PC.

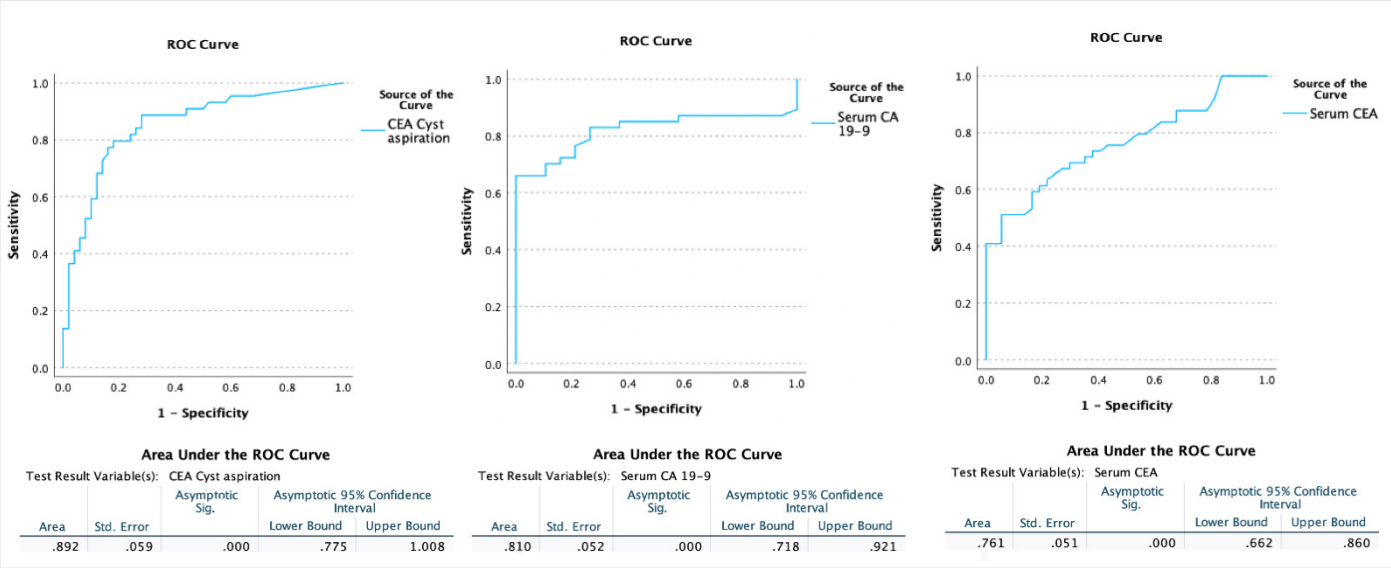
Table 3. Some findings reported in EUS related to the lesion, and cyst features

Vascular invasion	**13.2% (n=27)**	**Common bile duct and/or Wirsung dilatation**	**35% (n=71)**
Ascites	6% (n=12)	Double duct sign	10.8% (n=22)
Lymphadenopathy	15.1% (n=31)	Chronic pancreatitis	7.8% (n=16)
Suspected Liver Metastasis	2.8% (n=6)	Partial atrophy (no chronic pancreatitis)	18.4% (n=38)
Septation (cystic lesions)	58% (n=62)	String sign positivity	15% (n=14/92)
Cyst-Wirsung connection	45% (n=48)		

Table 4. Univariate and multivariate analyzes associated with PC

	Univariate analyses	**Multivariate analyses**	
	p	**p**	**OR**
Male sex	0.142	-	
Age	<0.001	0.012	1.08 (1.02-1.16)
Solid lesion	<0.001	0.025	6.6 (1.2-34.5)
Size	0.110	-	
Non-tail localization of lesion	<0.001	0.948	
Vascular invasion	<0.001	0.324	
Suspected liver metastasis	0.153	-	
Ascites	0.030	0.991	
Lymphadenopathy	<0.001	0.384	
Double duct sign	0.008	0.931	
Chronic pancreatitis	0.361	-	
Partial atrophy (without chronic pancreatitis)	0.005	0.041	3 (1.1-61)
Serum Ca19.9 >37	<0.001	0.017	13.3 (1.6-111)
Serum CEA >3.1	0.005	0.833	
Solid component/mural nodule$^{\varphi}$	0.243	NA	
Septation$^{\varphi}$	0.730	NA	
String sign$^{\varphi}$	0.212	NA	
Connection to Wirsung$^{\varphi}$	0.281	NA	

$^{\varphi}$Calculated for cystic lesions, OR: Odds ratio, PC: Pancreatic carcinoma



Area Under the ROC Curve

Test Result Variable(s): CEA Cyst aspiration

Area	Std. Error	Asymptotic Sig.	Asymptotic 95% Confidence Interval	
			Lower Bound	Upper Bound
.892	.059	.000	.775	1.008

Area Under the ROC Curve

Test Result Variable(s): Serum CA 19–9

Area	Std. Error	Asymptotic Sig.	Asymptotic 95% Confidence Interval	
			Lower Bound	Upper Bound
.810	.052	.000	.718	.921

Area Under the ROC Curve

Test Result Variable(s): Serum CEA

Area	Std. Error	Asymptotic Sig.	Asymptotic 95% Confidence Interval	
			Lower Bound	Upper Bound
.761	.051	.000	.662	.860

Figure 1. ROC analysis of cyst CEA value for mucinous pathology, serum CA19-9 and CEA for pancreatic carcinoma

Investigations performed in the whole group regarding PC were also repeated for the cystic or solid lesion subgroups. In multivariate analysis, for solid lesions, age [p=0.036; 1.1 (1.01-1.2)] and size more than 24 mm [p=0.014; 15.5 (1.7-137)]; and for cystic lesions, male gender [p=0.022, 8 (1.6-88)] and mucinous pathology [p=0.041, 6 (1.1-64)] were found to be associated with PC. The size cut-off value for solid lesions was calculated by ROC analysis (AUC 0.68).

Discussion

Our study revealed PC-related factors of EUS-FNA findings. While the solid nature of the lesion and serum CA19-9 increase were found to be associated with PC, the relationship between the presence of local/partial atrophy in EUS and PC should be emphasized. In cystic lesions, the mucinous character was associated with malignancy, and another important finding of our study is that the cut-off level we found for the cyst CEA value was 80 ng/mL, lower than the previously proposed value (9).

Pancreatic cancer (PC) is a malignancy in which early diagnosis is crucial due to its poor prognosis (10). Although surgery is the only curative treatment method, 5-year survival is better in patients with small tumors without lymph node involvement (11). However, in 80% of the patients, surgery is not possible due to locally advanced or metastatic disease (12). Recent studies on the pathophysiology of PC suggest that the precancerous stage can be quite long (13,14). Although there is no general recommendation for population-based PC screening, this long interval period provides the chance for early diagnosis when the disease is still surgically curable, especially for people suitable for screening with a defined genetic mutation or a familial PC history (15). EUS has its place in such PC screening because of its many advantages. EUS's success in revealing small pancreatic lesions and its contribution to early diagnosis is quite high (16). In addition, it can provide many accompanying findings related to the nature of the lesion. In addition, it can contribute to the pathological diagnosis in an accurate and safe way because it offers the possibility of FNA (17). In the differential diagnosis of malignant solid and cystic lesions of the pancreas; for solid lesions, lymphoma, metastasis, neuroendocrine tumor, chronic pancreatitis, autoimmune pancreatitis, solid pseudo papillary tumor; for cystic lesions, pseudocyst, serous cyst adenoma, and mucinous cystic neoplasia are pathologies that should be considered (1). While the role of surgery for treating most of these pathologies is quite limited, the recognition of early-stage PC is crucial for surgical curability (10).

EUS examination provides information about the location and size of the pancreatic lesion, its cystic or solid nature, its relation to the surrounding structures or pancreatic canal, and the characteristics of the extra-lesional pancreatic tissue, and may reveal extra-pancreatic findings such as accompanying lymphadenopathy, liver metastasis, or ascites in some patients (18). In our study, nearly half of the cases had solid lesions, and nearly half of them were located in the pancreatic head. Although no evaluation was made in the study design regarding the EUS indications of the patients, the accumulation of solid lesions in this region may be related to the higher potential of a lesion in the pancreatic head to be symptomatic due to its close relationship to the ampulla Vater and biliary system. On the other hand, no correlation was shown between the size and location of the lesion. The distribution of cystic lesions was found in favor of the pancreatic tail, which may be related to the more frequent localization of some cystic pathologies such as serous cyst adenoma and mucinous cystic neoplasia to this region (1).

Other rare findings that can be revealed by EUS examination may guide the clinician. Among these findings, vascular invasion (13%), suspicion of liver metastasis (approximately 3%), and accompanying lymphadenopathy (15%), which we found in our study, can be listed. Since histological sampling for lymphadenopathy was not performed and there were no liver lesion biopsies, it is not possible to comment on the contribution of these findings to histological diagnosis in our study, but the clinical guidance of these findings is clear.

In our study, the presence of partial atrophy in the pancreas related to the lesion was also associated with PC in regression analysis. The impact

of this finding, independent of the other two related factors age and the solid characteristic of the lesion is, to our knowledge, new to the literature and should be alarming for the clinician performing EUS in terms of PC. On the other hand, the double duct sign that is reported to be associated with PC in the literature could not be shown to be independently related to PC in our study.

Another parameter that we found to be related to PC is the high serum CA19-9 level (19). The cut-off value of CA19-9 that we found in distinguishing PC in our patient group was 37 U/mL, in line with the literature, and the sensitivity and specificity for this value were parallel to those reported in similar studies (79-81%, 82-90%, respectively) (20).

When solid and cystic lesions were evaluated separately, we showed that size was associated with the risk of PC for solid lesions, and a lesion larger than 2.4 cm was associated with PC regardless of other accompanying findings. In a study examining the diagnostic accuracy of EUS FNA, increased size was associated with higher diagnostic accuracy (21). In lesions smaller than 2.4 cm, the diagnostic contribution of EUS-FNA may be lower, which may have caused us to overestimate the cut-off value of size for predicting PC. On the other hand, in the same study, parallel to our findings, while the highest rates of PC were found for lesions more than 20 mm (20-30 mm 81.6%; 30-40 mm 86.4%; >40 mm, 80.8%), PC was reported as 13.9% in lesions <10 mm, and 64% in lesions of 10-20 mm.

Regarding cystic lesions, male gender and mucinous pathology were determined as independent risk factors related to PC. This effect of gender can be explained by the fact that some benign/relatively benign cystic neoplasms are more common in women (22). The cut-off value we found for the cyst fluid CEA level was lower than the value of 192 ng/mL emphasized in the literature, and for our cut-off value of 80 ng/mL, the sensitivity was 82% and the specificity was 90% (9). Increasing the cut-off value increased the specificity in exchange for a decrease in the sensitivity. In this study, we showed the relationship of mucinous pathology with PC in cystic lesions; we believe that the high sensitivity is more important for the recognition of mucinous lesions, and therefore, we think the cut-off value we calculated will have a place in clinical use. If a higher value is to be considered, other parameters such as string sign positivity and cyst-Wirsung connection may also be guiding. The serum CEA cut-off value (3.1 ng/mL) we found for predicting mucinous pathologies had low sensitivity and specificity in terms of predicting PC, so may be of value in predicting prognosis and in follow-up of patients, rather than as a diagnostic tool (23).

Study Limitations

The most important limiting factor of our study was its retrospective design. Therefore, parameters such as glucose level of cyst fluid, which may guide the diagnosis of mucinous pathology, or genetic and molecular profile of tissue acquired by FNA to support the diagnosis of PC could not be evaluated (24,25).

Conclusion

In conclusion, age, high CA19-9 values, and solid nature of the lesion as well as lesion-related partial atrophy of the pancreas are associated with PC, and these should be alarming for clinicians in practice. The mucinous character, which is a significant risk of PC for cystic lesions, can be optimally defined when the CEA cut-off value of 80 is used if cyst fluid analyses are available.

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Ethics Committee Approval: This study was approved by the İstanbul University-Cerrahpaşa, Cerrahpaşa Faculty of Medicine Local Ethics Committee (approval number: 83045809/604.01/02-279716).

Informed Consent: The study and according to local ethic committee guidelines, the study exempted from written informed consent.

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