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The Endoscopic Ultrasound Evaluation of Pancreatic Cystic Lesions

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Abstract

Background and aim: *Accurate preoperative diagnosis of pancreatic cystic lesions is essential to avoid unnecessary major or whole pancreatectomy. Relying solely on radiologic imaging features for diagnosing pancreatic cystic lesions can be misleading, as up to 40% of serous and mucinous lesions are incorrectly classified as pseudocysts. Endoscopic ultrasound (EUS) has emerged as a valuable tool for the diagnosis and evaluation of pancreatic cystic lesions. The aim of this study is to evaluate the diagnostic accuracy of endoscopic ultrasound in distinguishing between malignant and non-malignant pancreatic cystic lesions.* ***Methods:*** *This retrospective study analyzed 80 patients with pancreatic cystic lesions identified by CT and MRI who were referred for endoscopic ultrasound for further assessment.* ***Results:*** *Our results showed that validity of EUS in differentiating pancreatic malignancy from benign yielding sensitivity of 93.7%, specificity of 87.5% and* total *accuracy of 91.2%. Kappa agreement between histopathology and EUS was (0.968).* ***Conclusion:*** *The diagnostic accuracy of EUS in discriminating malignant potential versus non-malignant potential pancreatic cystic lesions was found to be of high accuracy raising its importance in the differential diagnosis and surveillance of PCLs.*

Introduction

Identification of patients with cancer or at risk for cancer is a major step in the management of pancreatic cystic lesions (PCLs), as it helps to reduce the need for unnecessary surgery and expedite curative surgery when necessary. Endoscopic ultrasound (EUS) plays a critical role in the differential diagnosis and follow-up of PCLs, and its potential use in the treatment of PCLs is developing[1]. Pancreatic cystic lesions are usually discovered without symptoms, and their detection is considered a result of the widespread use of cross-sectional imaging for non-pancreatic indications. The prevalence of PCLs varies from 2.4% to 21.5% of the population[2]. Around 2% of people in the general population have pancreatic cysts larger than 1 cm, and the prevalence of cysts rises in the elderly population, making the differential diagnosis of these lesions extremely difficult[3]. With up to 40% of serous and mucinous lesions being misdiagnosed as pseudocysts, it has been demonstrated that relying solely on radiologic imaging characteristics in pancreatic cystic lesions is misleading[4]. Endoscopic ultrasound creates high-resolution images of PCLs in real-time that are morphologically detailed and may help identify "suspicious" lesions[5]. Cross-sectional imaging plays a varying role in characterizing cystic pancreatic lesions, despite being the most frequent modality to detect these lesions[6]. However, computed tomography and magnetic resonance imaging have restrictions in differentiating pancreatic cystic lesions with low specificity and sensitivity[7]. The aim of this study is to assess the diagnostic accuracy of endoscopic ultrasound in differentiating between malignant and non-malignant pancreatic cystic lesions.

Materials and Methods

This retrospective study involved 80 patients with suspected pancreatic cystic lesions identified by cross-sectional imaging and referred for endoscopic ultrasound for further assessment and evaluation at Specialized Medical Hospital in Mansura and Egyptian Liver Hospital in Egypt. The study conducted between February 2017 and October 2021,

Inclusion criteria

included patients (aged ≥ 18 years) with pancreatic cystic lesions on the endoscopic ultrasound.

Exclusion criteria

Missing important data and contraindications for fine needle aspiration biopsy (FNA) such as coagulopathy and vascular invasion were not included in the study. All patients under-went a thorough evaluation, including a complete medical history, physical examination, and the following invest-igations:

1. *Laboratory tests*: Complete Blood Count (CBC), international normalized ratio (INR), and carcinoembryonic antigen (CEA).
2. *Radiological imaging*: Computed Tomography (CT) or Magnetic Resonance Imaging (MRI).

Ethical considerations

The study was thoroughly explained to all patients, and written consent was obtained from each of them. The study was reviewed and approved by the ethical committee and IRB of the Mansoura Faculty of Medicine. Patients were also informed of the results of this research.

Statistical analysis

Data was entered and analyzed using IBM-SPSS software (IBM Corp., released 2017). IBM SPSS Statistics for Windows, Version 25.0. (Armonk, NY: IBM Corp.). Qualitative data was presented as N and percentages (%). Quantitative

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data was initially tested for normality using Shapiro-Wilk's test, with data being considered normally distributed if p > 0.050. The presence of significant outliers (extreme values) was tested by inspecting the boxplots. Quantitative data was expressed as mean ± standard deviation (SD) if normally distributed, or median and interquartile range (IQR) if not. The IQR is the difference between the 75th percentile and the 25th percentile.

Results

Table 1 indicates that among the patients studied using endoscopic ultrasound, 22 (27.5%) lesions were heterogeneous, hypoechoic, irregular with cystic degeneration, 17 (21.2%) lesions were unilocular anechoic, 13 (16.2%) lesions exhibited a honeycomb appearance, 10 (12.5%) lesions were hyperechoic and heterogeneous, 9 (11.2%) lesions were hypoechoic, solid cystic with a thick capsule, and 6 (7.5%) lesions were macro-cystic hypoechoic. The EUS diagnosis breakdown was as follows: 22 (27.5%) had adenocarcinoma, 16 (22.5%) had pseudocyst, 13 (16.2%) had intraductal papillary neoplasm (IPMN), 13 (16.2%) had serous cystic neoplasm (SCN), and 10 (12.5%) had solid pseudopapillary neoplasm. (SPPN) and 4 (5%) Mucinous cystic neoplasm (MCN). In Table 2 statistically significant differences were observed in the age of patients with malignant PCLs (57.62± 11.77) compared to non-malignant PCLs. Malignant lesions were more common in males (62.5%) than females (37.5%), which was statistically significant. A history of pancreatitis was more prevalent in patients with non-malignant lesions (53%) compared to those with malignant lesions (8.3%), which was statistically significant. Abdominal pain was a common presentation in both malignant and non-malignant lesions, while jaundice and weight loss were more prevalent in patients with malignant PCLs, with statistically significant differences observed. Table 3 shows a statistically significant association between the type of lesion by histopathology (non-malignant or malignant) and pancreatic duct dilatation, as well as the involvement of the pancreatic head and tail. Table 4 illustrates the validity of EUS in differentiating malignant PCLs from non-malignant. For adenocarcinoma; sensitivity was 74%, specificity of 96.2% and total accuracy of 87.9%. For pseudocyst; sensitivity was 78.9%, specificity of 95% and total accuracy of 91.5%. For SCN; sensitivity was 76.9%, specificity of 95.5% and total accuracy of 92.5%. For MCN; sensitivity was 96.6%, specificity of 75% and total accuracy of 96.2%. For IPMN; sensitivity was 87.5%, specificity of 91.6% and total accuracy of 91.2%. For SPPN; sensitivity was 85.7%, specificity of 94.5% and total accuracy of 93.7%. Table 5 presents the validity of EUS in differentiating pancreatic malignancy from benign conditions, with a sensitivity of 93.7%, specificity of 87.5%, and an overall accuracy of 91.2%. The kappa agreement between histopathology and EUS was excellent at 0.968. Table 6 and figure 1 shows a statistically significant relationship between CEA levels and pathological types. The mean CEA levels are higher in MCN, followed by adenocarcinoma and then IPMN.

Table 1. Endoscopic ultrasound findings of the studied patients.

EUS findings	No= 80 (100%)
Heterogenous, hypoechoic, irregular cystic degeneration	22 (27.5%)
Unilocular anechoic	17 (21.2%)
Honeycomb appearance	13 (16.2%)
Hyperechoic, heterogenous	10 (12.5%)
Hypoechoic solid cystic, thick capsule	9 (11.2%)
Macro-cystic hypoechoic	6 (7.5%)
Hypoechoic, heterogenous	3 (3.8%)
EUS diagnosis	
Adenocarcinoma	22 (27.5%)
Pseudocyst	18 (22.5%)
SCN	13 (16.2%)
IPMN	13 (16.2%)
SPPN	10 (12.5%)
MCN	4 (5%)

***SCN:** Serous cystic neoplasm; **IPMN:** intraductal papillary neoplasm; **SPPN:** solid pseudopapillary neoplasm; **MCN:** mucinous cystic neoplasm.*

Table 2. Relation of socio-demographic characteristics and clinical presentations according to histopathol-ogical results.

Pathology	*Non-Malignant* n=32 (%)	*Malignant* n=48 (%)	*P value*
Age/years Mean ±SD	48.27±17.42	57.62±11.77	0.005*
Sex			
▪ ***Male***	11 (34.4%)	30 (62.5%)	0.013*
▪ ***Female***	21 (65.6%)	18 (37.5%)	
DM	15 (31.2%)	31 (64.5%)	0.116

Hypertension	12 (37.5%)	11 (22.9%)	0.158
Body mass index (kg/m^2) Mean ±SD	26.90±3.16	24.68±2.66	0.655
History of pancreatitis +ve	17 (53%)	4 (8.3%)	<0.001*
Presentation			
▪ ***Abdominal pain***	20 (62.5%)	28 (58.3%)	0.6
▪ ***Jaundice***	0	7 (14.5%)	0.02
▪ ***Accidentally discovered***	12 (37.5%)	3 (6.2%)	0.03
▪ ***Weight loss***	0	10 (20.8%)	0.005

Table 3. EUS findings in malignant and non-malignant pancreatic cystic lesions according to histopathological results.

	Non-Malignant	**Malignant**	**P value**
Size (cm)			
▪ ***<3***	4 (12.5%)	6 (12.5%)	1.0
▪ ***>3***	28 (87.5%)	42 (87.5%)	
Pancreatic duct Dilated	3 (9.4%)	17 (35.4%)	0.008*
Connection with PD Present	9 (28.1%)	11 (23%)	0.598
Mural nodules	1 (3.1%)	3 (6.2%)	0.529
Calcifications	0	5 (10.4%)	0.059
Lymphadenopathy	2 (6.2%)	10 (20.8%)	0.02*
Site of PCLs			
Head	7(21.9%)	23(47.9%)	0.018*
Body	12(37.5%)	15(31.3%)	0.562
Tail	7(21.9%)	3 (6.3%)	0.03*
Head and neck	2(3.1%)	3 (6.3%)	0.529
Uncinate process	2(6.25%)	1(2%)	0.336
Body and neck	1(3.1%)	0	0.22
Head and body	0	1(2%)	0.400

Table (4) Validity of endoscopic ultrasound in differentiation malignant versus non-malignant pancreatic cystic lesion in comparison with histopathological results.

EUS	**EUS** No.	**Pathology** No.	**Sensitivity %**	**Specificity %**	**PPV %**	**NPV %**	**Accuracy %**
Adenocarcinoma	22	27	74	96.2	88.7	90.9	87.9
Pseudocyst	18	19	78.9	95	83.3	93.5	91.5
SCN	13	13	76.9	95.5	76.9	95.5	92.5
MCN	4	5	60	96.6	75	97.3	96.2
IPMN	13	8	87.5	91.6	53.8	98.5	91.2
SPPN	10	7	85.7	94.5	60	98.5	93.7

Table 5. Validity of EUS in differentiating malignant from benign pancreatic cystic lesion.

	Sensitivity %	**Specificity %**	**PPV% %**	**NPV %**	**Accuracy %**	**Kappa agreement**
Malignant potential	93.7	87.5	91.8	90.3	91.2	0.968 P<0.001*

Table 6. Relation between intra-cystic CEA level and pathological types.

	CEA	**Test of significance**
Lesion (min-max)	***Mean±SD***	
Adenocarcinoma (1-422)	57.23±100.37	KW=2.75, P=0.02*
MCN (1-45)	18.71±18.59	
IPMN (2.5-13.0)	6.41±3.82	
SPPN (1.73-12.0)	5.92±3.58	
SCN (0.7-13.0)	2.89±3.35	
Pseudocyst (0.75-5)	1.93±1.30	

Kw: *Kruskal Wallis test, *statistically significant*

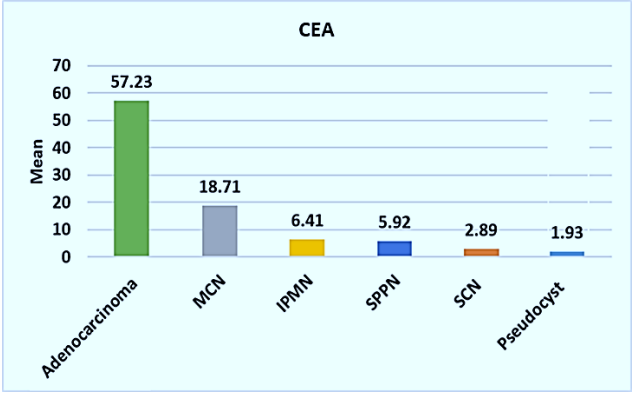

Figure 1. Mean intra-cystic CEA level according to histopathological types.

Discussion

Diagnosing pancreatic cystic lesions poses a significant challenge and has become a crucial issue in our practice. Some of these lesions have the potential for malignancy, increasing the risk of developing invasive neoplasms. Accurately identifying and categorizing pancreatic cystic lesions provides an opportunity for prevention or early management of malignant lesions. Incorrect diagnoses or unnecessary surgical interventions can significantly impact mortality and morbidity rates[8]. Computed tomography and magnetic resonance imaging have limited specificity and sensitivity in distinguishing pancreatic cystic lesions. Endoscopic ultrasound is the most sensitive tool for identifying the morphological details of pancreatic cystic lesions (PCLs). It can detect the site, size, wall thickness, solid components, mural nodules, calcifications, lymph nodes, and vascular invasions[10]. Additionally, EUS allows for fine-needle aspiration for cytological analysis. Studies have demonstrated that EUS increases the diagnostic yield of PCLs compared to cross-sectional imaging and is the preferred modality for select lesions with high-risk features[11]. The prevalence of pancreatic cystic neoplasms in the general population is estimated to be as high as 13.5%. Radiological studies have reported varying incidence rates of pancreatic cysts based on imaging modalities: 0.2% by ultrasonography, 1.2–2.6% by CT, and 2.4-13.5% by MRI[12]. Regarding demographic characteristics, patients with malignant PCLs were older than patients with non-malignant lesions, with an average age of 57.62±11.77 compared to 48.27±17.42 for patients with non-malignant PCLs, which was statistically significant. Our study aligns with Marzioni et al, who reported a mean age of 67±9 for patients with malignant lesions and 63±15 for patients with non-malignant lesions[12]. In contrast, Sun et al, found no significant difference in age among different pathological types, with a mean age of 58±16 for patients with malignant PCLs and 58±12.3 for patients with non-malignant PCLs[13]. Our study revealed that a history of pancreatitis was documented in 17 (53%) patients with non-malignant lesions and in 4 (8.3%) patients with malignant lesions, which was statistically significant. Regarding presentation, abdominal pain was reported in 28 (58.3%) patients with malignant lesions and in 20 (62.5%) patients with non-malignant lesions, which was statistically insignificant. Jaundice and weight loss were reported in 7 (14.5%) and 10 (20.8%) patients with malignant PCLs, respectively, which was statistically significant. In line with our findings, Henn et al, found a history of pancreatitis in 23% of non-malignant lesions and 19% in malignant lesions. Jaundice and weight loss were significantly more common in patients with malignant lesions, with 10% and 23% reporting these symptoms, respectively[14]. Our results are consistent with Hegazy et al, who reported that abdominal pain was the most common complaint among patients with symptomatic PCLs (13.7%), followed by weight loss (9.8%) and jaundice (7.8%)[15]. Our study revealed an association between different types of pancreatic cystic lesions and pancreatic duct (PD) dilatation. Among the 17 (35.4%) patients with malignant PCLs, a dilated PD was observed, whereas only 3 (9.4%) patients with non-malignant lesions had PD dilatation, showing statistical significance. These findings align with European guidelines, which suggest a high risk of high-grade dysplasia or invasive carcinoma when the pancreatic duct is dilated to ≥10 mm. Similarly, Sun et al, conducted a study involving 353 patients with PCLs, of which 125 had malignant PCLs and 228 had non-malignant PCLs. PD dilatation was present in 107 patients, with 54 (43.2%) of those with malignant PCLs showing dilated PD compared to 53 (23.2%) patients with non-malignant PCLs, indicating a statistically significant difference[13]. In contrast to our study, Bulcke et al, reported that 41 patients had a dilated main pancreatic duct (MPD), with 19 (46%) having malignant pancreatic cystic lesions (PCLs) and 22 (54%) having non-malignant PCLs. The difference in MPD dilatation between the malignant and non-malignant groups was not statistically significant[16]. Our study revealed that 30 (37.5%) lesions were located in the head of the pancreas, 27 (33.75%) in the body, and 10 (12.5%) in the tail. Malignant lesions were more prevalent in the head with 23 (47.9%) cases, followed by 15 (31.3%) in the body and 3 (6.3%) in the tail. There was a statistically significant association between the type of lesion and the involvement of the pancreatic head and tail. Malignant lesions were predominantly found in the head, while non-malignant lesions were more common in the tail. In contrast, Sun et al, reported similar findings regarding the distribution of malignant PCLs, with 47.9% in the head, 31.3% in the body, and 6.3% in the tail. However, they

found no statistically significant association between PCL types and the involvement of the pancreatic head and tail [13]. In our study, the CEA levels in cyst fluid ranged from less than 0.75 to >1000. The mean CEA levels were higher in adenocarcinoma (57.23±100.37), followed by MCN (18.71± 18.59) and then IPMN (6.41±3.82). There was a statistically significant relationship between CEA levels and different pathological types of PCLs. Our findings are consistent with Okasha et al. (2022), who reported that cyst fluid CEA levels were higher in malignant/potentially malignant cysts, with CEA levels of 525.5 (128-7391) ng/ml in mucinous PCLs and 9 (5-20.5) ng/ml in non-mucinous PCLs. Cyst fluid CEA levels showed a statistically significant positive correlation for predicting malignancy[17]. Cyst fluid CEA is a precise marker that distinguishes PCLs into mucinous and non-mucinous categories. A multicenter study found that a threshold of 192 ng/mL had a sensitivity of 79% and specificity of 84% for diagnosing mucinous PCLs. A low CEA level of less than 5 ng/mL can identify SCN or pseudocyst with a sensitivity of 50% and specificity of 95%[18]. Our study found that CA19-9 levels were significantly higher in malignant PCLs compared to non-malignant PCLs. Specifically, adenocarcinoma had the highest CA19-9 levels (294.38±378.94), followed by MCN (44.31±34.58), SPPN (19.41±11.22), and IPMN (17.90±20.35). This indicates a statistically significant association between CA19-9 levels and pathological types. Consistent with our findings, Sun et al, also observed higher CA19-9 levels in advanced PCLs (22.6 ± 374.5) compared to non-advanced PCLs (7.3 ± 56.5), with a statistically significant difference[13]. Serum CA19.9 is a diagnostic marker for cancerous growth in mucin-producing pancreatic cystic lesions. An elevated CA19.9 level above 37 U/mL indicates malignancy. European guidelines recommend surgery for any PCLs with increased serum CA19.9 levels[19]. This study found that EUS had varying sensitivity and specificity in distinguishing malignant PCLs from non-malignant ones. The sensitivity values were 87.5% for IPMN, 85.7% for SPPN, 78.9% for pseudocyst, 76.9% for SCN, 74% for adenocarcinoma, and 60% for MCN. The specificity values were 96.6% for MCN, 96.2% for adenocarcinoma, 95.5% for SCN, 95% for pseudocyst, 94.5% for SPPN, and 91.6% for IPMN. The accuracy values were 96.2% for MCN, 93.7% for SPPN, 92.5% for SCN, 91.5% for pseudocyst, 91.2% for IPMN, and 87.9% for adenocarcinoma. Hegazy et al. (2021) also reported similar findings, with sensitivity values of 94% for pseudocyst, 80% for IPMN, 78% for SCN, and 71% for MCN, and specificity values of 97% for pseudocyst, 95% for SCN, 93% for IPMN, and 92% for MCN[15]. In differentiating malignant pancreatic cystic lesions from non-malignant ones, endoscopic ultrasound (EUS) showed a sensitivity of 93.7% and specificity of 87.5%, with positive and negative predictive values of 91.8% and 90.3%, respectively, and an accuracy of 91.2%. The kappa agreement between EUS and histopathological results for detecting malignancy was excellent at 0.968. Our study is consistent with findings by Faias et al. (2020), who reported a sensitivity, specificity, positive predictive value (PPV), negative predictive value (NPV), and accuracy of 95% for EUS-FNA. In similar diagnostic scenarios[20]. Al–Haddad et al. (reported that endoscopic ultrasound-guided fine-needle aspiration is a highly effective technique for categorizing pancreatic cystic lesions, with most studies showing a specificity of over 90%[21].

Conclusion

Our study found that endoscopic ultrasound has high sensitivity, specificity, and accuracy in distinguishing between malignant and non-malignant pancreatic cystic lesions. However, EUS imaging alone is insufficient for accurate diagnosis. Additional cyst fluid analysis, including string sign, cyst wall cytology, and CEA levels, is essential for determining the nature of pancreatic cystic lesions.

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List of abbreviations

EUS: Endoscopic ultrasound
PCLs: pancreatic cystic lesions
FNA: Fine needle aspiration
CEA: Carcinoembryonic antigen
SCN: Serous cystic neoplasm
MCN: Mucinous cystic neoplasm
SPPN: Solid pseudopapillary neoplasm
IPMN: Intraductal papillary neoplasm

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