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Role of Endoscopic Ultrasound in Diagnosis of Pancreatic Cystic Lesions in Comparison to Computed Topography and Magnetic Resonance Imaging

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ABSTRACT

Background and aims:To evaluate the advantages of endoscopic ultrasound (EUS) in the assessment of detailed structures of pancreatic cystic lesions (PCLs) compared to computed tomography (CT) and magnetic resonance imaging (MRI).

Methods: This prospective cohort study was conducted in Tropical medicine department, Zagazig university hospitals and in Internal medicine department at Kasr Al Aini Hospitals, Cairo University, in the period between March 2018 and March 2020. The study included 72 patients with PCLs, 29 were males and 43 were females, there ages ranged from 25 to 75 years. All cases were subjected to the following careful history taking, thorough clinical examination, laboratory investigations (CBC, LFTs, KFTs, Coagulation profile, serum amylase, serum CA 19.9), imaging (CT and/or MRI abdomen), endoscopic ultrasound examination and EUS-FNA biopsies using the 22G or 19G needle.

Results:Validity of abdominal CT/MRI imaging, EUS, cytopathology and EUS with cytopathology was calculated using diagnostic performance depend on sample 2x2 contingency tables generation. Sensitivity, specificity, PPV, NPV and accuracy and their corresponding 95% CI were calculated. P-value < 0.05 was considered statistically significant, p-value < 0.001 was considered highly statistically significant, and p-value ≥ 0.05 was considered statistically insignificant.

In our study, all, EUS, FNA cytopathology and EUS with FNA cytopathology showed high significant statistical differences in the detection of malignant cysts from benign cysts with p-value of < 0.001, while abdominal CT/MRI imaging showed no significant difference. The diagnostic performance of EUS increased with the addition of FNA cytopathology which was more than of abdominal CT/MRI imaging. Sensitivity, specificity, PPV and NPV of abdominal CT/MRI imaging were 23.5%, 90.9%, 44.4% and 79.4% respectively, for EUS were 100%, 96.4%, 89.5% and 100% respectively, and for FNA cytopathology were 94.1%, 100%, 100% and

98.2% respectively. The accuracy of abdominal CT/MRI imaging, EUS, FNA cytopathology and EUS with FNA cytopathology were 75%, 97.2%, 98.6% and 100% respectively.
Conclusion: EUS can be considered a more accurate diagnostic modality for characterization of PCLs than the abdominal CT or MRI. Addition of FNA to EUS gives a better accuracy for diagnosis and differentiation of PCLs
Key words:Endoscopic ultrasound, Detailed structures, Computed tomography, Magnetic resonance imaging.

Introduction:

Pancreatic cystic lesions (PCLs) are a broad group of pancreatic tumors that have varying demographical, morphological, histological and clinical characteristics. There has been a large increase in the number of patients with PCLs in recent years. The rising prevalence might be caused by significant improvement of imaging technologies, increased awareness of their existence and the growth of the aging population. Besides, PCLs are being discovered increasingly in patients who are otherwise asymptomatic **(1)** .

Commonly, PCLs are diagnosed incidentally during investigation for often unrelated and nonspecific abdominal complaints using state-of-the art abdominal imaging, computed tomography (CT) or magnetic resonance imaging (MRI). The term, pancreatic cystic neoplasm (PCN) denotes a histologically heterogeneous collection of neoplasms showing a wide spectrum of diagnoses, ranging from completely benign to potentially malignant, to carcinoma in situ, to frankly invasive and malignant **(2)**.

Image-based studies report prevalence of PCLs ranging from 1.2% to 19% **(2).** Among 24,039 CT or MRI scans, 290 patients (1.2%) had pancreatic cysts, and a majority of the patients had no history of pancreatitis **(3).** In an autopsy series of 300 patients, 186 cystic lesions were found in 73 of 300 autopsy cases (24.3%) (Kimura et al., 1995). The prevalence of cysts increases with age **(4)**.

PCLs may be classified simply into two main classes such as non-neoplastic and neoplastic cysts. Neoplastic cysts are more commonly defined as PCNs. It is important to distinguish non-neoplastic cysts from neoplastic or non-mucinous from mucinous cysts because the latter are considered being premalignant lesions. In general, non-neoplastic cysts account up to 80% of all PCLs. However, the rate of PCNs increases significantly with age **(2)**.

Endoscopic ultrasound (EUS) is now used to investigate PCLs, particularly as a mean of EUS-guided cyst aspiration **(2).** Several EUS features of pancreatic cysts have been associated with an increased risk of malignancy, including thick wall, septations, presence of intramural nodules, and masses **(5).** However, recent studies indicated that pancreatic cyst appearance during EUS is not enough as an independent predictor of malignancy **(6)**.

The addition of fine-needle aspiration (FNA) to different imaging modalities has raised the accuracy for diagnosis of cystic pancreatic lesions by differentiating benign from neoplastic pancreatic cysts by evaluating cyst fluid Carcinoembryonic antigen (CEA), cancer antigen 19-9 (CA19-9), and amylase levels and cytopathological examination, including mucin stain **(7).**

In our study we aimed To evaluate the advantages of endoscopic ultrasound (EUS) in the assessment of detailed structures of pancreatic cystic neoplasms (PCNs) compared to computed tomography (CT) and magnetic resonance imaging (MRI).

Patients and Method:

This prospective cohort study was conducted in Tropical medicine department, Zagazig university hospitals and in Internal medicine department at Kasr Al Aini Hospitals, Cairo University, in the period between March 2018 and March 2020. The study included 72 patients with pancreatic cystic lesions (PCLs), 29 were males and 43 were females, there ages ranged from 25 to 75 years.

Patients who were included in this study were older than 18 years with radiological evidence (abdominal CT, abdominal MRI) of pancreatic cyst accidentally discovered and needed FNA for final diagnosis, patients with gall bladder stones and severe colicky abdominal pains in whom their pancreatic cysts are suggested to be inflammatory pseudocysts, patients with severe resistant abdominal pain proved to have a pancreatic cyst suggestive of intraductal papillary mucinous neoplasm (IPMN) and patients with unexplained common bile duct strictures or pancreatic duct dilatation by endoscopic retrograde cholangiopancreatography or magnetic resonance cholangiopancreatography and proved to have PCLs and sent for further delineation by EUS.

Patientswere excluded when: patients having pancreatic cyst smaller than 1 cm, patients having platelet count <50,000/cmm or Prothrombin concentration <60%, poor risk patients for deep sedation by Propofol, patients refused to sign the consent and patients missed for follow up or patients whose lab and histological examinations were not available, so the final diagnosis was not settled.

All patients were subjected to careful history taking, full detailed clinical examination, laboratory tests that were done included: Complete blood count: WBC's, Hemoglobin concentration, platelet count, liver function tests: bilirubin (total and direct), albumin, liver enzymes (ALT, AST), kidney function tests, coagulation profile, serum amylase and serum CA 19.9.

Imaging: CT and/or MRI abdomen:

CT was performed with high-speed advantage scanner using (siemens somatom plus and X-vision Toshiba) Routine technique for spiral CT and MRI was performed using (Philips achieva 1.5 tesla) for MR. The patient was asked to come fasting at least four hours. Oral contrast regimen: Contrast material (Gastrografin 2-3%) was administered as follows:

- The first cup (500ml) was given 45 min before examination together with an oral tablet of metoclopramide to facilitate filling of the distal small intestine and colon.
- The second cup (500ml) was given 30 min before examination which fill the proximal jejunum and ileum.
- The third Cup (150-200ml) was given when the patients is on the scanner to assure optimal filling of the stomach and duodenum.

Intravenous contrast regimen includes an intravenous injection of 80-100mL of 60% iodinated contrast medium for the abdomen. It was given by automatic intravenous injection immediately before scanning by rate 7ml/sec, precontrast non spiral sections to the liver, pancreas was obtained prior to spiral acquisition, starting from the level of diaphragmatic copula to the lower border of the liver, scanning time is one sec. Two spiral acquisitions were then performed post contrast injection. The first sequence consisted of thin-section images of the pancreas obtained during the pancreatic phase 40-70 seconds after initiation of the intravenous injection of contrast material. In second sequence, the liver was scanned during the maximal hepatic phase of enhancement 70-100 seconds after contrast material administration.

Endoscopic Ultrasound examination using a Pentax linear array EUS machine type EG-3870-UTK (HOYA Corporation, PENTAX Lifecare Division, Showanomori Technology Center, Tokyo, Japan) connected to a Hitachi EUB-7000 HV ultrasound unit (Hitachi Medical Systems, Tokyo, Japan).

- All examinations were performed by one endosongrapher. The patients performed the examination under sedation with IV propofol injection.EUS pancreatic examination was done in four main stations:
    - **A. Station one (just below the papilla):** for visualization of the uncinate process to the right of the aorta after clockwise rotation of the scope.
    - **B. Station two (facing the papilla):** with upward deflection of the tip of the scope the papilla is visualized with the bile and pancreatic ducts seen in cross sections (snake eyes) and pancreatic head seen in crescent shape.
    - **C. Station three (apex of the duodenal bulb):** with gentle upward deflection of the scope and counterclockwise rotation the entire pancreatic head and portal vein confluence can be visualized, EUS FNA is best taken at this station.
    - **D. Station four (at the gastro-esophageal junction):** with clockwise rotation of the scope aorta can be seen then traced till the origin of the celiac artery, further advancement of the scope with gentle down deflection of its tip makes the pancreatic body comes in view, more clockwise rotation and withdrawal images the pancreatic tail.
    - For EUS-FNA biopsies, we used the Cook needle 22G or 19G (Echotip®; Wilson-Cook, Winston Salem, NC, United States).
    - **<u>The final diagnosis was obtained by the presence of one of the following:</u>**
        - Positive mucin staining in the FNA.
        - CEA and amylase level in the FNA.
        - Presence of dysplastic or malignant cells in the FNA.
        - Follow up of benign lesions for at least 12 months with no change in size.

Surgical resection and biopsy results

Statistical Analysis:

All data were collected, tabulated and statistically analyzed using SPSS 22.0 for windows (IBM Inc., Chicago, IL, USA), MedCalc 13 for windows (MedCalc Software bvba, Ostend, Belgium) and Microsoft Office Excel 2010 for windows (Microsoft Cor., Redmond, WA, USA).

Continuous Quantitative variables were expressed as the mean ± SD & median (range), and categorical qualitative variables were expressed as absolute frequencies (number) & relative frequencies (percentage). Continuous variables were checked for normality by using Shapiro-Wilk test. Independent samples Student's t-test was used to compare between two groups of normally distributed variables while Mann Whitney U test was used for non-normally distributed variables. Categorical data were compared using Chi-square test or Fisher's exact test when appropriate.

Validity of CT/MRI imaging, EUS, cytopathology and EUS + cytopathology in diagnosis of malignant pancreatic cystic lesions was calculated using diagnostic performance depend on sample 2x2 contingency tables generation using final diagnostic criteria as gold standard reference. Sensitivity, specificity, positive predictive value, negative predictive value and accuracy and their corresponding 95%CI were calculated. All tests were two sided. P-value < 0.05 was

considered statistically significant (S), p-value < 0.001 was considered highly statistically significant (HS), and p-value ≥ 0.05 was considered statistically insignificant (NS).

Results:

Demographic data and clinical presentation of the studied patients showed that. 59.7% of the studied group were females and 40.3% of them were males, with mean age 49.48 years, 62.5% of them were ≤50 years and 37.5% were >50 years. 56.9% of the studied group complained of abdominal pain, 13.9% of them developed recurrent pancreatitis and 2.8% developed new onset diabetes. **(Table 1)**.

In comparison between benign and malignant pancreatic lesion regarding serum amylase & CA 19-9 among the studied patients, there was a high significant difference regarding to serum CA19.9 level between benign and malignant pancreatic lesion (p-value <0.001) and no significant difference regarding serum amylase **(Table 2)**.

In comparison between benign and malignant pancreatic lesion regarding CT/MRI imaging, EUS, cytopathology and EUS with cytopathology diagnosis among the studied patients, the resulting data showed a high significance of EUS, cytopathology and EUS with cytopathology in comparing between benign and malignant pancreatic lesion (p-value <0.001) while showed no significance regarding CT/MRI imaging(**Table 3)**.

Diagnostic performance of CT/MRI imaging, EUS, cytopathology and EUS with cytopathology diagnosis among the studied patients showed that EUS with cytopathology had higher sensitivity and specificity than the others(**Table 4)**.

Table (1): Demographic data and clinical presentation of the studied patients (N=72).

Demographic data and clinical presentation	All studied patients (N=72)	
	No.	%
Sex		
Male	29	40.3%
Female	43	59.7%
Age (years)		
Mean±SD	49.48±11.90	
Median (Range)	50 (25 – 75)	
≤50 years	45	62.5%
>50 years	27	37.5%
Clinical presentation		
Abdominal pain	41	56.9%
Recurrent pancreatitis	10	13.9%
New onset diabetes	2	2.8%

Table (2): Laboratory findings and serum markers of the studied patients (N=72).

Laboratory findings and serum markers	All studied patients (N=72)	
	Mean ±SD	Median (Range)
WBCs (x10^3/mm^3)	7.34 ±1.42	7.35 (4.50 – 9.80)
Hemoglobin (g/dl)	13.55 ±0.88	13.60 (11.90 – 15.20)
Platelet count (x10^3/mm^3)	263.22 ±60.12	260.50 (163 – 411)
TSB (mg/dl)	1.03 ±0.16	1 (0.70 – 1.80)
DSB (mg/dl)	0.20 ±0.18	0.20 (0.10 – 1.20)
S. Albumin (g/dl)	4.40 ±0.49	4.30 (3.50 – 5.30)
AST (U/L)	22.65 ±3.70	22 (16 – 30)
ALT (U/L)	22.72 ±4.35	22 (13 – 30)
S. Creatinine (mg/dl)	0.99 ±0.17	1 (0.70 – 1.30)
PC (%)	99.11 ±1.04	99 (96 – 100)
Serum Amylase (U/L)	42.68 ±162.56	8.50 (2 – 1185)
Serum CA19.9 (U/mL)	7.04 ±4.60	5.50 (1 – 20)

Table (3): Comparison between benign and malignant pancreatic lesion regarding CT/MRI imaging, EUS, cytopathology and EUS+ cytopathology diagnosis among the studied patients

	All studied patients (N=72)		Pancreatic cystic lesions				Test	p-value (Sig.)
			Malignant (N=17)		Benign (N=55)			
Diagnosis	No.	%	No.	%	No.	%		
CT/MRI imaging								
Malignant	9	12.5%	4	23.5%	5	9.1%	2.475‡	0.201
Benign	63	87.5%	13	76.5%	50	90.9%		(NS)
EUS								
Malignant	19	26.4%	17	100%	2	3.6%	**62.078‡**	**<0.001**
Benign	53	73.6%	0	0%	53	96.4%		**(HS)**
Cytopathology								
Malignant	16	22.2%	16	94.1%	0	0%	**66.555‡**	**<0.001**
Benign	56	77.8%	1	5.9%	55	100%		**(HS)**
EUS + Cytopathology								
Malignant	17	23.6%	17	100%	0	0%	**72.000‡**	**<0.001**
Benign	55	76.4%	0	0%	55	100%		**(HS)**

Table (4): Diagnostic performance of CT/MRI imaging, EUS, cytopathology and EUS+ cytopathology diagnosis among the studied patients (N=72)

Method of diagnosis	TP	FN	FP	TN	SN (95%CI)	SP (95%CI)	PPV (95%CI)	NPV (95%CI)	Acc. (95%CI)
CT/MRI	4	13	5	50	23.5%	90.9%	44.4%	79.4%	75%

imaging					(6.8-49.8)	(80-96.9)	(19.5-72.6)	(74.5-83.5)	(63.4-84.5)
EUS	17	0	2	53	100% (80.5-100)	96.4% (87.5-99.6)	89.5% (68.6-97.1)	100%	97.2% (90.3-99.7)
Cytopathology	16	1	0	55	94.1% (71.3-99.6)	100% (93.5-100)	100%	98.2% (89.1-99.7)	98.6% (92.5-99.9)
EUS+ Cytopathology	17	0	0	55	100% (80.5-100)	100% (93.5-100)	100%	100%	100% (95-100)

Discussion:

PCLs, usually are asymptomatic or have atypical clinical presentations. Meanwhile, the diagnosis and management of the PCLs are arguable. Much emphasis is placed on the diagnosis of the PCLs. So, it is important to distinguish mucinous from non-mucinous cysts and benign from malignant cysts, and also to decide which cysts require surgery and which may be followed-up conservatively**(8, 9).**

Approximately, pancreatic cancer has an overall five-year survival rate of 5% **(10)**, meanwhile, the prognoses of different types of PCLs vary. SCNs are considered as benign lesions with a low possibility of malignant transformation, while MCNs and IPMNs are regarded to have a malignant potential **(11)**. SPNs are considered low grade malignant lesions **(12)**. Therefore, an accurate diagnostic tool of PCLs is particularly a need to prevent its progression to true malignancy.

Abdominal CT and MRI are considered primarily non-invasive diagnostic modalities for the diagnoses of PCLs, especially CT, which remains to be the most used diagnostic tool. Parenchymal changes, cystic lesions, and a pancreatic duct diffuse dilatation are the most common findings on CT scans **(12).** Meanwhile, abdominal CT and MRI cannot exactly characterize PCLs **(13, 14)**. Therefore, an accurate modality is a need for further characterization of PCLs.

According to the demographic data in our study, there were 43 female patients (59.7%) more than 29 males (40.3%), these data were similar to the data were found by **Sun et al., (15)**, **Du et al., (16),Lu et al., (17), Lee et al., (18), Leeds et al., (19)** and **Maimone et al., (20)**. The patients in our study were with mean age of 49.5 years, ranging from 25 to 75 years, these data also are similar with **Sun et al., 15)**, **Du et al., (16)** and **Lu et al., (17)** and inconsistent with the data found by **Lee et al., (18), Leeds et al., (19)** and **Maimone et al., (20)**, in which their median ages were 59.8, 60.6, 71 years respectively, due to different patient's samples ages. These findings revealed that PCLs are more common in females than males with wide age ranges.

As regard the laboratory findings, mean level of serum CA 19-9 had a high significant difference between the benign and the malignant pancreatic cysts with a p-value <0.001, and no significant difference in concern to serum amylase level these data was similar to **You et al., (21), Jones et al., (22)** with a p-value 0.006, 0.001 respectively.

In our study, all, EUS, FNA cytopathology and EUS with FNA cytopathology showed high significant statistical differences in the detection of malignant PCLs from benign cysts with p-value of < 0.001, while abdominal CT/MRI imaging showed no significant difference. These data

are consistent with **Lu et al., (17)** who compared the diagnostic yield of abdominal CT, MRI, and EUS with or without FNA in PCLs and showed that EUS was significantly more sensitive in accurately differentiating the pancreatic cyst into benign or malignant than abdominal CT (p-value 0.002) and abdominal MRI (p-value 0.006). **Du et al., (16)** found that EUS was used to differentiate PCNs from other PCLs and characterize the PCN subtype better than either abdominal CT or MRI.

The diagnostic performance of EUS in our study increased with the addition of FNA cytopathology in our study which was more than of abdominal CT/MRI imaging diagnostic performance. Sensitivity, specificity, PPV and NPV of abdominal CT/MRI imaging were 23.5%, 90.9%, 44.4% and 79.4% respectively, for EUS were 100%, 96.4%, 89.5% and 100% respectively, and for FNA cytopathology were 94.1%, 100%, 100% and 98.2% respectively. The accuracy of abdominal CT/MRI imaging, EUS, FNA cytopathology and EUS with FNA cytopathology were 75%, 97.2%, 98.6% and 100% respectively.

Du et al., (16)reported that EUS was the optimal diagnostic method in distinguishing benign cysts from malignant cysts and in characterizing the PCNs, outperforming both abdominal CT and MRI and the sensitivity of EUS for diagnosing PCNs and the accuracy for characterizing PCNs were higher than abdominal CT and MRI. Abdominal CT was able to differentiate PCNs from other PCLs with a sensitivity of 73.1%, abdominal MRI was able to differentiate PCNs from other PCLs with a sensitivity of 81.3% and EUS was able to differentiate PCNs from other PCLs with a sensitivity of 98.5%. The diagnostic sensitivity of EUS was higher than those of both abdominal CT (P-value < 0.001) and MRI (P-value = 0.001).

Khashabet al., (23) reported the incremental increase in diagnostic yield of EUS over abdominal CT and MRI for prediction of a neoplastic cyst is 36% and 54%, respectively. The addition of EUS-FNA significantly increases overall accuracy for diagnosis of neoplastic pancreatic cysts.

Oguz et al., (24) found EUS with or without FNA was better than abdominal CT and MRI in differentiation between benign and malignant PCLs (p-value < 0.0001). EUS increased the rate of neoplastic cysts prediction in 36% and 54% in comparison to abdominal CT and MRI, respectively.

Conclusion

EUS can be considered a more accurate diagnostic modality for characterization of PCLs than the abdominal CT or MR. Addition of FNA to EUS gives a better accuracy for diagnosis and differentiation of PCLs

Conflict of Interest: No conflict of interest.

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