The Role of Endoscopic Ultrasound-Guided Fine-Needle Aspiration Cytology in Diagnosis of Pancreatic Masses: Review of 40 Cases in Iraq.

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ABSTRACT:

BACKGROUND:

Pancreatic masses are often initially identified by magnetic resonance imaging or computed tomography, during evaluation of varied symptoms. Endoscopic ultrasound (EUS)-guided fine-needle aspiration (FNA) has been proved to be safe and useful method for tissue sampling including the pancrease.

OBJECTIVE:

In this study we aim to find out some of the factors which may influence successful EUS-FNA of pancreatic masses, like: location of the mass, size, consistency and other significant factors.

PATIENTS AND METHODS:

A retrospective study of 40 patients underwent EUS-FNA of pancreatic masses, referred to Gastroenterology and Hepatology Teaching Hospital in Baghdad, from March 2005 to December 2007 (this is the first study done in Iraq); all patients were clinically suspected to have pancreatic malignancy. Cytology samples were evaluated and many other clinical variables were examined for association with EUS-FNA diagnosis.

RESULT:

Twenty six (65%) patients were males, and 14(35%) patients were females. Age ranged between 13-65 years with a mean of 46.6 years, the size of pancreatic masses range between 1.7-13cm, the masses were divided into 3 groups according to their sizes: <5cm 26(65%) cases, between 5-10cm 13(32.5%) cases, and >10 cm 1(2.5%) case. Consistency wise the masses were characterized as solid 34(85%) cases, mixed solid and cystic 6(14%) cases. In 13(32.5%) cases the mass was located in the body of pancrease, 25(62.5%) cases in the head, and 2(5%) cases in the tail. Regarding the cytological diagnosis: 19(47.5%) cases were benign (inflammatory conditions), and 21(52.5%) cases were malignant; including 17(80.9%) cases adenocarcinoma, 2(9.5%) cases malignant mucinous tumor, and small cell carcinoma 1(4.8%)case, and papillary and solid epithelial neoplasm (solid pseudopapillary tumor SPPT) 1(4.8%)case. Lymph node enlargement was found in 10(25%) cases.

CONCLUSION:

EUS-FNA can be used to sample pancreatic tumors in most patients. Communication clinical background information and imaging findings to the cytopathologist can facilitate the interpretation of the FNA specimens.

KEYWORDS: endoscopic ultrasound, fine-needle aspiration, cytology, pancreatic masses.

INTRODUCTION:

Pancreatic masses are often initially identified by magnetic resonance imaging (MRI) or computed tomography (CT) during evaluation of various symptoms such as abdominal pain, weight loss, or jaundice. In fact up to 37% of these lesions may be discovered incidentally. [1] Differential diagnosis of pancreatic masses is a frequent clinical challenge. Therapeutic decision in this context is mainly based on the ability to establish or exclude malignancy. [2]

Although ductal adenocarcinoma is the most frequent cause of pancreatic masses, other neoplasms (e.g. lymphoma, cystic tumors) and benign conditions (e.g. chronic pancreatitis) can arise in pancrease. [3]

Endoscopic ultrasound-guided (EUS) fine needle aspiration cytology (FNA) of pancreatic masses has sensitivity ranging from 85%-90% and a specificity of almost 100% for malignancy. [4, 5]

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EUS-FNA has been proved to be a safe and useful method for tissue sampling of intramural and extramural gastrointestinal lesions including the pancrease. [4, 5]

Pseudotumoral masses can be a consequence of chronic pancreatitis [6], the EUS appearance of pancreatic cancer can be mimicked by focal pancreatitis. Both chronic pancreatitis and pancreatic cancer may coexist because chronic pancreatitis is a risk factor for pancreatic cancer. [6, 7] some pancreatic cancers are associated with a marked desmoplastic reaction creating peritumor fibrosis. [6, 7]

Variation in the diagnostic yield of EUS-FNA could be affected by many factors.

In this study we aim to find out some factors which may influence successful EUS-FNA of pancreatic masses like, location, size, and consistency of the mass.

PATIENTS AND METHODS:

This is a retrospective study of 40 patients underwent EUS-FNA of pancreatic masses, referred to The Gastroenterology and Hepatology Teaching Hospital in Baghdad from March 2005 to December 2007, all patients were clinically suspected to have a pancreatic malignancy.

In additional to abdominal ultrasound, all patients had a previous evaluation of the pancreatic mass by CT scan; no MRI evaluation was done for the patients.

EUS was carried out by the same endosonographer using: 7.5 MHz endoscope Pentax FG 38UX and Hitachi ultrasound EUB 525.

EUS-FNA was performed by Echotip 22 gauge (Cook endoscopy), under conscious sedation and cardiorespiratory monitoring, none of the patients needed general anesthesia even the young aged.

FNA was performed from the duodenum or the stomach according to the location of the lesion, in the head or the body/tail of the pancrease respectively. The number of shots of the needle until satisfactory aspirations were obtained was between 5-10. Once aspiration was done the material was expelled onto slides, nearly half the slides were air dried for immediate processing with Leishman stain. The other half were fixed in absolute ethanol for later Hematoxylin and Eosin staining.

No pathologist was present in the endoscopy room during the procedure; samples were initially processed by the endoscopist who was specifically trained with this aim by the pathologist. Thus no microscopic evaluation of the sample adequacy was performed at that time. The on-site cytopathological examination has a value in the determination of the adequacy of the samples.

Two experienced pathologists examined the smears. Cytology samples were evaluated for cellular preservation, background substance, cellularity, architectural integrity, and cytoplasmic and nuclear details. Accordingly the results were either positive or negative for malignancy.

Many variables were examined for association with a EUS-FNA diagnosis, like: patient characteristics (sex, age), location, consistency and size of the pancreatic masses and presence of regional lymph node enlargement, and correlates these variables with the final diagnosis obtained from the cytological examination.

Statistical analysis for the data was done by using SPSS 9 soft ware, P value less than 0.05 was considered as significant.

RESULTS:

1- Age and sex distribution:

Forty patients were included in this study, 26(65%) patients were males, and 14 (35%) patients were females. The youngest patient was a female aged 13 years, and the oldest patient was a male aged 65 years, mean of age was 46.6 years, 40% of the patients aged between 50-59 years. Table 1 show age and sex distribution of the cases.

Table 1: Age and sex distribution of the cases

Age	Sex		Total	
	Female	Male	NO.	%
10-19	1	2	3	7.5
20-29	-	2	2	5
30-39	1	4	5	12.5
40-49	3	4	7	17.5
50-59	6	10	16	40
60-69	3	4	7	17.5
Total	14	26	40	100

2- Size and consistency of the pancreatic masses:

The size ranged between 1.7-13cm, we divided the masses to three groups according to their sizes:

1st group: mass size <5cm: 26(62.5%) cases.

2nd group: mass size between 5-10cm: 13(35%) cases.

3rd group: mass size >10cm: 1(2.5%) case.

The consistency of the pancreatic masses was classified into:

Solid in 34(85%) cases, solid and cystic in 6(15%) cases.

Table 2 shows the relationship between size and consistency of the pancreatic masses. P value was >0.05 the correlation was not significant.

Table 2: The relationship between size and consistency of the pancreatic masses.

Size	consistency				Total	
	solid		Solid and cystic		NO.	%
	NO.	%	NO.	%		
<5cm	25	62.5	1	2.5	26	65
5-10cm	9	22.5	4	10	13	32.5
>10cm	-	-	1	2.5	1	2.5
Total	34	85	6	15	40	100

P value >0.05 not significant

3- Site of the pancreatic masses:

In 26(62.5%) cases the mass was located in the head of the pancrease, in 13(32.5%) cases the mass was located in the body of the pancrease, and in 2(5%) cases the mass was in the tail of the pancrease.

Table 3 shows the correlation between the site of the pancreatic masses and the sex of the patients. P value was 0.02 the correlation was significant

Table 3: The correlation between the site of the pancreatic masses and the sex of the patients.

Site of the mass	Sex of the patients				Total	
	Male		Female			
	NO.	%	NO.	%	NO.	%
Head	16	40	9	22.5	25	62.5
Body	9	22.5	4	10	13	32.5
Tail	1	2.5	1	2.5	2	5
Total	26	65	14	35	40	100

P value 0.02 correlation was significant.

Table 4 shows the site of the pancreatic masse and the consistency of the masses.

Table 4: The relationship between the site of the pancreatic masses and their consistency.

Site of the mass	Consistency of the mass				total	
	Solid		Solid and cystic			
	NO.	%	NO.	%	N0.	%
Head	23	57.5	2	5	25	62.5
Body	9	22.5	4	10	13	32.5
Tail	2	5	-	-	2	5
Total	34	85	6	15	40	100

P value 0.01 correlation was significant

Pancreatic masses in the head: 16(40%) cases males, 9(22.5%) cases females, 23(57.5%) cases were solid and 2(5%) cases were solid and cystic.

Pancreatic masses in the body: 9(22.5%) cases males, 4(10%) cases females, 9(22.5%) cases were solid, and 4(10%) cases were cystic and solid.

Pancreatic masses in the tail: 2(5%) cases one male and one female, both were solid in consistency.

Regarding correlation was significant with a p value <0.05

4- Cytological diagnosis:

Ten cytological criteria were evaluated, these include: loss of polarity, nuclear enlargement (1.5X size of RBC) nuclear membrane irregularity, pleomorphisim, chromatin pattern (pale or granular), gaps between cells versus confluence, increased cellularity, hyperchromasia, macronuclolei, and necrosis.

The presence of at least three criteria was required for a malignant diagnosis to be rendered. [8]

Nineteen (47.5%) cases were cytologically diagnosed as benign lesions (all consistent with inflammatory conditions as chronic pancreatitis), 21(52.5%) cases were diagnosed as malignant lesions, and these were cytologically diagnosed as: 17(80.9%) {42.5% of the total cases} cases adenocarcinoma, 2(9.5%) {5% of the total cases} cases malignant mucinous tumors, 1(4.8%) {2.5% of total cases} case small cell carcinoma and 1(4.8%) {2.5% of total cases} case papillary and solid epithelial neoplasm (solid pseudopapillary tumor SPPT). Since there was no histological definite diagnosis of the biological behavior of the lesions, we were unable to determine if there was a false negative or positive result.

Table 5 shows the cytological diagnosis of the pancreatic masses.

Table 5: The cytological diagnosis of the pancreatic masses.

Cytological diagnosis	Number of cases	
	NO.	%
Adenocarcinoma	17	42.5
Malignant mucinous tumors	2	5
SPPT	1	2.5
Small cell carcinoma	1	2.5
Inflammatory conditions	19	47.5
Total	40	100

5- Lymph node enlargement:

Regional lymph node enlargement was found in 10(25%) cases, 7 malignant cases and 3 benign cases. no aspiration was done to the lymph nodes. Lymph node enlargement showed no significant correlation.

Table 6 shows correlation between the cytological diagnoses of EUS-FNA of the pancreatic masses all the other criteria's included in this study (sex of the patients, site, consistency, and size of the pancreatic masses and lymph node involvement).

Table 6: The correlation between cytological diagnosis and other criteria.

Criteria	Cytological diagnosis		Total
	Benign	malignant	
Sex Male	11	15	26
female	8	6	14
Site head	14	11	25
body	4	9	13
Tail	1	1	2
consistency Solid	13	21	36
Solid and cystic (mixed)	6	-	6
Size			
<5 cm	11	15	26
5-10 cm	7	6	13
>10 cm	1	-	1
L.N involvement Positive	3	7	10
Negative	16	14	30

DISCUSSION:

Several studies have evaluated the accuracy of cytology after EUS guided FNA for the diagnosis assessment of pancreatic masses. [3, 6, 8] Successful EUS-FNA requires a thorough knowledge of normal and abnormal anatomy and the necessary techniques. [6]

Initially EUS was limited to only few centers, but now it is being performed in daily practice by increasing number of gastroenterologists through out the world. [9]

In this study 40 patients were included, 26(65%) males, 14(35%) females, mean age of 46.6 years.

The mass was located in the head of pancrease in 25(62.5%) cases, in the body 13(32.5%) cases, and 2(5%) cases in the tail, 34(85%) case solid masses, 6(15%) cases solid and cystic masses, 21(52.5%) cases malignant and 19(47.5%) cases benign.

Ardengh JC et al 2007 [10] studied 595 pancreatic masse, 67.1% masses in the pancreatic head, 26.3% in the body, and 6.6% in the tail, lesions less than 3 cm encountered 43% of the cases, 66.3% solid masses, 30.9% cystic collections and 2.8% mixed pattern, 57.6% malignancies and 42.2% benign cases, among the malignancies, pancreatic adenocarcinoma accounted for 67% of the lesions. These results were somewhat to the results in our study.

Location of the lesion is one of the factors influencing FNA results, lesions located in the unicate process of the pancrease are the most difficult to puncture, the easiest lesion to sample is when the scope is shortened and relatively straight, this is usually possible when the sampling masses in the body or tail of the pancrease. [11] In our study no lesion was located in the unicate process.

Small lesions < 2cm not only requires greater targeting accuracy but may affect FNA because of the tendency of the needle to displace the target during advancement. Ardengh JC et al 2001 [12] used the power shot needle in 59 pancreatic lesions including 42 solid masses, the sensitivity for solid masse was 91% and the specificity was 90%.

Pancreatic masses incite a desmoplastic reaction and the resulting fibrosis may be difficult to penetrate. Failure to penetrate indurated lesions has been reported in 10-15% of attempted EUS guided FNA procedures. [13]

Difficult penetration of indurated pancreatic lesions can be overcome with an automated spring loaded power shot needle, that enter the target lesion at high velocity. [12, 13] In two cases inadequate material necessities a repeat in our study.

Developed by Binomeller KF et al [14] the automated device was designed to function analogous to spring loaded biopsy needles used.

The literature reports a sensitivity of 100% to detect pancreatic tumors bigger than 3cm, higher than that obtained by CT or US and similar to the findings from ERCP. [15, 16]

Nonetheless for small tumors EUS-FNA presents a better sensitivity in relation to CT or ERCP. [17]

Regarding cytological diagnosis: loss of polarity, nuclear enlargement and irregularity of the nuclear membrane are the most consistent findings in difficult cases of pancreatic adenocarcinoma, and the most common causes for false negative cases are paucity of cells or little cytologic aberrations, which might be minimized by experienced endoscopic and cytopathologist. [18]

FNA on solid pancreatic lesions has a higher and more consistent accuracy rate of 75-96%, however; adenocarcinoma appears to have a higher accuracy rate compared to other solid lesions. [19]

While literature on etiology of a frankly bloody FNA of the pancrease is lacking, the differential diagnosis for hypervascular pancreatic lesions can theoretically be applied to bloody aspirate as shown in table 7. [20] In our study ten cases were bloody and to overcome this problem we depended on the dry smears that were done.

Table 7: Differential diagnosis of hypervascular or bloody FNA of pancreatic mass.

Malignant solid masses	Benign solid masse	Cystic masses	Other
Neuroendocrine tumor	Hematoma	Aneurysm	Puncture of vessel on FNA
lymphoma	Hemangioma	Thrombosed varix	Coagulopathy
Metastases	Splenosis (heterotopic splenic tissue)	Hypervasacular cystic neoplasm	Peripancreatic lymph node
Extramedullary plasmacytoma	Inflammatory mass		
Small cell carcinoma			
GIST			

However; many authors stated that a bloody aspirate is not necessarily a contraindication for repeated FNA. Multiple passes are often required to attend a sufficient aspirate for analysis. [20]

Solid tumors can match all the entities described for the pancrease, with the most frequent diagnosis being that of ductal carcinoma with all the variants reported in the WHO classification. [21]

The diagnosis of adenocarcinoma can be confirmed by studying the immunoexpression of type 1 mucoglycoprotein (MUCI). The malignant transformation of ductal cells is associated with a modification of expression of MUC1 which becomes intracytoplasmic intense, where as the normal expression is limited to the apical pole of the ductal or acinar cells, endocrine cells do not express MUC1. [22]

The differential diagnosis is made between chronic pancreatitis nodule and the tumor nodule on chronic pancreatitis. The study of MUC1 is of great interest to differentiate signs of dysplasia from malignant transformation which are accompanied by hyperexpression of MUC1. [22]

Shah SM et al 2008 [23] stated that adding EUS-Trucut biopsy does not significantly improve the yield of EUS guide biopsy, possibly molecular techniques applied to FNA cytological samples hold a better future than Trucut biopsy in pancreatic masses.

EUS-FNA is now frequently used to identify mucinous cysts and to differentiate benign from malignant neoplasms, cytology and cyst fluid levels of Carcinoembryonic antigen have been the most useful tool in analyzing the fluid obtained by EUS-FNA, [8] and this was not performed in our study because of the limited facilities. We were able to diagnose two cases of malignant mucinous tumors depending on the mucoid background and atypia of the nuclei.

Regarding the lymph node enlargement, in cases of staging when the original cancer is known, EUS-FNA biopsy have clear therapeutic impact for cancers of many organs such as the pancrease. For a lymph node mass of unknown origin, the efficacy of the biopsy is less. [24]

Increasing the diagnostic accuracy of the EUS-FNA for pancreatic lesions is a continuous challenge for endosonographers and pathologists. Accuracy depends on many factors including: operator learning curve, availability of an experienced on-site cytopathologist and tumor histopathological characteristics.

Eloubeidi MA et al [25] reported their experience of EUS-FNA in 300 patients with pancreatic masse and demonstrated that proficiency increases overtime as expertise with the procedure increase. However; even in expert hands EUS-FNA and cytological interpretation can be difficult in masses with a large amount of necrosis, chronic pancreatitis, or in very well differentiated cancers. In our study three cases were associated with extensive necrosis, but significant cellularity and nuclear atypia were obvious.

CONCLUSION:

EUS-FNA can be used to sample pancreatic masses in most patients, important application of EUS-FNA include the diagnosis of pancreatic cancer and characterization of malignant and pre-malignant lesions of the pancrease. Communicating clinical background informations and imaging findings to the cytopathologist can facilitate the interpretation of the FNA specimens.

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