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Role of EUS-FNA and Percutaneous US-FNA in diagnosis of pancreatic head lesions, Egyptian Experience

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Abstract:

Background: pancreatic carcinoma is one of the leading cancer morbidity and mortality worldwide. Endoscopic Ultrasound (EUS) provides good direct visualization of the pancreas and EUS-FNA raises the accuracy for diagnosing pancreatic malignancies. US-FNA is another established method for diagnosing pancreatic malignancies.

Aim: to determine the Role of Percutaneous US-FNA and EUS-FNA in diagnosis of pancreatic lesions.

Subjects & Methods: 131 patients with pancreatic masses were included in the study and sub-classified into 2 groups according to the imaging tool used, US-FNA (group I) and EUS-FNA (group II).

Results: using the appropriate statistical tools, sensitivity, specificity, positive predictive value (PPV), negative predictive value (NPV) and diagnostic accuracy were calculated for both groups. It was 88.2%, 93.9%, 96.8%, 97.5% and 90.1% respectively in group I. It was 77.8%, 100%, 100%, 75% and 86.7% respectively in group II.

Conclusion: US-FNA/EUS-FNA are safe reliable tools for diagnosis of pancreatic lesions.

Key words: Pancreatic lesions, US-FNA, EUS FNA

Introduction:

Pancreatic cancer is the fourth leading cause of cancer-related death in the United States (Jemal et al., 2008) and the fifth in Europe (Ferlay et al., 2007). Comparisons of age-specific mortality demonstrated higher rates in Egypt compared to the United States for subjects under age 20 years and significantly higher rates in the United States compared to Egypt for subjects 40 years and older. In Egypt, the rate of pancreatic cancer mortality is 2.85 more in Northern provinces than Southern provinces. The highest mortality rates were observed in the Nile Delta compared to southern Egypt and the oasis (Soliman et al., 2006). At least 80% of patients have unresectable disease at diagnosis owing to locoregional involvement or distant metastasis.

In comparison to other imaging modalities EUS is able to visualize tumors less than 2 cm in diameter (Stefan et al., 2007). The ability to obtain high quality images and perform fine-

needle aspiration (FNA) has led EUS to become the diagnostic test of choice when evaluating the pancreas (Kyung et al., 2007). Endoscopic ultrasound-fine needle aspiration (EUS-FNA) was shown to be a highly reliable and a very effective diagnostic technique, both based on data from clinical trials and from large clinical practice studies, EUS-FNA results are reported to be in good-to-very good agreement with the final diagnosis, and the agreement significantly exceeded the chance agreement. The overall sensitivity and specificity of EUS and of EUS-FNA are very good. EUS-FNA is an effective diagnostic technique for the evaluation of pancreatic lesions, either reported with other imaging tests or suspected on the basis of clinical and biochemical features. EUS-FNA may be performed in most cases, and the results of EUS-FNA are particularly important for their excellent positive predictive value. Nonetheless, in a few cases EUS-FNA cannot be feasible, or can give false negative or inconclusive results (Rocca et al., 2007). In evaluating solid pancreatic masses, the result of EUS-FNA is excellent, with a sensitivity of 64–94.7% and specificity of 97–100 %(Legmann et al., 1998). Ultrasonography guided percutaneous fine-needle (US-FNA) aspiration biopsy is a well established method for obtaining tissue for cytological examination since the 1970s. US-FNA of the liver and pancreas has been shown to be an accurate method for the cytological diagnosis of malignancy; the diagnostic yield has been reported to be from 84% to 95 % (Hodenak et al., 1982). Moreover, US-FNA is nearly without complications if contraindications are followed (Mitty et al., 1981).US-FNA is advisable in many circumstances like suspecting rare malignant tumor (e.g., lymphoma) or with previous history of malignant disease, because nonoperative therapy may be most appropriate for metastatic disease (Hartwig et al., 2009).For greatest effectiveness, (US-FNA) must be performed by experienced sonographists and cytopathologists (Harter et al., 1983).

Aim of the work:

The purpose of this prospective study was to assess the accuracy and reliability of US-FNA & EUS-FNA for diagnosis of pancreatic head lesions.

Patients and methods:

This prospective collaborative work was designed between internal Medicine department, Cairo University and Tropical Medicine Department, National Hepatology & Tropical Medicine Research Institute (NHTMRI), Cairo, over 3 years (2008-2010), the study was approved by the institutional ethical committee. It included 131 patients presented with pancreatic head masses based on CT, MRI and/or EUS confirmation. According to accessibility and feasibility they were sub-classified into 2 main groups:

Group (I) - including 101 patients, underwent Percutanous ultrasound guided FNA.

Group (2) - including 30 patients, underwent Endoscopic ultrasound guided FNA.

Ultrasound Examination:

US examination was done using (Hitachi machine, EUB 8500, Japan). FNA was done using Chiba needles, 20-22G. It was done under complete sonographic guidance with a biopsy attachment.

Endoscopic Ultrasound Examination:

EUS examination was done using a Pantax EG-3830UT machine connected to a Hitachi machine EUB-5500 and EUB-8500, Japan). FNA was done using 19 and 22G Echotip needles (Cook Endoscopy, Winston-Salem, NC). One to 3 passes were done to every patient, no on- site cytopathologic examination was available. The samples were preserved in formalin after preparing at least two dry slides.

All EUS-FNA and US-FNA were done by a single sonographist. The cytopathologists were blinded to the US and EUS findings. No mortality or serious complications as serious bleeding or infection was encountered. One of the 30 patients underwent EUS-FNA (3.33%) and 3 of the 101 patients underwent US-FNA (2.97%) (Four patients, 3.05%) had severe epigastric pains that responded to NSAIDs within 1 to 3 days, one of them (the patient underwent EUS-FNA) had acute pancreatitis requiring hospitalization for 3 days.

Follow-up and final diagnosis:

A final diagnosis was based on definitive cytology, surgical pathology, and clinical follow-up for more than 18 months. Cytology that was ‘‘suspicious’’ for malignancy was repeated for confirmatory purpose.

Statistical analysis:

Analysis of data was performed using SPSS 18 (Statistical Package for Scientific Studies) for Windows. Description of variables was presented as follows:

- Description of quantitative variables was in the form of mean, Standard Deviation (SD), median, 25th and 75th percentiles.
- Description of qualitative variables was in the form of numbers (No.) and percents (%).
- Comparison between quantitative variables was carried out by student T-test of two independent samples. Comparison between non parametric quantitative variables was carried out by Mann–Whitney U test. Results were expressed in the form of P-values.

The significance of the results was assessed in the form of P-value that was differentiated into:

- Non-significant when P-value > 0.05
- Significant when P-value ≤ 0.05
- Highly significant when P-value ≤ 0.01

Evaluation of FNA for diagnosing malignancy was done by calculating sensitivity, specificity, positive predictive value, negative predictive value and accuracy.

Results: The mean (SD) age of the 101 patients in the study was 55±9.9 years. a male predominance was noted in this group being 75 patients (74.3%) vs. 26 female patients (25.7%).The mean CA19.9 level was 1144.2±4687.4 IU/ml. The number of fine needle passes to obtain adequate tissue was 1 pass in 54 patients (53.5%), 2 passes in 44

patients (43.6 %) and 3 passes in only 3 patients (3%) [table1].

Table 1. Patient characteristics of group I (no. patients 101):	
Mean (SD) age (y)	**55±9.9**
Sex :	
Males	**75**
Females	**26**
CA19.9 Mean (SD)(IU/ml)	**1144.2±4687.4**
No. Of FN passes:	
1 pass	**54**
2 passes	**44**
3 passes	**3**

Table 2,3 and Fig.1 showed the primary diagnosis of US FNA Vs the final diagnosis and the sensitivity, specificity of the US FNA as a diagnostic tool for pancreatic head masses . Out of 62 cases diagnosed by US FNA as malignant pancreatic head masses , 60 cases were true positive ,2 cases are false positive and out of 39 cases diagnosed by US FNA as benign pancreatic masses 31 cases were true negative and 8 cases were false negative , with sensitivity of 88.2%,specificity of 93.9%,PPV 96.8% ,NPV 79.5% & accuracy of 90.1%.

Table 2. Diagnosis by US FNA Vs. final diagnosis in group I:				
	US FNA		**Final diagnosis**	
	N.	**%**	**N.**	**%**
Benign	**39**	**38.6**	**33**	**32.7**
Malignant	**62**	**61.4**	**68**	**67.3**

Table 3. Measures of sensitivity and specificity of US FNA in diagnosing malignancy in group I:			
		Final Diagnosis	
		Malignant	**Benign**
US FNA Diagnosis	**Malignant**	**60 "True positive"**	**2 "False positive"**
	Benign	**8 "False negative"**	**31 "True negative"**

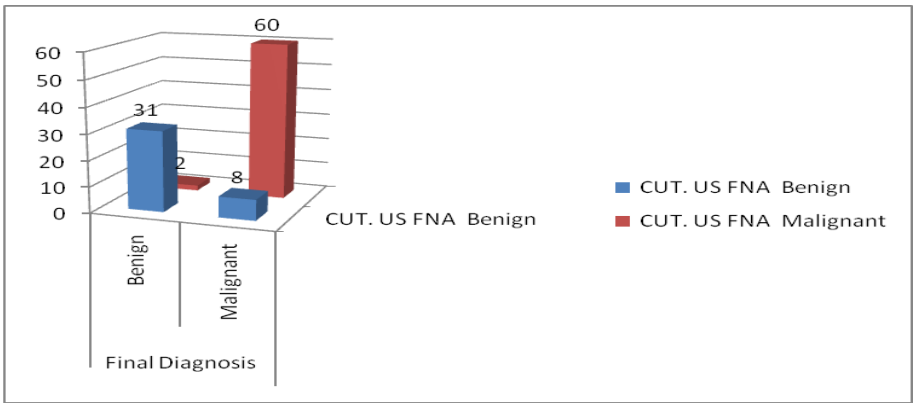

Fig. 1. Sensitivity and specificity of US FNA in diagnosing malignancy in group I.

The characteristics of the group II patients are summarized in **Table 4**. The mean (SD) age of the 30 patients in the study was 53.4±9.6 years. A male predominance was noted also in this group being 22 patients (73.3%) vs. 8 female patients (26.7%).The mean CA19.9 level was 187.8±382.6 IU/ml. The Number of fine needle passes to obtain adequate tissue was 1 pass in 8 patients (26.7%), 2 passes in 17patients (56.7 %) and 3 passes in 5 patients (16.6%).

Table 4. Patient characteristics of group II (no. patients 30):	
Mean (SD) age (y)	**53.4±9.6**
Sex :	
Males	**22**
Females	**8**
CA19.9 Mean (SD)(IU/ml)	**187.8±382.6**
No. Of FN passes:	
1 pass	**8**
2 passes	**17**
3 passes	**5**

Table 5, 6 and Fig.2 showed the primary diagnosis of EUS FNA Vs the final diagnosis and the sensitivity, specificity of the EUS FNA as a diagnostic tool for pancreatic head masses. out of 14 cases diagnosed by EUS FNA as malignant pancreatic head masses, 14 cases were true positive, no cases with false positive results, and out of 16 cases diagnosed by EUS FNA as benign pancreatic masses ,14 cases were true negative and 4 cases were false negative , with sensitivity of 77.8%,specificity of 100%,PPV 100% ,NPV 75.0% & accuracy of 86.7 %. **Table 5**. Diagnosis by EUS FNA Vs. final diagnosis in group II:

	EUS FNA		**Final diagnosis**	
	N.	**%**	**N.**	**%**
Benign	**16**	**53.3**	**12**	**40.0**
Malignant	**14**	**46.7**	**18**	**60.0**

Table 6. Measures of sensitivity and specificity of EUS FNA in diagnosing malignancy in group II:			
		Final Diagnosis	
		Malignant	**Benign**
EUS FNA Diagnosis	**Malignant**	**14 "True positive"**	**0 "False positive"**
	Benign	**4 "False negative"**	**12 "True negative"**

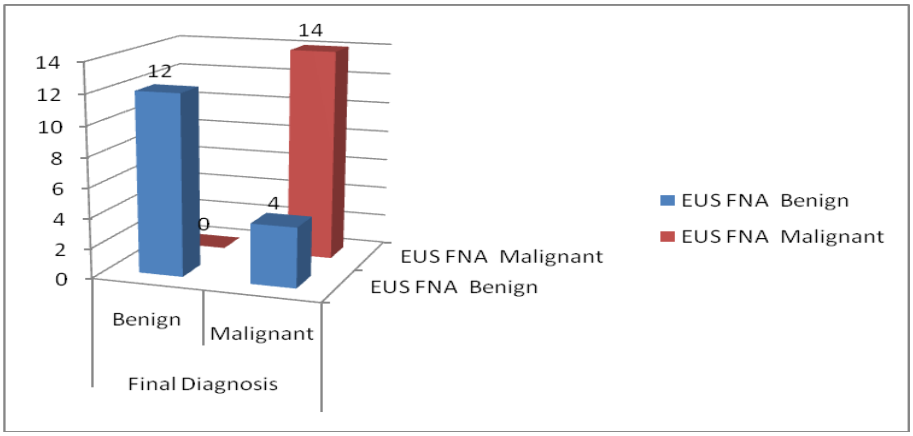

Fig. 2. Sensitivity and specificity of EUS FNA in diagnosing malignancy in group II.

Table 7. sensitivity , specificity,PPV,NPV & accuracy of US FNA/EUS FNA in diagnosing malignancy both groups:		
	Cut. US FNA	**EUS FNA**
Sensitivity	**88.2%**	**77.8%**
Specificity	**93.9%**	**100.0%**
PPV	**96.8%**	**100.0%**
NPV	**79.5%**	**75.0%**
Accuracy	**90.1%**	**86.7%**

Discussion

Pancreatic malignancies became one of the leading cancer morbidity and mortality worldwide. The presentation of pancreatic malignancies may be obstructive jaundice with biliary stricture shown on ERCP image or a mass lesion on CT scan or MRI (Domagk et al., 2002).Sometimes the ordinary imaging tools like CT, MRI doesn't provide a paved way for definite diagnosis and a necessity for cytopathological diagnosis is mandatory to define the protocol of therapy. US-FNA and EUS-FNA has been established during the last

decades as a diagnostic and prognostic tools for many Hepato-biliary and pancreatic malignancies. In 2012, Hewitt et al. pooled 4984 patients in his wide meta-analysis research and demonstrated a pooled sensitivity of 85% and a pooled specificity of 98% and an area under the sROC (Summary Receiver Operator Characteristic) curve of 95. EUS-FNA also has a high positive predictive value (99%) and a reasonable negative predictive value (64%).

In order to reduce any inherent heterogeneity, they extracted and analyzed the data based on two classifications: classification 1—a high stringency analysis with malignant cytology results considered the only positive endpoint; classification 2—included atypical and suspicious as well as malignant cytology results as determinants of a positive result. Classification 2 improved the sensitivity to 91%, but somewhat predictably decreased the specificity to 94%. The positive predictive value was 98%, and the negative predictive value rose to 72%. On subgroup analysis, a higher sensitivity was reported in studies with larger numbers (>100 patients) and in multicenter studies. Other subgroups were not determinants of heterogeneity in this analysis.

These results when compared to our work showed that the highest sensitivity was in classification 2 in Hewitt et al.'s work (91%), followed by cutaneous US guided FNA (88.2%) in our work, then classification 1 in Hewitt's et al. pooled results (85%) and the least was in EUS FNA (77.8%). As regards specificity the best was in EUS FNA in our work (100%), which was slightly higher than class 1 in Hewitt et al. (98%), class 2 in Hewitt et al. (94%) as well as cutaneous US guided FNA (93.9%). There was no much difference in the PPV, but it was the best in the EUS FNA group of our work (100%), then class 1 in Hewitt et al. (99%), then class 2 in Hewitt et al. (98%), and least in cutaneous US FNA (96.8%). The NPV was higher in our work than the pooled NPV, where NPV in the cutaneous US FNA group was (97.5%), then EUS FNA in our work (75%), then class 2 in Hewitt et al .(72%) and was least in class 1 in Hewitt et al. (64%). The low NPV of US FNA/EUS FNA is mentioned in most of the reviewed literature, this makes the Negative results of US FNA/EUS FNA, should be viewed with caution (Karlson et al., 1996), in the appropriate clinical setting.

The false +ve results of EUS-guided FNA of solid pancreatic tumors is rather low, as demonstrated by Siddiqui et al . The FP rate for EUS-FNA was 4 of 367 (1.1%) when only “positive” cytology findings were interpreted as malignant and 14 of 367 (3.8%) when both suspicious and positive cytology findings were interpreted as malignant. Among the 4 cases falsely interpreted as positive, 1 was falsely diagnosed cytologically as a neuroendocrine tumor and 3 as adenocarcinomas. All false positive specimens showed chronic pancreatitis on surgical pathology. The incidence of discordance between cytology

and surgical pathology did not change over time (2000-2006: 8/188 [4.3%] vs 2007-2010: 6/179 [3.4%]; P= 0.79).

Eloubeidi et al. studied major complications in total of 355 consecutive patients with a solid pancreatic mass underwent EUS FNA. Major complications were encountered in 9 patients (2.54%, 95% CI 1.17-4.76). Acute pancreatitis occurred in 3 of 355 (0.85 %, 95% CI 0.17-2.45); 2 patients were hospitalized, and 1 patient recovered with outpatient analgesics. Three patients were admitted for severe pain after the procedure; all were treated with analgesics and subsequently discharged with no sequele. Two patients (0.56%, 95% CI 0.07-2.02) developed fever and were admitted for intravenous antibiotics; 1 patient recovered with intravenous antibiotics and the other required surgical debridement for necrosis. One patient required the use of reversal medication. Overall, 1.97% (95% CI 0.80-4.02) of the patients were hospitalized for complications (range 1-16 days). None of the patients experienced clinically significant hemorrhage, perforation, or death. No clear predisposing risk factors were identified.

In our work the incidence of major complication was less, 3 patients experienced severe pains, one of them had acute pancreatitis requiring hospitalization for 3 days.

This was also the conclusion of Hewitt et al who demonstrated that the observed complication rate was also low, at 1% to 2%, with complications occurring more commonly when EUS-FNA was performed on cystic lesions than on solid lesions. Examples of complications include bleeding, infection, self-limiting pancreatitis, and tumor seeding; however, there are similar risks for CT-guided biopsy (Vilmann & Saftoiu., 2006).No major complications were reported for any of the procedural data included in this meta-analysis.

In conclusion, there is literature consensus for obtaining a histopathological diagnosis prior to cytotoxic treatment, but a wide variability in the modalities for sampling (US, CT, EUS; FNA, or core biopsy), the American Joint Committee on Cancer has selected EUS-guided FNA as the ‘‘procedure of choice’’ if available. US FNA and EUS FNA provide safe, accurate methods for diagnosis of pancreatic lesions.

Conflicts of interest

The authors declared no conflict of interests at all study levels.

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دور سحب العينات الدقيقة الموجهة بمنظار الموجات الصوتية والموجهة بالموجات الصوتية عن طريق الجلد في تشخيص أمراض رأس البنكرياس , الخبرة المصرية

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تعتبر أورام رأس البنكرياس من أكثر الأورام شيوعا على مستوى العالم وأحد أهم أسباب الوفيات دولياَ. يمثل منظار الموجات الصوتية وسيلة حديثة لرؤية البنكرياس بكفاءة وتمثل العينات المسحوبة بمساعدة هذا المنظار وسيلة تشخيصية هامة لأورام رأس البنكرياس.

الهدف من الدراسة: تقييم سحب العينات الدقيقة الموجهة بمنظار الموجات الصوتية والموجات الصوتية عن طريق الجلد في تشخيص أمراض رأس البنكرياس.

النتائج والخلاصة: بعد فحص 131 مريض مقسمين الى مجموعتين أ(مجموعة العينات الموجهة بالموجات الصوتية عن طريق الجلد), ب(مجموعة العينات الموجهة بمنظار الموجات الصوتية).أظهرت النتائج أمان وفاعلية وأعتمادية الفحص الباثولوجي المسحوب موجهاَ بالموجات الصوتية عن طريق الجلد أو عن طريق منظار الموجات الصوتية في تشخيص أمراض رأس البنكرياس.