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THE ROLE OF ENDOSCOPIC ULTRASOUND ELASTOGRAPHY IN DIAGNOSIS OF PANCREATIC LESIONS

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ABSTRACT

Objective: **To evaluate the accuracy of elastography in differentiating benign from malignant pancreatic masses for patients.**
Design: **A prospective, consecutive, study**
Setting: **Kasr Alini hospital department of internal Medicine, university of Cairo, Egypt.**
Subjects: **Thirty patients had a solid-appearing pancreatic mass at conventional ultrasound, EUS and CT abdomen were included in the study.**
Results: **A total of 30 patients were included in the study. The age of the Patients ranged between 38 and 70 years with a mean value of 54± 8.6 Years. The study included 22 (73.3%) males and eight (26.7%) females. The mean size of pancreatic masses was 35.6 ± 11.8 mm. The final diagnosis were pancreatic adenocarcinoma (n =25) papillary adenocarcinoma (n =1), papillary adenoma (n =2) and chronic pancreatitis (n =2). The strain ratio was significantly higher among patient with pancreatic malignant tumour compare with those with inflammatory masses. The sensitivity, specificity, positive predictive value, negative predictive value and accuracy for elastograpgy to Differentiate malignant from benign pancreatic masses were: 88%, 80%, 95.6%, 57.14% and 86% respectively (area under receiver operating curve 0 .974).**
Conclusion: **EUS elastography is a useful tool for differentiating malignant from benign pancreatic masses through objective evaluation of tissue stiffness.**

INTRODUCTION

Endoscopic ultrasound (EUS) has evolved over time into a diagnostic and therapeutic modality that has major impact on both digestive and meditational diseases (1). Nevertheless, the main indication for EUS has remained the diagnosis and staging of pancreatobiliary diseases for which EUS is currently considered to be first choice examination and has almost displaced ERCP as a diagnostic modality for studying the common bile duct and pancreases. Elastography is a recent addition to the tools use by EUS endoscopists to visualise and evaluate tissue elasticity. The principle of elastography is based on the assumption that compression of a target tissue by an echo-endoscopic probe creates a strain (that is, displacement of one tissue structure by another) that differs according to the hardness and softness of the tissue (2).

Thus, by calculating the elasticity of tissue, it is possible to differentiate benign (soft) tissue from malignant (hard) tissue (3).

MATERIAL AND METHODS

A prospective, consecutive, study during the period from September 2009 to October 2010 was conducted to evaluate the accuracy of EUS elastography to differentiate benign from malignant pancreatic masses.

EUS examinations was performed over the 12-month study period at the Gastroenterology Unit of the Department of Internal Medicine of Kasr Alini Hospital, 30 patients (mean age, 54 years; range, 38 – 70 years; 22 men and eight women) had a solid-appearing pancreatic mass at conventional ultrasound, EUS and CT abdomen were included in the study. No patient with pancreatic solid mass was excluded over the stud in order to avoid bias except cystic lesions, predominant cystic masses and previously diagnosed metastatic masses.

The study included nine patients (mean age, 53 years; range, 30 – 66 years; six men and three women) as a control. They underwent EUS because of other gastrointestinal complain seven patients

for evaluation of submucosal masses and two were investigated for mediastinal lymaphadenopathy.

There was no history of pancreatic diseases, gastrointestinal symptom related to digestion, history of alcohol abuse, smoking or elevation of pancreatic enzymes among the controls.

EUS linear scanning echoendoscope, pentax EG 3830 UT/HITACHI in which the real-time tissue elastography module and software were installed. This module enables real-time elastographic evaluation and recording. Elastography technology is bases on detecting tissue deformation caused by compression with different strain for benign and malignant tissues. The degree of deformation is used as an indicator of the stiffness of the tissue.

Elasticity value for different pathological masses are marked with different color, which are shown overlaid to conventional grayscale EUS image. The system is set-up to use a hue color map (red– green– blue), where hard tissue areas are shown in dark blue, medium hard tissue areas are shown in cyan (greenish-blue color), intermediate tissue areas are shown in green, medium soft tissue areas are shown in yellow, and soft tissue areas are shown in red. The procedure included performing EUS and EUS elastography and recorded in a video by our single expert endosonographer.

When performing elastography, the probe was attached to the duodenal wall just exerting the pressure needed for an optimal and stable B-mode image (7.5 MHz) at the region of the mass (21). Then manually adjusting the probe to include the whole target lesion when possible as well as the surrounding tissue to maximize the sensitivity for elastography.

As the images of elastography rapidly change their color, a stable image for at least seven second was recorded to define elastographic patterns4. The quotient (B/A) is used for elastographic evaluation, area A represent the mass and B the healthy surrounding tissue which is red in color. The elastography of the normal pancreas was evaluated at the head which is selected as are A.

The elastographic pattern also was defined according to the predominant color and the homogeneity or heterogeneity of color distribution (4).

After performing EUS and defining the mass as benign or malignant through this tool, the elastographic pattern was defined for each mass, then EUS-FNA was performed using 22 gauge needle for all masses to make pathological diagnosis possible (5-7). Samples were collected and sent to pathology department to draw a final diagnosis.

Final diagnosis of malignant or benign tumour was defined according to the following reference methods: (1) histology of surgical specimens taken after surgery; (2) confirmed positive cytology for malignancy together with compatible EUS and contrast enhanced computed tomography (CT) scan findings for final diagnosis of malignant masses deemed unresectable and (3) EUS and CT scan suggestive for malignancy at admission, clinical presentation, and (4) a minimum follow-up period of six months including EUS - FNA and CT scan, for final diagnosis of benign disease in cases of benign cytology (4).

All patients gave consent for enrollment for the study. The study was approved by a local ethics committee and conducted in accordance with the Good Clinical Practice guidelines.

Data Analysis: In our study data were shown as mean and standard deviation, and mean, quartiles, and 95% confidence intervals (CIs), as appropriate. Both strain ratio (quotient B/A) and tumour elasticity for differentiating malignant from benign masses were calculated after drawing the corresponding receiver operating curve to determine the diagnostic accuracy of EUS elastography. Statistical analyses were performed with the software SPSS.

RESULTS

EUS elastography and EUS–FNA were applicable in all 30 patients without complication throughout the study. Size of pancreatic masses was 35.6 ± 11.8 mm (mean standard deviation) in diameter. Tumours were located in the head of the pancreas in 24 patients, in the body in four patients, and in the tail of the pancreas in two patients. EUS-FNA was performed in all patients to obtain cytological diagnosis after a mean of two needle pass, final diagnoses are shown in Table 1.

Table 1

Characteristics of Patients and Solid Pancreatic Masses Included in the Study

Final diagnosis	Male/female	Mean age, y range	Localisation, head/body/tail	Mean size ± standard deviation, mm
Pancreatic adenocarcinoma	19/6	58 (45 -69)	21/3/1	33.0 ± 10.0
Papillary adenocarcinoma	1/0	50	1/0/0	38.3 ± 11.0
Papillary adenoma	0/2	53 (32–54)	1/0/1	25.0 ± 3.8
Chronic Pancreatitis	2/0	50 (36–62)	1/1/0	24.0 ± 4.9

Pancreatic adenocarcinoma was diagnosed in all 25 cases by cytology, and confirmed by histology of surgical specimens after surgery in ten cases. Diagnosis of chronic pancreatitis (2) was based on presence of inflammatory cell on cytology. Both masses remained the same size and shape on EUS and CT scan through six month follow up (8). After this follow up period, malignancy was excluded in both masses through EUS –FNA cytology. The cause of pancreatitis was alcohol abuse in one case and idiopathic in the other case. Finally the diagnosis of papillary adenoma and papillary adinocarcinoma was based on cytology.

Analysisof thye elastography of the masses: The elastographic pattern in all the control patients showed homogenous green color indicating normal pancreas. Both of the two inflammatory masses showed heterogeneous green predominant elastographic pattern also indicating benign nature of the masses Figure 1.

The sensitivity, specificity and accuracy of EUS alone in diagnosing pancreatic masses were 66.6%, 83.3%, and 83.6%, respectively, when elastography is added accuracy of both modalities for differentiating malignant from benign masses is 80% , 88% and 90% Table 2.

Table 2

The specificity , sensitivity and accuracy of EUS elastography in different studies

Author	year	Sensitivity	specificity
Giovannini	2006	100%	67%
Giovannini	2009	92.3%	80%
Janssen	2007	93.8%	65.4%
Iglesia-garcia	2009	100%	85.5%
Hirche	2008	41%	53%
Iglesia-garsia qualitative	2010	100%	71.4%
Iglesia-garsia quantitative	2010	100%	92.9%
Our study	2010	88%	80%

Figure 1

EUS elastographic evaluation of (1) healthy pancreas, and(2) inflammatory mass (3) malignant mass(4) malignant mass with the green area within the mass indicating vascular green area
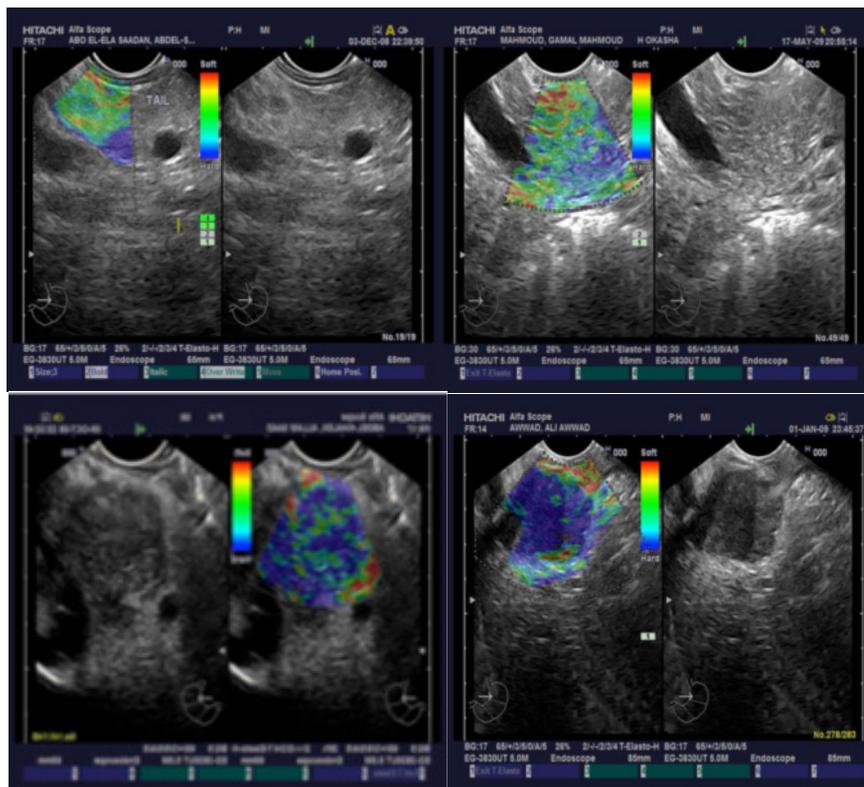

Calculating elasticity Value of Pancreatic Masses: Area A: The pancreas in the control group showed a mean elasticity value of 0.53% (95% confidence interval [CI], 0.45 to 0.61). Inflammatory masses showed lower elasticity values (mean, 0.23%; 95% CI, 0.17%–0.29%) (P .001), higher than pancreatic cancer (mean, 0.02%; 95% CI 0.02%-0.03% (p < .oo1). Mean of range amplitude for healthy pancreas was 0.18 ±0.12 for inflammatory masses was 0.14 ± 0.09, for pancreatic adenocarcinoma was 0.015 ± 0.00621. This figures indicate that elasticity value is higher in healthy smooth tissues than the hard pathological tissues.

Figure 2

Strain ratio (quotient B/A; mean, quartiles, and 95% CI) of the different groups of solid pancreatic masses included in the study Inflammatory mass (IM), Pancreatic cancer (PC), Neuroendocrine pancreatic tumour (NEPT), Metastasis (Met), Solid pseudopapillary neoplasm.
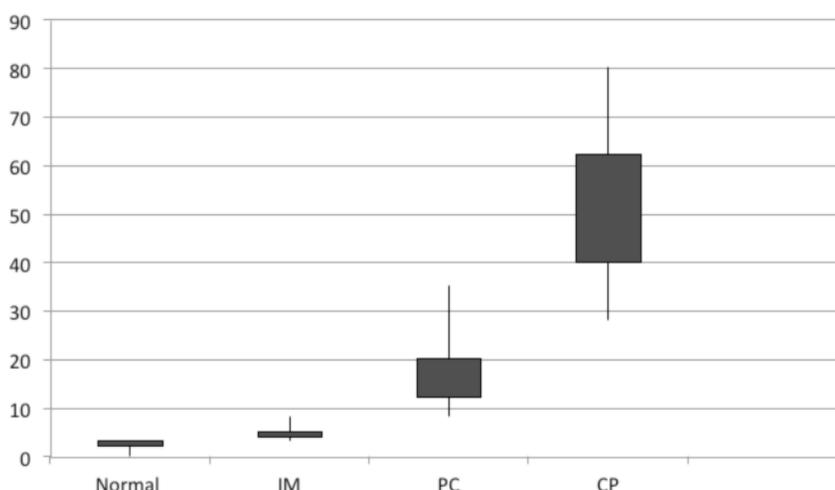
Impact of Elastography on final diagnosis: Malignant tumours were diagnosed using B-mode through their irregular shape and nearby vascular invasion these finding were founded in 11 (36%) of the 30 pancreatic masses ;and this diagnosis was supported by EUS elastograhpy in these cases.

The malignant nature was not clear in the remaining 19 cases on EUS although , 15 cases were found to be malignant on final diagnosis and EUS elastography was consistent with malignancy in all of them and this was proved with EUS –FNA. On the other side, elastography supported the benign cytologic finding in all inflammatory masses except one.

DISCUSSION

This study support some earlier studies about the accuracy of EUS elastography as a useful tool for the differentiating malignant from benign pancreatic masses.

EUS elastography proved to be useful by adding important and objective information to EUS by providing a quantitative evaluation of tissue stiffness, which supports the benign or malignant nature of the disease. A strain ratio higher than 6.04 Figure 2 or a mass elasticity lower than 0.05% are 100% sensitive for correctly classifying tumours as malignant, or benign with a specificity close to 93% and 86%, respectively. In this context, a strain ratio higher than 15.41 or a mass elasticity value below 0.03% are 100% specific for malignancy In addition, EUS elastography is helpful for differentiating pancreatic cancer from inflammatory masses (with a sensitivity of 100% and a specificity of 96%) (2).

The major drawbacks of pancreatic EUS is the inherent bias introduce by static image analysis selected by one experience examiner with previous knowledge of patient history in addition to its limited ability to determine the benign or malignant nature of solid lesions . The accuracy of EUS in detecting pancreatic malignancy is relatively low 85% to 90% , to improve this, EUS-FNA is being use as an aid to diagnose solid pancreatic masses (3,6), however, due to technical difficulties cytology frequently provides false negative results due to sampling variability, interposed malignant tissue, and vascular structures; and it is associated with small but not significant complications (7,8). In our study, the negative predictive value of EUS FNA for malignancy was as high as 90.3%, similar to other studies (9,10,11).

To try to overcome these limitations, a modified software (12) has been allowed to assess and measure tissue stiffness, it allows the hardness of biological tissues to be estimated and imaged using conventional ultrasound instruments, the technique is known as elastography. The principle of this technique is based on mapping the stiffness from analysis of the strain in tissue under stress when small displacement is apply externally. It is well known that some pathologic conditions, such as malignant tumours, often produce changes in the mechanical properties of the tissue. Benign tissue has uniform elastic characteristics. In contrast, malignant tissue grows in a much unorganised way that give heterogeneous elastic property throughout the tumour. Using this advantage EUS elastography has been introduce in clinical practice for evaluation of tissue elasticity during EUS examination of pancreatic tumours to differentiate benign from malignant masses.

Elasticity measurements have been reported to be useful for the differential diagnosis between benign and malignant tumours in different tissue (13-16). One of the limitation of elastography is that it is subjective tool. Elastographic pattern is defined according to predominant color, and homogeneity or heterogeneity of color distribution, is essential. This definition according to mass color was first used by Giovanni *et al* in his study of pancreatic masses (14).

In his study, we used the same elastographic pattern for masses diagnosis. Pancreatic masses appearing mostly blue were considered malignant, whereas other patterns were considered as benign. Through these classification all malignant masses has been correctly identified although one benign case was diagnosed as a as malignant. In a multicenter study (18) including 121 patients with pancreatic masses done in different European counties, sensitivity and specificity of qualitative elastography for diagnosing malignancy were 92.3% and 80%, respectively.

In our study 30 patient the diagnostic sensitivity, specificity, positive predictive value negative predictive value and overall accuracy were: 88%, 80%, 95.6%, 57.14% and 86% respectively. In our study(2 3) cases score 5 on elastography scoring and indicating that the masses were malignant but, one of them was proved to be benign on histolopathology after surgical exploration .(5) patients scored 3, of these, (3) cases were proved to be malignant on final diagnosis. So we have one false positive and 3 false negative , the false negative is attributed to the fact that score 3 is difficult to interpenetrate as a malignant or benign due to tissue interposition , a limitation encountered in Giovannoni *et al* study (17).

The false positive is due to the fact sometimes it is difficult to differentiate between chronic pancreatitis and pancreatic malignant masse, particularly in cases of advanced pancreatitis due to the solid nature of the calcified pancreas (18,19,20). This why accuracy of EUS for diagnosis chronic pancreatitis is low (75%). In this case EUS-FNA may be of help although, it has limited sensitivity in this setting. Accuracy of elastography for differentiating chronic pancreatitis from malignancy has been improved by means of the quantitative second-generation elastography technology used by Julio I Garcia *et al* 2009 (3).

We show in our study the results of different study of elastography for the differential diagnosis of pancreatic masses Table 2.

In these studies the results of using EUS elastography in differentiating benign from malignant pancreatic masses showed slightly higher accuracy than that of our study, this may be due the small number of the patients enrolled in our study.

To avoid selection bias, all patients with pancreatic masses were included in the study and there was no withdrawal . In addition, elastography as applicable for all patients and non had to be excluded. The diagnostic accuracy of B-mode EUS for differentiating malignant from benign pancreatic masses has been improved by adding quantitative elastography.

In our study when we examined pancreatic masses using EUS, we found that the echo pattern is highly suggestive of malignancy in 22 cases and benign masses in 2. EUS findings, however, are inconclusive in the remaining 6 cases, in which elastography provides important information suggesting the true nature of the tumour. Although elastography provides highly valuable diagnostic information, it cannot supplant, however, EUS guided FNA. Finally we successfully used standard methods for final diagnosis of the benign or malignant nature of the masses which supports the accuracy of our results.

Our study had some limitations first, although the sensitivity is nearly similar to that of other studies, the specificity is low 80% which we attribute to the small number of patient enrolled in comparison to other studies. Second, this study was performed in just one center, and only a highly experienced endosonographer was involved.

Elastography has some intrinsic limitations as mention in other studies (14). The main pitfall of EUS elastography are the difficulty of controlling tissue compression by the EUS transducer, the motion artifacts secondary to respiratory and heart movements, and the density and stiffness from the region of interest, such as the heart, major vessels, or spine. Most of these limitations can be minimised in experienced hands. A stable elastographic image for seven seconds was required in the our study for elasticity measurement to avoid these limitations, and the mean of three measurements from each lesion was considered as the result. Despite these technical difficulties sometimes encountered, we found EUS elastography to be an accurate method for evaluation of pancreatic masses.

In conclusion, we strongly suggest that EUS elastography imaging offers complementary information added to conventional EUS imaging improving it is accuracy in differentiating malignant from benign pancreatic mass. The results in our study deserve further confirmation by other studies.

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