

Endoscopic Ultrasound (EUS) Elastography and Contrast Enhanced EUS for Discrimination of Pancreatic Masses

MOSTAFA IBRAHIM, M.D.*; DINA HAMZAWY, M.Sc.*; AYMAN ABD EL-RAHIM, M.D.**;
AHMED ABDEL FATTAH, M.D.* and NAGLAA ZAYED, M.D.**

Theodor Bilharz Research Institute and Tropical Medicine Department, Faculty of Medicine, Cairo University**, Cairo, Egypt*

Abstract

Background: Investigate the clinical utility of contrast-enhanced endoscopic ultrasound (CEEUS) and endoscopic ultrasound elastography (EUS-E) in diagnosis of pancreatic masses.

Patients and Methods: 30 patients with solid pancreatic focal lesions were included. All patients were subjected to laboratory investigations, conventional ultrasound, triphasic computed tomography (CT) scan, EUS-E, CEEUS, and EUS FNA. Diagnostic accuracy of EUS-E and CEEUS were compared and correlated to the pathology for pancreatic lesions.

Results: Malignant lesions were larger in size (32.2 ± 10.3), and had greater SR-E-EUS and more hypovascular pattern. The mean strain ratio was 16.4 ± 8.14 for benign and 67.76 ± 72.45 for malignant lesions ($p=0.001$). Hypovascular pattern after contrast injection was present in 76% of malignant and 60% of benign lesions ($p=0.66$). ROC analysis for the mean SR-E-EUS of the region of interest yielded an optimal cutoff of 74.4 with an AUC of 0.91 (95% CI: 0.74-0.98) for the best power distinction for malignancy. It provided a sensitivity and specificity of 75% and 80%, respectively.

Conclusion: EUS based novel modalities (CE-EUS and EUS-E) could distinguish between benign and malignant lesions and improve the identification of the vascular pattern respectively. Both techniques could be considered a complementary imaging modality in the characterization of pancreatic tumors.

Key Words: Contrast-enhanced ultrasound – Endoscopic ultrasound elastography.

Introduction

PANCREATIC lesions have a wide differential diagnosis that includes benign and malignant etiologies. Fine needle aspiration (FNA) of the pancreas is associated with a small, but not insignificant, risk of pancreatitis. Hence, the ability to evaluate masses and LN more accurately prior to their puncture in an effort to aid in targeting lesions

Correspondence to: Dr. Mostafa Ibrahim,
Theodor Bilharz Research Institute, Cairo, Egypt

for FNA and possibly reduce complications would be welcomed by echoendoscopists. Two strategies have been developed with these goals in mind: contrast-enhanced endosonography and sonoelastography [1].

Endoscopic Ultrasonography (EUS) provides imaging of tumors and enhances the accuracy of TNM staging. It can also provide guidance for fine-needle aspiration (FNA) and biopsies of undiagnosed masses and lymph nodes suspicious for malignant invasion [2]. However, FNA is technically demanding, and multiple puncturing of lymph nodes or masses is sometimes required in order to obtain sufficient tissue for histological assessment. In addition, when several lymph nodes appear suspicious, the choice of which to puncture is not always clear [3].

It is well known that some diseases, such as cancer, lead to changes in the hardness of tissue. EUS Elastography (EUS-E), a technique that allows the elasticity of tissue to be assessed during ultrasound examination, provides the ultrasonographer with important additional information that can be used for diagnosis. Elastography allows assessment of the elastic properties of tissues by applying slight compression to the tissue and comparing the images obtained before and after compression [1]. Routine use of EUS-E thus offers supplemental information that enhances conventional EUS imaging, with a possible decrease in the number of unnecessary EUS-FNA procedures. Furthermore, enhancements of the EUS elastography technology will probably establish the clinical impact of dynamic elasticity imaging [4].

Baseline gray-scale and color Doppler ultrasonographic (US) examinations have limited accuracy in the characterization of solid pancreatic

lesions because the depicted benign and malignant lesions may have similar echo patterns and vascular architectures [5].

Contrast-enhanced Endoscopic ultrasound (CEEUS) is highly efficient for the detection of tumor vascularity in pancreatic tumors, regardless of histological differentiation which can be characterized as hyper vascular lesions in the early arterial and arterial phase with irregular tumor vessels using CEEUS. During CEEUS, SonoVue® (from Bracco Diagnostics, Inc) is used as the contrast agent. It allows continuous real time examination during the different phases of contrast enhancement using low transmission power, expressed as mechanical index (MI) [5].

In addition to B-Mode scan sonomorphology, CEEUS may offer helpful information in patients with pancreatitis and focal lesions [6].

Material and Methods

This study was conducted on thirty patients with solid pancreatic focal lesions attending the Hepatology and Gastroenterology Department, Erasme hospital, Brussels, Belgium and at the endoscopy unit, Paoli-Calmettes Institute, Marseilles, France and Theodor Bilharz Research Institute (TBRI) in the period between June 2009 and December 2011.

Informed consent according to the ethical guidelines of the declaration Helsinki 1975, was obtained from all patients after the patients were informed of the purpose of the study before examination was started. The study was approved by TBRI-Institutional Review Board (IRB).

This study included 18 males and 12 females with the mean age of 70 ± 8 years. Pancreatic lesions were detected by abdominal ultrasound and triphasic computed tomography (CT) scan.

All of the patients underwent full clinical assessments and routine laboratory investigations were performed including hematological tests, biochemical tests (liver function and renal function) and tumor markers (serum Carcinoembryonic antigen and Carbohydrate antigen 19-9).

Imaging:

The following imaging was performed for all of the patients:

1- Conventional US B-mode and Doppler scanning; provided an assessment of the pancreas, focal lesions, pancreatic duct, patency of vessels, etc.

2- Triphasic CT scan; provided similar assessment as #1.

3- EUS (B-mode) and power Doppler scanning; provided similar assessment as #1 & #2.

4- Elastography (EUS-E); Imaging was performed with a Pentax EG38-UT EUS scope (Pentax Europe Ltd., Hamburg, Germany).

A- Qualitative EUS-E for pancreatic solid lesions:

EUS-E was performed during the EUS examinations with 2 movies of 20 seconds recorded. A 2-panel image with the usual conventional gray-scale B-mode EUS image on the right side and with the elastography image on the left side was used.

A scoring system shown below (Table 1) was generated [7].

B- Quantitative EUS-E for pancreatic solid lesions:

Calculation of the tissue elasticity distribution was carried out in real-time. Elastographic and B-mode images were displayed side-by-side. Strain ratio was calculated (focal lesion area strain %/ surrounding tissue area strain%).

5- Contrast-enhanced EUS scanning (CE EUS):

CE EUS was applied using a single injection of SonoVue® 2.4ml (BR1, Bracco, Italy) to evaluate if this contrast application could improve the characterization of tumor vascularity. SonoVue® (2.4mL) was injected following a flash of 10ml saline solution via a catheter (1.2mm in diameter or larger) into a cubital vein.

Protocol outlined by Dietrich et al., 2008, was followed to identify the pancreatic lesion and predict malignant lesions [9].

6- Endoscopy-guided fine needle aspiration (EUS FNA):

EUS-FNA was performed by using a 22-G FNA needle (Echotip, Cook Endoscopy, Winston-Salem, North Carolina USA). Direct smears were prepared by the endoscopist and were stained by May-Grunwald-Giemsa on air dried slides. ThinPrep® preparation (monolayer cytology, Cytoc Corp., Boston, Massachusetts, USA) was used in all cases. Protocol outlined by Schmidt et al., was followed [10].

The final diagnosis was based on the histological assessment of the EUS-FNA samples and/or surgical specimens when available. A positive cytological diagnosis was taken as a final proof of malignancy.

Table (1): Qualitative scoring system for pancreatic solid lesions.

Score	Elastography image	Description	Elastography colors	Possible diagnosis
1	• Homogenous	• Soft	• Green	• Normal pancreatic tissue
2	• Heterogeneous	• Soft ranging to hard	• Green, yellow, and red	• Corresponds to fibrosis
3	• Minimal heterogeneity	• Hard	• Blue	• Small, early pancreatic adenocarcinoma (less than 25mm size)
4	• Hypechoic region in the centre of the tumor		• Green surrounded by blue	• Hyper vascular lesion such as a neuroendocrine tumor or small pancreatic metastasis
5	• Heterogeneous	• Hard with softer tissue inside	• Blue on with of green, red inside	• Representing necrosis, and is seen in advanced pancreatic adenocarcinoma



(Giovanni et al., 2006).

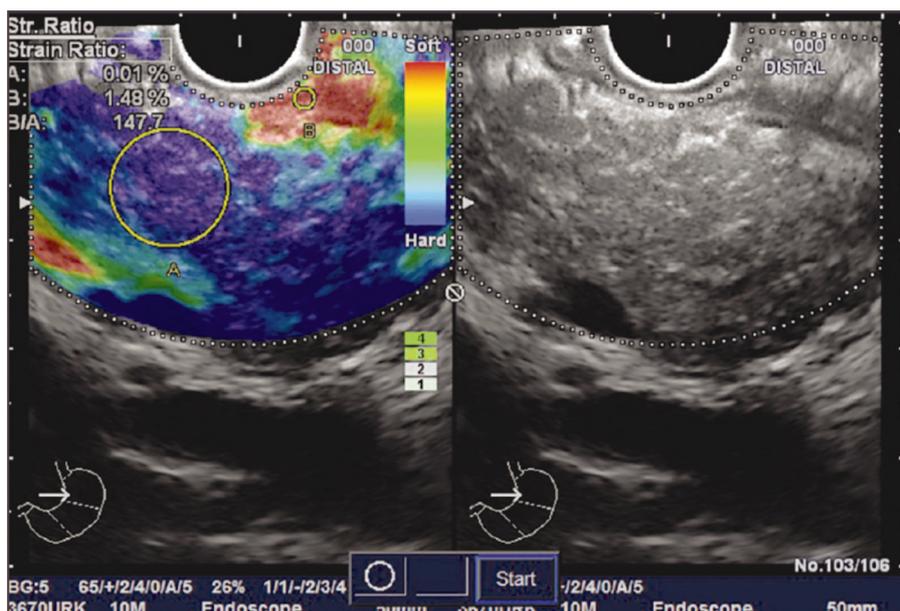


Fig. (1): Qualitative EUS-E and Strain ratio for pancreatic solid lesions.

The statistical analysis was done using SPSS 13.0 (SPSS Inc., Chicago) software. The categorical variables were expressed by their absolute (n) and relative frequency (%) and compared using the

Chi-squared test or Fisher Exact test. The continuous variables were expressed by mean and standard deviation and compared by using Student's *t*-test or Mann-Whitney U test. An association was

considered to be statistically significant at $p < 0.05$. Stepwise logistic regression analysis was carried out to search for independent predictors of malignancy. The sensitivity, specificity, positive (PPV) and negative predictive values (NPV), with 95% confidence intervals (95% CI), and overall accuracy were calculated.

Data was analyzed by sensitivity and specificity derived from the receiver operating characteristic (ROC) curve and area under the ROC curve (AUC). The McNemar test was used to compare these calculated sensitivities and specificities.

Results

Contrast Enhanced Endoscopic Ultrasound (CE EUS):

Contrast Enhanced Endoscopic Ultrasound (CE EUS) after SonoVue injection revealed that the mean \pm SD diameter of the lesions were 35.90mm \pm 11.81 with no statistically significant difference compared to computed tomography (CT) or B mode EUS. Early hypoenhancement was seen in 19 patients (63.4%) while early hyperenhancement was seen in 4 (13.3%). No complications were observed after SonoVue injection.

EUS FNA:

From the 30 focal pancreatic lesions included, 19 were diagnosed as adenocarcinoma, 6 as neuroendocrine tumors, 3 as benign nodules and 2 as chronic pancreatitis.

Benign lesions were proven by EUS FNA and contrast enhanced imaging CT follow-up.

Table (2): Comparative analysis between benign and malignant pancreatic lesions using EUS.

	Benign lesion (5)	Malignant lesion (25)	P-value
Age (yr) Mean \pm SD	69.42 \pm 14.95	69.99 \pm 6.92	0.93
Gender Male:Female n (%)	4:1	14:11	0.31
Size of the lesion (mm)	28.4	32.2	0.68
<i>Localization n (%):</i>			
Head	0 (0%)	18 (72%)	0.03
Body	0 (0%)	2 (8%)	
Tail	2 (40%)	2 (8%)	
Neck	3 (60%)	3 (12%)	
<i>B Mode EUS Echogenicity:</i>			
Iso Echoic	2 (40%)	12 (48%)	0.74
Hypo Echoic	3 (60%)	13 (52%)	
Hyper Echoic	0 (0%)	0 (0%)	
<i>CEEUS Early Phase:</i>			
Hypo Enhancement	3 (60%)	16 (64%)	0.65
Iso Enhancement	2 (40%)	5 (20%)	
Hyper Enhancement	0 (0%)	4 (16%)	
<i>CEEUS Late Phase:</i>			
Hypo Enhancement	3 (60%)	16 (64%)	0.50
Iso Enhancement	2 (40%)	4 (16%)	
Hyper Enhancement	0 (0%)	5 (20%)	
Strain ratio (EUS-E) Mean \pm SD	16.4 \pm 8.14	67.76 \pm 72.45	0.0019

Endoscopic Ultrasound Elastography Strain Ratio SR-E-EUS:

ROC analysis for the mean SR-E-EUS of the region of interest yielded an optimal cutoff of 74.4 with an AUC of 0.91 (95% CI: 0.74-0.98) for the best power distinction for malignancy. It provided a sensitivity and specificity of 75% and 80%, respectively.

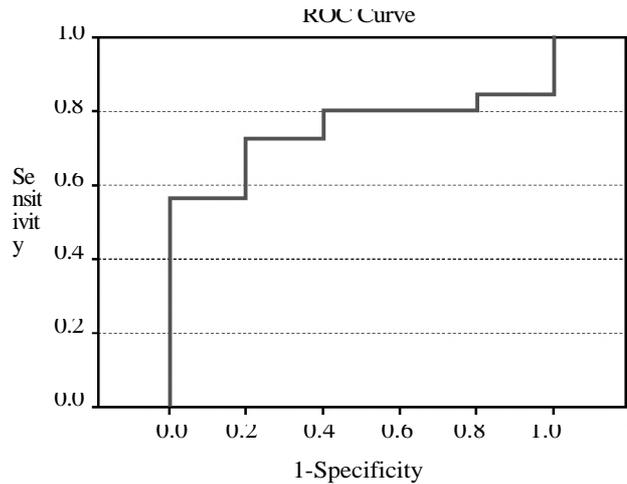


Fig. (2): The receiver operating characteristic (ROC) curve of the mean strain ratio obtained by endoscopic ultrasonography-elastography (EUS-E) of the region of interest used for the discrimination between benign and malignant lesions (sensitivity of 75% and specificity of 80% for a cutoff value of 74.4).

Table (3): Comparative analysis between adenocarcinoma and neuroendocrine tumors using EUS.

	Adeno-carcinoma (19)	Neuro-endocrine tumors (6)	P-value
Age (yr) Mean \pm SD	69.16 \pm 6.	72.63 \pm 8.16	0.37
Gender Male:Female n (%)	50 10: 9	4 : 2	0.54
Size of the lesion (mm)	32.57	31	0.72
<i>Localization n (%):</i>			
Head	14 (73.7%)	4 (66.6%)	0.15
Body	2 (10.5%)	0 (0%)	
Tail	0 (0%)	2 (33.4%)	
Neck	3 (15.8%)	0 (0%)	
<i>B Mode EUS Echogenicity:</i>			
Iso Echoic	10 (52.7%)	2 (33.4%)	0.40
Hypo Echoic	9 (47.3%)	4 (66.6%)	
Hyper Echoic	0 (0%)	0 (0%)	
<i>CEEUS Early Phase:</i>			
Hypo Enhancement	16 (84.2%)	0 (0%)	0.003
Iso Enhancement	3 (15.8%)	2 (33.4%)	
Hyper Enhancement	0 (0%)	4 (66.6%)	
<i>CEEUS Late Phase:</i>			
Hypo Enhancement	16 (84.2%)	0 (0%)	0.003
Iso Enhancement	2 (10.5%)	2 (33.4%)	
Hyper Enhancement	1 (5.3%)	4 (66.6%)	
Strain ratio (EUS-E) Mean \pm SD	68.52 \pm 82.74	65.33 \pm 23.19	0.88

Table (4): Performance of the criteria used for differential diagnosis between benign and malignant pancreatic focal lesions by the different modalities of EUS.

Diagnostic Performance	EUS-E	SR-EUS-E	CE-EUS
Sensitivity % (CI 95%)	100%	75%	64%
Specificity % (CI 95%)	0%	80%	40%
PPV* % (CI 95%)	84%	81%	84%
NPV % (CI 95%)	0%	0%	18%

EUS-FNA : Endoscopic ultrasonography-guided fine needle aspiration.
 SR EUS-E : Strain ratio by EUS-Elastography (cut-off point > 74.4 as sign of malignancy)
 CE-EUS : Contrast enhanced EUS (Hypovascular pattern as sign of malignancy)
 PPV : Positive predictive value. NPV: Negative predictive value.

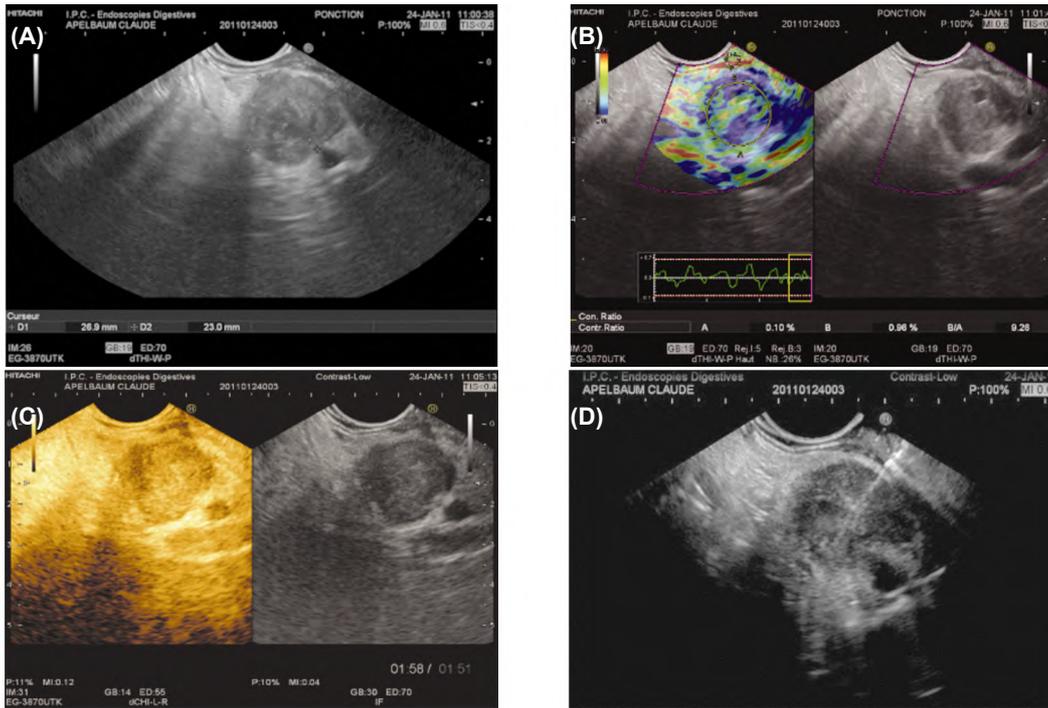


Fig. (3): (A) EUS, (B) CE-EUS, (C) EUS-E and (D) EUS FNA of a benign pancreatic lesion.

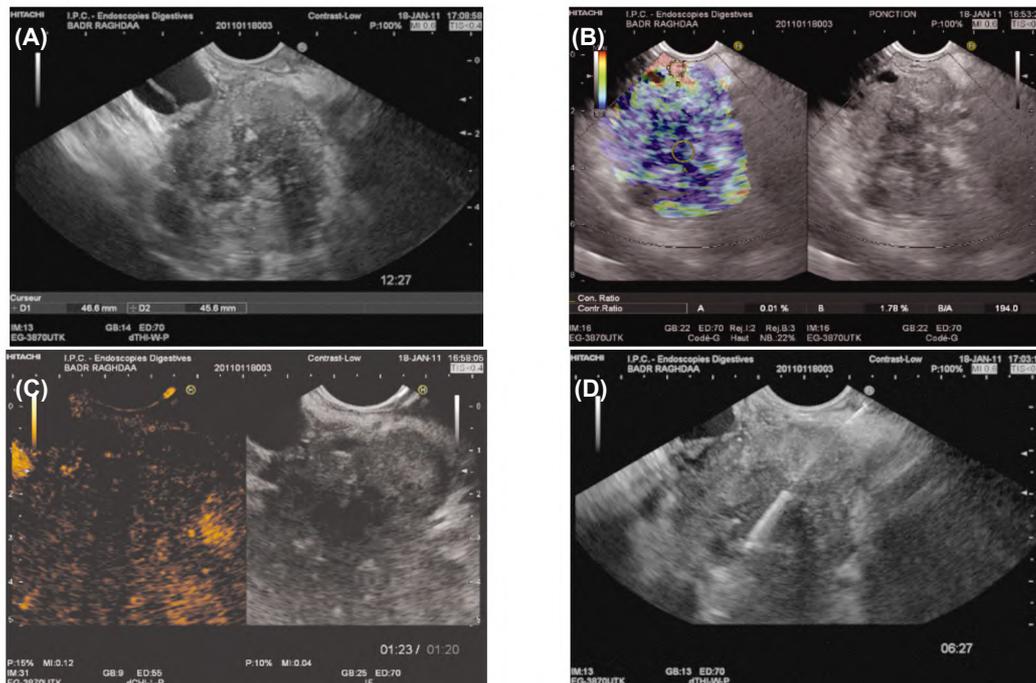


Fig. (4): (A) EUS, (B) CE-EUS, (C) EUS-E and (D) EUS FNA of a malignant pancreatic lesion.

All confirmed benign lesions as shown in (Fig. 3) were blue on qualitative EUS-E with a SR-EUS-E of 16.4 ± 8.14 and 60% of them were hypo enhancing on CE-EUS. While all confirmed malignant lesions as shown in (Fig. 4) were also blue on qualitative EUS-E with a SR-EUS-E of 67.76 ± 72.45 and 64% of them were hypo enhancing on CE-EUS.

Discussion

In this study, we assessed the appropriate technique for the diagnosis of solid pancreatic lesions. All of the lesions appeared to be blue on the EUS-E and then were differentiated using the SR-EUS-E.

EUS FNA of the 30 patients with pancreatic solid lesions revealed malignant lesions; adenocarcinoma in 19 (63.4%) and neuroendocrine tumors in 6 (20%). While benign lesions were diagnosed in 5 (16.6%) patients.

In our study, from 25 malignant lesions that had CE-EUS, 19 were diagnosed as adenocarcinoma where 16 of them (85%) showed a hypovascular pattern. These patients with CEEUS Early Phase showing Hypo Enhancement in 84.2% and strain ratio of 68.52 ± 82.74 . Neuroendocrine tumors were diagnosed in 6 patients with CEEUS Early Phase showing Hyper Enhancement in 66.6% and strain ratio of 65.33 ± 23.19 . Hypoenhancement after contrast injection within CE-EUS examination was statistically significant for the detection of adenocarcinoma compared to neuroendocrine tumors ($p = 0.003$).

When comparing benign and malignant lesions using EUS, malignant lesions were larger, had greater strain ratio and more hypovascular pattern. The mean strain ratio was 16.4 ± 8.14 for benign and 67.76 ± 72.45 for malignant lesions ($p = 0.0019$).

Our high sensitivity for CE-EUS (64%), presented, is similar to that demonstrated in previous studies [9,11].

Studies have shown ambivalent results for EUS-E. Taken as a whole, our sensitivity, specificity, PPV, NPV, and accuracy rates were comparable to those of Janssen et al., [12].

When assessing the accuracy of the combination of CE-EUS and EUS-E, our accuracy rates were 79% for CE-EUS and 82% for SR-EUS-E. This is similar to the study done by Sftoiu et al., 2010, where they reported overall accuracy of 83% for CEE-EUS and 82% for EUS-E [13]. Both rates, theirs and ours, are still suboptimal and their place

should probably be reserved for cases with inconclusive EUS-FNA.

We should highlight in our study the sensitivity rate (84%) and the high PPV (81%) for SR-EUS-E above 74.4 as a sign of malignancy. Therefore this technique could assist physicians in making decisions between surgery and follow-up when the biopsy is inconclusive.

The strength of this study may be a direct comparison between CE-EUS and SR-EUS-E in the same session because most studies on these new imaging modalities are single arm with possible selection bias. It is a relatively small series, but one of the larger studies directly comparing CE-EUS to EUS-E.

Despite the small sample size, this is a preliminary study to highlight the importance of both EUS-E and CEEUS. Future design would include a large sample size study on each technique separately to study each technique thoroughly.

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استخدام الموجات فوق الصوتية بالصبغة وتقنية مطاطية الأنسجة بمنظار الموجات فوق الصوتية لتشخيص أورام البنكرياس

يعتبر سرطان خلايا البنكرياس من أشهر أنواع الأورام انتشاراً بالعالم ومن أشهر أسباب الوفيات. هدف هذه الدراسة هو مدى جدوى استخدام الموجات فوق الصوتية بالصبغة (CE-EUS) وتقنية المطاطية للأنسجة (EUS-E) بمنظار الموجات فوق الصوتية لتشخيص البؤر الصلبة للبنكرياس، وتعتبر تقنية المطاطية للأنسجة بمنظار الموجات فوق الصوتية هي تقنية حديثة في مجال مناظير الموجات فوق الصوتية ولها قابلية التفرقة بين الألياف الحميدة والخبيثة، كما لوحظ أن استخدام الموجات فوق الصوتية بالصبغة يستطيع تشخيص أورام البنكرياس بنفس حساسية الأشعة المقطعية بالصبغة.

في هذا العمل، تم استخدام الموجات فوق الصوتية بالصبغة وتقنية المطاطية للأنسجة بمنظار الموجات فوق الصوتية لتشخيص الأورام الخبيثة للبنكرياس ولقد اشتملت الدراسة على ٣٠ مريضاً يعانون من بؤر صلبة للبنكرياس، من المترددين على قسم الجهاز الهضمي والكبد بمعهد تبادور بلهارس للأبحاث وجامعة بروكسا - بلجيكا وذلك ما بين شهر يونيو ٢٠٠٩ وشهر ديسمبر ٢٠١١.

تم إجراء البحث على ثلاثون مريض يعانون من بؤر بنكرياس صلبة (١٨ ذكر و ١٢ أنثى) وكان متوسط عمرهم (٧٠ ± ٨ عام) ولقد تم تقييم جميع المرضى بواسطة الموجات فوق الصوتية والتحليل والأشعة المقطعية بالصبغة ولقد تم أخذ عينة من البؤر من جميع المرضى عن طريق منظار الموجات فوق الصوتية.

في هذه الدراسة، تم حساب الحساسية، الخصوصية، القيمة التنبؤية الإيجابية والقيمة التنبؤية السلبية لتقنية المطاطية للأنسجة بمنظار الموجات فوق الصوتية وتشخيص أورام البنكرياس الخبيثة وقد أوضحت الدراسة أن الحساسية والقيمة التنبؤية الإيجابية كانت ٨٤٪، ٨١٪، على التوالي.

تعتبر خاصة المطاطية للأنسجة بمنظار الموجات فوق الصوتية وخاصة استخدام الموجات فوق الصوتية بالصبغة من التقنيات الجديدة وسوف يكون لهما دور في المستقبل في التفريق بين الأورام الحميدة والخبيثة للبنكرياس.