

The Role of EUS and EUS-FNA in Detection of Small Sized Liver Metastatic Lesions in Patients with Pancreatic and Gastro-Intestinal Primary Malignancy

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Abstract

Background: Liver is common site of metastasis. Small liver masses (<2cm) are not easily detected by ultrasound or computed tomography. Endosonography allows visualization of liver anatomy.

Aim of Study: To assess usefulness of endosonography and EUS-FNA in detecting small sized liver metastasis; not diagnosed by CT scan during TMN staging of gastro-intestinal and pancreatic malignancy.

Patients and Methods: This prospective comparative study included 92 cases with pancreatic, peri-ampullary and GI malignancies. Patients undergone:

CBC, serum bilirubin, AST, ALT, ALP, GGT, serum protocol albumin, prothrombin concentration, creatinine, AFP and CA19.9, abdominal ultrasound, pancreatic computed tomography scan and endosonography. EUS-FNA and cytological examination were performed in 23 patients.

Results: CT scan detected 27 patients with liver focal lesions, one patient was missed. While EUS detected 27 cases, and also one patient was missed. Among cases diagnosed by EUS, 4 cases were cholangitic abscesses, EUS-FNA was performed in 23 cases, revealing metastatic lesions in 21 patients, benign lesions in 2 patients (focal fat depletion). EUS had 95.45% sensitivity, 97.14% specificity, 91.3% positive predictive value (PPV), 98.55% negative predictive value (NPV) and 96.74% accuracy. CT had 95.45% sensitivity, 91.43% specificity, 77.78% PPV, 98.46% NPV and 92.39% accuracy. EUS-FNA, had 95.45% sensitivity, 100% specificity, 100% PPV, 98.5% NPV and 98.91% accuracy.

Conclusions: EUS and EUS-FNA play a significant role in detecting small sized liver metastasis, where EUS and EUS-FNA showed a higher diagnostic accuracy compared to that of CT scan.

Key Words: *Endosonography – Liver metastasis – Pancreatic malignancy – Gastro-intestinal malignancy.*

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Introduction

FOCAL hepatic lesions include benign lesions (as hepatic cysts, focal nodular hyperplasia, regenerative nodular hyperplasia, abscess, adenoma or hemangioma), and malignant lesions (as hepatocellular carcinoma, intrahepatic cholangiocarcinoma and metastatic liver disease) [1].

Since the mesenteric veins drain blood from the colon, small bowel, pancreas, and stomach to the liver, this explains that the liver is a common site for metastatic deposits for these organs' primary malignancy [2]. Histologically, pancreatic adenocarcinoma represents the majority of pancreatic cancer cases. Liver is the most common site of metastasis for pancreatic adenocarcinoma [3]. Colorectal cancer (CRC) is the most common gastrointestinal tumor. Similar to pancreatic adenocarcinoma, liver is the most common site of CRC metastases with an incidence of 15%-20% at diagnosis [4]. Also as regard gastric cancer, 35% of patients have evidence of distant metastases, and 4% to 14% have metastatic liver disease, with a very poor prognosis, at time of diagnosis [5].

Endoscopic ultrasound (EUS) is an important diagnostic tool [6]. Due to the close proximity of the transducer to the liver, from the transgastric and transduodenal routes, EUS allows a good visualization of the liver anatomy and its vasculature providing detailed images [7].

Small liver masses (<2cm) are not easily accessible by ultrasound or CT guided percutaneous biopsy [8]. In recent review by Srinivasan et al., [1], EUS has shown superiority in detecting small focal hepatic lesions.

Fujii-Lau et al., [9] concluded that EUS criteria may help in distinguishing benign from malignant hepatic lesions, and can guide the decision to perform EUS-FNA on a liver mass or not.

Aim of study:

To assess usefulness of endosonography and EUS-FNA in detecting small sized liver metastasis; not diagnosed by CT scan during TMN staging of gastro-intestinal and pancreatic malignancy.

Patients and Methods

Study design:

This prospective comparative study was conducted on 92 cases with suspected or confirmed pancreatic, periampullary or GI malignancies. The patients were recruited from Kasr Al-Aini Faculty of Medicine, Cairo University, during the period from October 2017 to March 2019. The selection and stratification of the patients were based on sample size calculation and the competence of the availability of the data. A written informed consent was taken from each patient after the nature of the procedure was fully explained. The study protocol was approved by the Ethical Committee of Cairo University. The study protocol conforms to the ethical guidelines of the 1975 Declaration of Helsinki as revised in Brazil 2013.

Methods:

Patients were subjected to thorough history taking and clinical examination with special emphasis on jaundice, pallor, cachexia, bleeding tendency, ascites, organomegaly and peripheral lymphadenopathy.

Patients were selected between 18 and 75 years, of both sexes, with suspected or proved pancreatic, periampullary masses or GI cancer (detected by ultrasound, CT, MRI or oesophago-gastro-duodenoscopy, with or without biopsy).

Patients were excluded if they were below 18 or above 75 years, or pregnant, or suffering from coagulopathies that contraindicate EUS-FNA, or if they were unfit for propofol deep sedation, or those with distant metastases.

The laboratory work up performed included: complete blood count, serum bilirubin (total and direct), AST, ALT, alkaline phosphatase, GGT, serum albumin, prothrombin concentration, serum creatinine, alpha feto protein (AFP) and CA 19-9.

All patients undergone abdominal ultrasound using Toshiba SSA-340A machine with a 3.5MHZ

convex linear transducer, with a built in color flow mapping (CFM) and Doppler functions.

All patients were subjected to pancreatic protocol computed tomography scan, which was done using Toshiba Aquilion 64 CT scanner multidetector device. Non ionic contrast (Ultravist) was injected at dose 1-2ml per Kg with rate 4-5ml per second. Imaging was done in arterial and venous phases after intravenous injection of contrast. The arterial phase of enhancement, which corresponds to the first 30 seconds after the start of the contrast injection, provided excellent opacification of the celiac axis, superior mesenteric artery, and peri-pancreatic arteries. The portal venous phase, which was obtained at 60 to 70 seconds after the start of the contrast injection, provided better enhancement of the superior mesenteric vein, splenic and portal veins as well as the pancreas itself and any liver metastases that may be present.

Patients were sent for EUS examination for detection, staging or EUS-FNA for possible neo-adjuvant or adjuvant chemotherapy. EUS was done to all patients using an EUS linear array Echoendoscope, Pentax EG-3870UTK attached to Hitachi Avius US machine under propofol deep sedation. During EUS examination, identification of the liver segments was done through the stomach and/or duodenum accordingly. The liver was examined thoroughly to detect hepatic focal lesions with possible EUS-FNA of any detected lesions.

Target lesions were initially identified and their detailed endosonographic features were assessed, then EUS-FNA was carried out using a 22 or 19-gauge needles.

Cytological examination:

The aspirate was spread over glass slides and fixed by 95% alcohol, also formalin block was provided, then the specimens were subjected to cytological examination, including immunopathological staining if needed.

The final diagnosis was made by the presence of malignant cells in cytological examination.

Statistical analysis:

Data was entered on the computer using "Microsoft Office Excel Software" program (2010) for windows. Data was then transferred to the Statistical Package of Social Science Software program, version 23 (IBM SPSS Statistics for Windows, Version 23.0. Armonk, NY: IBM Corp.) to be statistically analyzed.

Data was presented using range, mean, standard deviation median and interquartile range for quantitative variables and frequency and percentage for qualitative ones.

Inter-rater agreement was assessed to estimate the degree of agreement between the studied techniques.

Results

The demographic features and baseline clinical and laboratory characteristics of the studied patients are summarized in Table (1). From all the studied patients; 53 patients were males (57.6%) and 39 were females (42.4%), with a mean age of 56.2 ± 12.7 years. The majority of patients presented with nausea and vomiting (77 patients 84%), and jaundice (72 patients 78.3%). Laboratory data showed markedly elevated AFP level with a range of 536.5ng/ml, and CA19.9 level with a range of 301.1mg/dl.

The majority of the studied patients suffered from pancreatic o-biliary tumours (82 patients 89.1 %), which included pancreatic adenocarcinoma (81.5%), papillary malignancy (3.3%) and cholangiocarcinoma (4.3%). Other presentations included; 5 patients (5.4%) with oesophageal adenocarcinoma, 2 patients with gastric adenocarcinoma, and 3 patients with gastro-intestinal stromal tumours (GIST), as shown in Table (2).

Work up done included pancreatic protocol computed tomography scan and endosonography, and revealed that 28 patients (30.4%) had hepatic focal lesions. These lesions were detected in the right hepatic lobe in four patients, in the left lobe in 11 patients, and bilobar in 13 patients. In 50% of the patients with detected hepatic focal lesions (14 patients), the focal lesions were small sized (≤2cm), as shown in Table (3).

On analyzing the results of the pancreatic protocol computed tomography scan, we found that among the 28 patients with hepatic focal lesions, the CT detected the lesions in 27 patients (96.4%), where one missed patient was diagnosed by EUS to have a 4 mm single hypoechoic focal lesion in the left lobe, which proved to be metastatic lesion by EUS -FNA. The CT confirmed that the lesions are metatatic in 16 patients (57.1%), and suggested that they are probably metastatic in 11 patients (39.3%), as shown in Table (4). Among these 11 patients with probably metastatic lesions, four patients were proved by EUS to have cholangitic abscesses.

Table (1): Description of demographic, clinical and laboratory data of studied patients.

Variables	Description (n=92)
<i>Age (years):</i>	
Mean ± SD	56.2±12.7
<i>Gender:</i>	
Male, number (%)	53 (57.6%)
<i>Presentation Number (%):</i>	
Jaundice and related symptoms	72 (78.3%)
Cachexia	57 (62%)
Nausea and Vomiting	77 (84%)
Hepatomegaly	38 (41%)
Abdominal pain	61 (66%)
Diabetes	3 (3.2%)
<i>Hemoglobin (g/dL):</i>	
Mean ± SD	13.7±2.2
<i>WBCs x10³ (cell/mm³):</i>	
Mean ±SD	10.2±18.2
<i>Platelet count (cell/mm³):</i>	
Mean ± SD	239214.2±224138.8
<i>Total bilirubin (mg/dL):</i>	
Mean ± SD	9.2±1.29
<i>Direct bilirubin (mg/dL):</i>	
Mean ± SD	5.85±1.18
<i>Serum ALT (IU/L):</i>	
Mean ± SD	47.8±21.5
<i>Serum AST (IU/L):</i>	
Mean ± SD	37.5±12.2
<i>Serum creatinine (mg/dL):</i>	
Mean ± SD	0.88±0.26
<i>AFP (ng/mL):</i>	
Median (IQR)	536.5 (8-4840)
<i>CA19-9 (mg/dL):</i>	
Median (IQR)	301.1 (106.7-810.1)

IQR : Interquantile range.
 SD : Standard deviation.
 ALT : Alanine aminotransferase.
 AST : Aspartate aminotransferase.
 AFP : Alpha feto protein.
 Data are presented as mean ± SD, median (Range), or number (%).

Table (2): Description of primary tumors in studied patients.

Primary tumors	Description (n=92)	
<i>Pancreatico-biliary:</i>	82	89.1%
Pancreatic Adenocarcinoma	75	81.5%
Papillary malignant mass	3	3.3%
CBD stricture secondary to cholangiocarcinoma	4	4.3%
<i>Other GIT malignancies:</i>	10	10.9%
Esophageal adenocarcinoma	5	5.4%
Gastric adenocarcinoma	2	2.3%
GIST	3	3.3%

GIST: Gastro-intestinal stromal tumour.

Table (3): Description of liver focal lesions of studied cases.

	Description (n=92)
<i>Presence of liver focal lesions:</i>	
Yes	28 (30.4%)
No	64 (69.6%)
<i>Lobe:</i>	
Right lobe	4 (14.3%)
Left lobe	11 (39.3%)
Bilobar	13 (46.4%)
<i>Number:</i>	
Single	10 (35.7)
Multiple	18 (64.3)
<i>Size (mm):</i>	
Range	4-70
Mean \pm SD	26.9 \pm 16.9
Median (IQR)	22.5 (15-34.5)
<i>Size:</i>	
Small (\leq 2cm)	14 (50)
Large ($>$ 2cm)	14 (50)

Table (4): Description of EUS, EUS-FNA and pancreatic protocol CT scan findings in the studied cases.

	Description
<i>CT (n=92):</i>	
Hepatic focal lesion	27 (29.3%)
No hepatic focal lesion	65 (70.7%)
<i>CT diagnosis (n=28):</i>	
METs	16 (57.1%)
Probably METs	11 (39.3%)
Missed lesions (detected by EUS FNA)	1 (3.6%)
<i>EUS (n=92):</i>	
Hepatic Focal lesion	27 (29.3%)
No hepatic focal lesion	65 (70.7%)
<i>FNA (n=27):</i>	
Malignant metastases	21 (77.8%)
Benign focal lesions	2 (7.4%)
Not done	4 (14.8%)

METs: Metastatic lesions.

As regard the EUS findings, the EUS detected hepatic focal lesions in 27 patients (96.4%), and one patient was missed (3.6%) with a right lobe, single focal lesion, hyperechoic, 25mm in size, which was detected by CT scan. Among these 27 patients, EUS-FNA was not performed in four cases (14.8%) with EUS findings characteristics of cystic lesions in the liver and the patients received antibiotics and follow-up clinically and by trans-abdominal ultrasound confirmed the diagnosis of cholangitic abscesses. The rest of the 23 patients undergone EUS-FNA, and malignant metastatic hepatic focal lesions were confirmed in 21 patients (77.8%), and two patients (7.4%) were diagnosed to have focal fat depletion area, as shown in Table (4).

Among the 23 patients who underwent EUS and FNA; there were no (0%) minor or major complications during the follow-up period (2 weeks) after the procedure.

On assessing the validity of the studied techniques, our results showed that EUS had 95.45% sensitivity, 97.14% specificity, 91.3% positive predictive value (PPV), 98.55% negative predictive value (NPV) and 96.74% accuracy. CT had 95.45% sensitivity, 91.43% specificity, 77.78% PPV, 98.46% NPV and 92.39% accuracy. And EUS-FNA, had 95.45% sensitivity, 100% specificity, 100% PPV, 98.5% NPV and 98.91% accuracy, as shown in Table (5).

Table (5): Validity measures of EUS, CT, EUS-FNA.

Final diagnosis	Sensitivity	Specificity	PPV	NPV	Accuracy
EUS	95.45%	97.14%	91.3%	98.55%	96.74%
CT	95.45%	91.43%	77.78%	98.46%	92.39%
EUS-FNA	95.45%	100%	100%	98.5%	98.91%

PPV: Positive predictive value. NPV: Negative predictive value.

Discussion

Carcinomas that commonly metastasize to the liver include colorectal carcinoma, breast carcinoma, neuroendocrine tumors, lung carcinoma, and gastric carcinoma [10]. Recently, it has been suggested that EUS is a useful tool for detection of liver metastasis [11]. We aimed in this study to assess usefulness of EUS and EUS-FNA in detecting small sized liver metastasis; not diagnosed by CT scan during TMN staging of GI and pancreatic malignancy, which can affect the management plan.

In the current study the mean age of the studied patients was 56.2 ± 12.7 years. This matches with the recent global figures, which show that the risk of developing pancreatic and GI cancers increases with age, and most people who develop pancreatic cancer are older than 45 years. The majority of our patients were males (57.6%), which matches the higher worldwide incidence of pancreatic cancer in males than females [12].

In terms of characteristics of the detected focal hepatic lesions, our results showed that the majority of the lesions were multiple and bilobar; and half of them were larger than 2 cm. This is explained by the fact that most liver metastases are multiple. Multiple tumors often vary in size; this is because tumor seeding occurs in episodes [13].

In the present study, the EUS yielded a sensitivity of 95.45% and a specificity of 97.14%, while CT scan yielded a sensitivity of 95.45%, a specificity of 91.43% for the detection of small-sized liver metastasis. EUS showed a slightly higher diagnostic accuracy (96.7%) for detecting small-sized liver metastasis, compared to that of CT scan (92.4%). One case with liver metastatic lesion was missed by EUS, and one case was missed by CT scan. Although, this difference in accuracy is statistically small, yet practically, it is a significant difference, and warrants further studies on a larger sample.

In concordance with our findings, Singh et al., [14] compared the accuracy of the EUS/EUS-FNA with CT scan for detection of the liver metastases. The diagnostic accuracy of EUS/EUS-FNA was higher than CT scan (98% and 92%, respectively).

However, Nguyen et al., [15] work showed a more significant superiority of EUS over CT scan for diagnosis liver metastatic lesions. They studied 574 patients with history or suspicion of gastrointestinal or pulmonary malignant tumor. Fourteen (2.4%) patients were found to have focal liver lesions by EUS; while the CT detected liver lesions in only 3 of the 14 (21%) patients. Thus, the diagnostic yield of EUS was significantly higher than CT. This more obvious difference between CT scan and EUS compared to our study, may be explained by the larger sample size in Nguyen et al., study, and by the enrollment of patients with pulmonary malignant tumors; who were not included in our study.

Regarding the diagnostic accuracy of EUS-FNA, EUS-FNA was performed in 23 patients who were identified with definite liver lesions. It had a sensitivity of 95.45%, specificity of 100%, PPV of 100%, NPV of 98.5% and a diagnostic accuracy of 98.91%.

This matches with the results of Ichim et al., [16], who conducted a systematic review in order to assess the evidence supporting the diagnostic yield of endoscopic ultrasound-guided biopsy of focal liver lesions (9 studies included), and concluded that endoscopic ultrasound-guided biopsy proved to be superior to CT scan in diagnostic accuracy (98% versus 82%).

Also in agreement with our findings, Hollerbach et al., [17] conducted a prospective study on 41 patients with clinical findings suggestive of liver malignancies. The EUS-FNA had a sensitivity of 94% and specificity of 100%, with a negative

predictive value of 78% and positive predictive value of 100%.

In contrast to our study, the work done by Fujii-Lau et al., [9] over a 12-year period, and studied 332 patients, showed much lower EUS-FNA diagnostic accuracy in comparison to our study. EUS-FNA of a hepatic mass had a diagnostic accuracy of 73% and a positive predictive value of 88%. The exact causes of such heterogeneities in results between both studies are unclear. However, it can be attributed to difference in sample size, study design, or level of experience of investigators who performed EUS-FNA.

As regard the safety of the procedure, none of our patients suffered from major or minor complications during the procedure, during the follow-up period (2 weeks) after the procedure.

This matches with the work done by DeWitt et al., 2004 [18], who performed EUS-FNA from 77 liver lesions in 77 patients, and no complications were reported.

Conclusion and recommendations:

In conclusion, EUS and EUS-FNA play a significant role in detecting small sized liver metastasis, and differentiating it from benign lesions, during TMN staging of GI and pancreatic malignancy, where EUS and EUS-FNA showed a slightly higher diagnostic accuracy compared to that of CT scan.

Study's Limitations:

We report that the present study had some limitations. These limitations included the relatively small sample size, in addition to the high cost of the procedure, as well as the cost of the needles used in EUS-FNA technique.

Declaration of interest:

- The authors declare no conflict of interest.
- There is no source of funding.

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دور التنظير الداخلي بالموجات فوق الصوتية وسحب الخلايا من خلال إبرة رفيعة بإستخدام التنظير الداخلي بالموجات فوق الصوتية فى الكشف عن أورام الكبد الثانوية صغيرة الحجم فى المرضى الذين يعانون من ورم خبيث فى البنكرياس والمعدة والأمعاء

الكبد هو عضو شائع لثانويات الأورام. يصعب الوصول إلى البؤر الصغيرة فى الكبد (أقل من 2 سم) عن طريق الموجات فوق الصوتية أو الأشعة المقطعية. يسمح التنظير الداخلي بالموجات فوق الصوتية بتصوير تشريح الكبد.

تهدف هذه الدراسة لتقييم مدى فائدة التنظير الداخلي بالموجات فوق الصوتية وسحب الخلايا من خلال إبرة رفيعة بإستخدام التنظير الداخلي بالموجات فوق الصوتية فى الكشف عن أورام الكبد الثانوية صغيرة الحجم، التى لم يتم تشخيصها عن طريق التصوير بالأشعة المقطعية كجزء من تصنيف الورم والعقد والنقائل TMN لأورام البنكرياس والمعدة والأمعاء الخبيثة.

شملت هذه الدراسة الاستشرافية المقارنة 92 حالة أورام خبيثة بالبنكرياس، والمعدة والأمعاء. خضع المرضى للتحاليل الآتية: صورة دم كاملة، الصفراء فى الدم، AST، ALT، ALP، GGT، الزلال فى الدم، تركيز البروثرومبين، الكرياتينين، AFP وCA19.9، وكذلك الموجات فوق الصوتية على البطن، والتصوير الطبقي المحوسب بالأشعة السينية (الأشعة المقطعية) بإستخدام بروتوكول البنكرياس، والتنظير الداخلي بالموجات فوق الصوتية. تم إجراء الشفط بإبرة رفيعة بإستخدام التنظير الداخلي بالموجات فوق الصوتية والفحص الخلوى للعينات بالنسبة لـ 23 مريض.

أكتشفت الأشعة المقطعية وجود بؤر فى كبد فى 27 حالة، وأغلقت التشخيص فى مريض واحد. بينما أكتشف التنظير الداخلي بالموجات فوق الصوتية 27 حالة، كما أغفل التشخيص فى مريض واحد. من بين الحالات التى تم تشخيصها من قبل التنظير الداخلي بالموجات فوق الصوتية، كانت 4 حالات تم تشخيصها كخراجات قناة الصفراء. تم إجراء سحب الخلايا من خلال إبرة رفيعة بإستخدام التنظير الداخلي بالموجات فوق الصوتية فى 23 حالة، وكشف ذلك عن أورام ثانوية بالكبد فى واحد وعشرين مريض، كما كشف عن بؤر حميدة بالكبد فى اثنين من المرضى (استنزاف الدهون البؤرى). حقق التنظير الداخلي بالموجات فوق الصوتية حساسية 95.45٪، وخصوصية 97.14٪، وقيمة تنبؤية إيجابية 91.3٪، وقيمة تنبؤية سلبية 98.55٪ ودقة تشخيصية 96.74٪. بينما حققت الأشعة المقطعية حساسية 95.45٪، وخصوصية 91.43٪، وقيمة تنبؤية إيجابية 77.78٪، وقيمة تنبؤية سلبية 98.46٪، ودقة تشخيصية 92.39٪. وحقق سحب الخلايا من خلال إبرة رفيعة بإستخدام التنظير الداخلي بالموجات فوق الصوتية حساسية 95.45٪، وخصوصية 100٪، وقيمة تنبؤية إيجابية 100٪، وقيمة تنبؤية سلبية 98.55٪ ودقة تشخيصية 98.91٪.

ونستنتج من هذه الدراسة أن التنظير الداخلي بالموجات فوق الصوتية وسحب الخلايا من خلال إبرة رفيعة بإستخدام التنظير الداخلي بالموجات فوق الصوتية تلعب دوراً هاماً فى الكشف عن الأورام الثانوية بالكبد صغيرة الحجم، حيث أظهر كل من التنظير الداخلي بالموجات فوق الصوتية وسحب الخلايا من خلال إبرة رفيعة بإستخدام التنظير الداخلي بالموجات فوق الصوتية دقة تشخيصية أعلى بالمقارنة مع التصوير بالأشعة المقطعية.