Value of Endoscopic Ultrasound in Detection of Hepatic Occult Metastasis during Staging of Pancreatic and Upper Gastro Intestinal Malignancies

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Background: Endoscopic ultrasound (EUS) is a useful tool for detection of liver metastasis as compared to conventional CT scan and ultrasound imaging modalities. **This study aimed to**; assess the value of Endoscopic Ultrasound (EUS) in detection of hepatic occult metastasis during staging of pancreatic and Upper gastro intestinal (GI) malignancies. **Methods:** this study included 150 cases with pancreatic and upper GI malignancies; all patients were subjected to laboratory investigations and abdominal US & CT abdomen. EUS was done to all these cases who were admitted at Maadi military hospital in the period from April 2020 to march 2021, During EUS examination the liver was examined thoroughly to detect hepatic focal lesions with fine needle aspiration (EUS FNA) of hepatic occult metastasis which were not discovered by conventional ultrasound or CT. **Results:** The mean age of the included patients was 57.4 ± 11.2 years and the majority were males. The most common type of primary tumors among the studied patients was pancreatic cancer. Conventional ultrasound detected 19 cases of metastatic hepatic focal lesions, triphasic CT detected 27 cases, while EUS detected 32 cases. EUS FNA was done for 5 occult small hepatic focal lesions, which were not detected by conventional ultrasound or triphasic CT, and histopathological examination revealed them to be metastatic in nature. EUS yielded 93% sensitivity and 99% specificity in the detection of small-sized liver metastasis, compared with a72% sensitivity and 97% specificity through triphasic CT. **Conclusion:** EUS and EUS-FNA is a useful diagnostic modality for the detecting small-sized liver metastasis that may be missed by other methods during TNM staging of pancreatic and upper GI malignancy.

Keywords: EUS, hepatic metastasis, pancreatic cancer, Gastro intestinal malignancies.

Introduction

EUS has the advantage of using both ultrasound and endoscopy to give the exact diagnostic features of the GI tract. EUS role has grown dramatically to include both diagnostic and therapeutic advantage in gastrointestinal, pancreatic and hepatobiliary tree diseases(1).

Abdominal imaging [CT, magnetic resonance imaging (MRI), and transabdominal ultrasonography (USG)] are the diagnostic tests of choice to detect hepatic lesions suspicious of metastasis. Unfortunately, these modalities are limited in their ability to detect hepatic lesions less than 1 cm (2).

In addition, although rare, percutaneous FNA for suspected metastatic lesions carries the risk of implantation metastasis (3).

Although unable to completely visualize the entirety of the liver, EUS can detect small hepatic lesions that may be otherwise missed by conventional imaging. EUS can delineate detailed anatomy of the liver from the trans gastric and trans duodenal routes with the exception of the right posterior segments(4).

Due to the close proximity of the transducer to the liver, from the transgastric and transduodenal routes, EUS allows a clear visualization of the liver anatomy of the left lobe, most of the right lobe and its vasculature providing accurate and detailed images (3).

The prospect to obtain precise, ultrasound-guided biopsies of possible metastatic liver lesions can drastically alter the therapeutic plan (5).

Furthermore, the use of on-site cytopathology interpretation has further improved the diagnostic yield of EUS-FNA by helping to ensure that the samples obtained are representative of the target organ and adequate for diagnostic purposes(6).

Small liver masses and those that are difficult to differentiate from the background parenchyma are not easily accessible by ultrasound (US)- or computed tomography (CT)-guided percutaneous biopsy. On the other hand solid liver lesions accessible by EUS may be safely sampled by EUS-FNA (7).

This study aimed to assess the value of Endoscopic Ultrasound (EUS) in detection of hepatic occult metastasis during staging of pancreatic and Upper GI malignancies.

Patients and methods

This was a cross-sectional prospective, retrospective study that was conducted in Maadi Military Hospital in the period from April 2020 to March 2021on 150 patients and all patients fulfilling the inclusive criteria were enrolled in the study, after ethical approval obtained from hospital ethical committee and Benha faculty of medicine and patient medical consent.

Inclusion Criteria:

- Ages eligible for study: 18 Years and older.
- All patients were diagnosed with either pancreatic or upper gastrointestinal malignancies and had undergone a triphasic CT scan of the abdomen before being referred for EUS for staging.
- NB: Gastric and esophageal malignancies were diagnosed endoscopically and histopathologically.

Exclusion criteria:

- Patients whom previously known to had primary hepatic malignancies (HCC, Cholangiocarcinoma, etc.).
- Unfit patient for deep sedation by Propofol injection or had history of Propofol hypersensitivity.
- Patients with bleeding disorders (platelets less than 50,000, prothrombin time more than 16 second or INR more than 2) contraindicating EUS-FNA.

All the patients were subjected to thorough history taking, clinical general and local abdominal examination, Abdominal US & CT abdomen and laboratory investigations, and upper endoscopy for detection of primary malignancies.

- Oesophagus: Site, size and the shape of the lesion.
- Stomach: Site, size and shape of the lesion.
- Duodenum: Site, size and shape of the lesion.

Procedure of EUS

All EUS examination was done using EUS linear array Echoendoscope, Pentax EG-3870UTK attached to Hitachi Avius US machine under propofol deep sedation.

Patient preparation:

Fasting for at least 6 hours of all patients was requested. Some patients were asked to stop some medications as anticoagulants after consultation of specialist (15).

EUS was done to all patients. The image orientation in this study was with the cranial aspect of the patient displayed toward the right side of the screen unless otherwise noted.

Various anatomical landmarks were used in the EUS determination of segmental location. They included the portal vein, hepatic veins, IVC, ligamentumteres, ligamentumvenosum, gallbladder, and right kidney. In the left lobe, the important landmarks were the left hepatic vein and middle hepatic vein, which separate S2 from S3 and S4 from the right anterior segments (S5 and S8), respectively. The left portal vein, ligamentumteres, and ligamentumvenosum were also useful landmarks for the determination of segments in the left lobe.

The IVC and the ligamentumvenosum marked the boundary between the caudate lobe (S1) and the left lobe. In the right lobe, the main landmark is the right hepatic vein, which separates the right anterior segment (S5 and S8) from the posterior segment (S6 and S7). The gallbladder was located in the gallbladder fossa on the inferior surface of the liver between S4 and S5. The right kidney was served as a landmark to identify S6.

Identification of the liver segments was done through the stomach and/or duodenum accordingly.

During EUS examination, the liver was examined thoroughly to detect hepatic focal lesions with EUS-FNA of hepatic occult metastasis which were not discovered by conventional ultrasound or CT

Target lesions were initially identified and their detailed endosonographic features were assessed with possibility of doing EUS-FNA using a 22 or 19-gauge needles (Cook®, Winston-Salem, NC, USA).

Informed consent voluntarily to participate in this trial according to the approval of permission of the ethical committee of the hospital was obtained. Objectives, purposes of the study, the expected benefits, and types of information to be obtained were explained to the health care staff. Confidentiality of data was insured.

Statistical Analysis:

Data entry, processing and statistical analysis was carried out using MedCalc ver. 18.11.3(MedCalc, Ostend, Belgium). Tests of significance (logistic regression analysis, Spearman's correlation, and ROC Curve analysis) were used. Data were presented and suitable analysis was done according to the type of data (parametric and non-parametric) obtained for each variable. P-values less than 0.05 (5%) was considered to be statistically significant.

Results

This was a prospective, retrospective study conducted on 150 patients who had a primary malignant lesion in pancreas, esophagus, stomach and duodenum at Maadi military hospital to evaluate the value of Endoscopic Ultrasound (EUS) in detection of hepatic occult metastasis not had been detected by conventional imaging modalities (pelvi-abdominal US, triphasic CT abdomen and pelvis) during staging of pancreatic and Upper GI malignancies. The mean age of all patients was (57.4 ± 11.2) years. Regarding gender of the patients, (47.3%) of patients were females; while (52.7%) were males. (Table 1)

Regarding HFL detection by US; (12.7%) of patients had HFL lesions, with (57.8.6%) of them were > 3 cm and (73.7%) were multiple lesions. (Table 2)

Regarding CT data, (2.7%) of theses lesions were duodenal masses, (4%) were esophageal masses, (2%) were gastric GIST, (12%) were gastric masses, (1.3%) were gastric wall thickening, (77.3%) were pancreatic masses, and (0.7%) were retro peritoneal masses.(Table 3)

Regarding HFL detection by CT;(18%) of patients had HFLs. with (40.7%) of them were them were > 3 cm and (66.7%)were multiple lesions. (Table 3)

Regarding EUS data, (0.7%) of theses lesions were duodenal GIST and duodenal masses, (4%) were esophageal masses, (2%) were gastric GIST, (13.3%) were gastric masses, (77.3%) were pancreatic masses, (1.3%) were papillary masses, and (0.7%) were retro peritoneal masses. (Table 4)

Regarding HFL detection by EUS; (21.3%)of patients had HFL lesions detected by EUS, with (65.6%)of them were less than 3 cm, (59.4%) were multiple lesions. (Table 4)

Comparison between the 3 imaging modalities according to detection of metastatic hepatic focal lesions in different sites of primary lesions among the studied patients are shown in (Table 5)

Roc-curve of each modality to predict patients with metastatic hepatic focal lesions among the studied patients had pancreatic and gastric malignancies, are shown in (Table 6).

Regarding outcome data; (3.3%) of patients had occult metastatic HFLS lesions discovered by EUS (not detected by conventional abdominal US or triphasic CT). EUS FNA from the Hepatic focal lesions was done for these five patients and reveled metastatic HFLS.(Table 7).

By using ROC-curve analysis, Abdominal US predicted patients with metastatic HFLs, with fair (74.9%) accuracy, sensitivity= 51% and specificity= 98% ($p < 0.014$). By using ROC-curve analysis, CT predicted patients with metastatic HFLs, with good (85%) accuracy, sensitivity= 72% and specificity= 97% ($p < 0.002$). By using ROC-curve analysis, EUS predicted patients with metastatic HFLs, with excellent (96.5%) accuracy, sensitivity= 93% and specificity= 99% ($p < 0.001$). (Table 8)

Table (1): Descriptive data of the studied patients.

	Variables	Frequency (%) / Mean ± SD
Age (years)		57.4 ± 11.2
Gender	Female	71 (47.3%)
	Male	79 (52.7%)
Residence	Rural	39 (26%)
	Urban	111 (74%)
Smoking	+ve	58 (38.7%)
Alcohol	+ve	4 (2.7%)

Table(2): Detection of metastatic hepatic focal lesions by conventional Pelvi abdominal US among the studied patients (150 patients):

Variables			Frequency (%) / Mean ± SD
HFL detection by abdominal US	**HFL detection**	+ve	19 (12.7%)
	Size of HFL	< 3 cm	8 (42.1%)
		> 3 cm	11 (57.8.6%)
	Number of HFL	Solitary	5 (26.3%)
		Multiple	14 (73.7%)

US: ultrasound. HFL: hepatic focal lesion.

Table(3): Triphasic CT data among the studied patients(150 patients) :

Variables			Frequency (%) / Mean ± SD
Primary lesions detected by triphasic CT	**Primary lesion detected**		150 (100%)
	Site of primary lesion	Duodenal mass	4 (2.7%)
		Esophageal mass	6 (4%)
		Gastric GIST	3 (2%)
		Gastric mass Gastric wall	18 (12%)
		thickening	2 (1.3%)
		Pancreatic mass	116 (77.3%)
		Retro peritoneal mass	1 (0.7%)
HFL detection by CT *	**HFL detection**	+ve	27 (18%)
	Size of HFL	< 3 cm	16 (59.3%)
		> 3 cm	11 (40.7%)
	Number of HFL	Solitary	9 (33.3%)
		Multiple	18 (66.7%)

CT: tri-phasic computed tomography.

Table(4): EUS data among the studied patients(150 patients):

Variables	Frequency (%) / Mean ± SD		
Primary malignancy detected by EUS	**Primary lesion detected**	+ve	150 (100%)
	Site of primary lesion	Duodenal GIST	1 (0.7%)
		Duodenal mass	
		Esophageal mass	1 (0.7%)
		Gastric GIST	
		Gastric mass	6 (4%)
			3 (2%)
			20 (13.3%)
		Pancreatic mass	116 (77.3%)
		Papillary mass	2 (1.3%)
		Retro peritoneal mass	1 (0.7%)
HFL detection by EUS *	**HFL detection**	+ve	32 (21.3%)
	Size of HFL	< 3 cm	21 (65.6%)
		> 3 cm	11 (43.3%)
	Number of HFL	Solitary	13 (40.6%)
		Multiple	19 (59.4%)

EUS: Endoscopic Ultra Sound.

Table (5): Comparison between the 3 imaging modalities according to detection of metastatic hepatic focal lesions in different sites of primary lesions among the studied patients.

Site of primary lesion among the Studied patiens(150)	Number of primary malignancy in different sites.	HFLS detection in US	HFLS detection in CT	HFLS detection in EUS	Chi square test P value
Duodenal GIST	1	0 (0%)	0 (0%)	0 (0%)	= 1.000
Duodenal mass	1	0 (0%)	0 (0%)	0 (0%)	= 1.000
Lower Esophageal mass	6	0 (0%)	0 (0%)	0 (0%)	= 1.000
Gastric GIST	3	0 (0%)	0 (0%)	0 (0%)	= 1.000
Gastric mass	20	1 (5%)	2 (10%)	2 (10%)	= 0.829
Pancreatic mass	116	18 (15.5%)	25 (21.6%)	30 (25.9%)	= 0.2879
Papillary mass	2	0 (0%)	0 (0%)	0 (0%)	= 1.000
Retro peritoneal mass	1	0 (0%)	0 (0%)	0 (0%)	= 1.000

Table (6): Roc-curve of each modality to predict patients with metastatic hepatic focal lesions among the studied patients had pancreatic and gastric malignancies:

	US		CT		EUS	
	Gastric mass	**Pancreatic mass**	**Gastric mass**	**Pancreatic mass**	**Gastric mass**	**Pancreatic mass**
AUC	0.862	0.869	0.873	0.921	0.917	0.944
SE	0.0438	0.0434	0.0432	0.0326	0.0329	0.0308
Sensitivity (%)	90	90	90	95	95	97
Specificity (%)	82.31	83.8	84.62	89.23	88.46	93.85

ROC (Receiver operating characteristic), AUC= Area under curve, SE= Standard Error.

Table (7): Occult metastatic hepatic focal lesions detected by EUS (not detected by conventional abdominal US or triphasic CT) among 32 malignant patients:

Variables		**Frequency (%)**
Occult lesions discovered by EUS		5 (15,6%)
Size of lesion (cm)		0.88 ± 0.58 (0.3 to 1.8)
Number of HFL *	-Solitary -Multiple	4 (80%) 1 (20%)

Table (8): Roc-curve of each modality to predict patients with metastatic hepatic focal lesions:

Variable	**AUC**	**SE**	**Sensitivity (%)**	**Specificity (%)**	**P value**
Conventional US	0.749	0.0574	51.52	98.29	<0.014*
Triphasic CT	0.851	0.0478	72.73	97.44	<0.002**
EUS	0.965	0.0247	93.94	99.15	<0.001**

ROC (Receiver operating characteristic), AUC= Area under curve, SE= Standard Error.

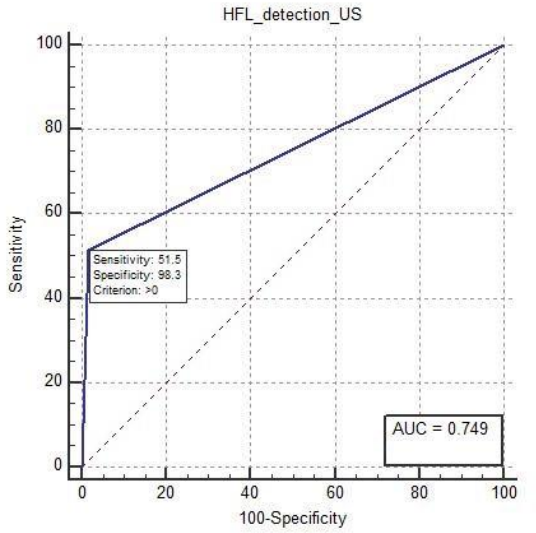

Figure (1): ROC curve of US in detection of metastatic HFLS.

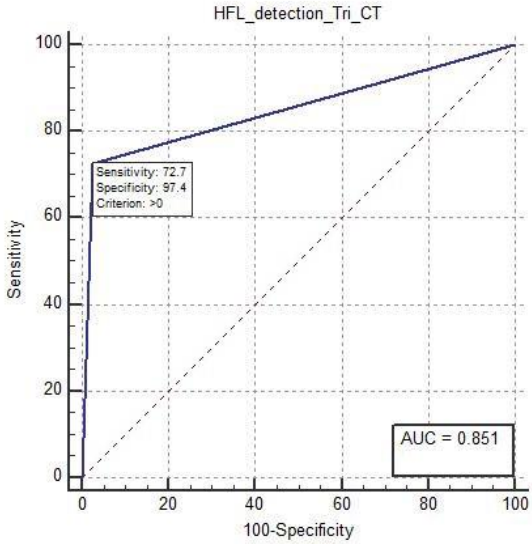

Figure (2): ROC curve of triphasic CT in detection of metastatic HFLS.

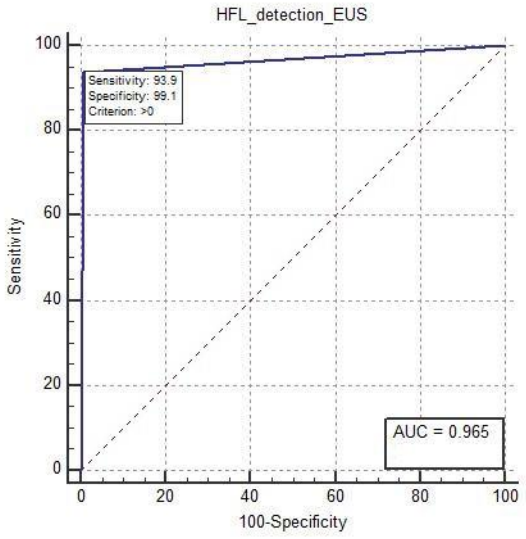

Figure (3): ROC curve of EUS in detection of metastatic HFLS.

Discussion

In the current research study, we included 150 cases with pancreatic and upper GI malignancies who were recruited from Maadi Military Hospital in the period from April 2020 to March 2021 after ethical approval obtained from hospital ethical committee and Benha faculty of medicine and patient medical consent. Metastatic hepatic focal lesion were discovered in 27 patients by CT and 32 were discovered by EUS among 150 patients, the EUS yielded a sensitivity of 93% and specificity= 99% for the detection of metastatic hepatic focal lesions compared to a sensitivity= 72% and specificity= 97% for CT. Hence, EUS in this setting has an imperative role in detecting liver metastasis, not otherwise detected by other imaging modalities in patients suffering from other primary malignancies; an innovation that has a fabulous impact on patient management (8). A previous study (2) showed the superiority of EUS over CT scans in uncovering occult small liver metastases that were not definitely diagnosed by CT scans, in which EUS identified new or additional lesions in 28% (4 of 14) of the patients, all less than 0.5 cm in size not detected by CT influencing the clinical management. In 2 of 14 patients EUS identified liver lesions, previously described as suspicious by CT scan, to be hemangiomas. This is similar to our study

that revealed that the EUS detected occult lesions in (15.6%) 5 of the 32 patients with HFLs not detected by CT.

In concordance with this study, a study from 2009 (9), compared the accuracy of the EUS with CT scan for detection of the liver metastasis. In this prospective study, 132 subjects with newly diagnosed tumors of the lung, pancreas, biliary tree, esophagus, stomach, and colon were enrolled. The diagnostic accuracy of EUS and CT scan was 98% and 92%, respectively. In comparison to CT scan, EUS detected significantly higher number of metastatic lesions in the liver.

A previous study (8), showed a more significant superiority of EUS over CT scan for diagnosis of liver metastatic lesions. They conducted a prospective study in which 574 consecutive patients with a history or suspicion of gastrointestinal or pulmonary malignant tumor undergoing upper EUS examinations. Fourteen (2.4%) patients were found to have focal liver lesions by EUS; while the CT depicted liver lesions in only 3 of 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 this study, may explained by the larger sample size in their study, and by the enrollment of patients with pulmonary malignant tumors; who were not included in this study.

The optimal approach to screening of the liver for metastases is unclear. A multi-observer study found that dual-phase spiral CT and MRI have sensitivities of, respectively, 94% and 99%, for liver lesions larger than 1 cm.(10)**,**But even these techniques have sensitivities closer to 50% for metastases smaller than 1 cm when intra-operative US is used as the reference standard. (11)

A PET may be even more sensitive for liver metastases, based on studies of patients with GI and pancreatic tumors, although a PET also may over- look small lesions (12)**.** Compared to that EUS has resolution sufficient to detect and sample lesions as small as 5 mm in diameter, but the technique is more operator-dependent than other noninvasive modalities (13).

This was also demonstrated in this study where the 5 lesions detected by EUS and missed by CT ranged from 0.3 to 1.8 cm. Furthermore, EUS is semi- invasive and exposes patients to a small risk of complications, including those related to

conscious sedation, bleeding, and bowel injury.

Additionally, a large retrospective study (12)**,** showed the sensitivity of the EUS to be in the range of 82% to 94%. EUS detected 17 malignant hepatic lesions in patients with a previously normal CT scan. These findings are in agreement with our results (sensitivity 93.94%). This supports the hypothesis that the accuracy of the EUS is superior to the CT scan. The reason for the high accuracy was as a result of high sensitivity of the EUS for the visualization of the hepatic lesions and high specificity of the EUS-FNA for establishing the cytologic nature of the lesions.

In another retrospective study (13),EUS detected metastatic lesions overlooked by conventional, cross-sectional imaging studies in 5 of 222 cases (2.3%) compared to 15.6% in our study. This difference could be due to a larger sample size and inclusion of malignancies other than upper gastro-intestinal lesions in the former study.

A distinct advantage of EUS is that EUS examination and EUS-FNA can be performed simultaneously and, therefore, confirmation of malignancy can usually be accomplished in a single procedure, whereas conventional imaging studies typically require 2 sessions to accomplish these tasks, one for detection and another for FNA.(9)

This was demonstrated in our study where EUS/FNA was done in the same setting for 5 of the patients with HFLs not detectable by CT and the biopsy results were conclusive in all patients revealing metastatic HFLs.

As regard the safety of the procedure, and the incidence of the complications, none of our patients suffered from major or minor complications during the procedure, or during the short term period about 3 days following the procedure.

This matches with a previous study (14), who tested the safety of EUS-FNA, and reported only 1% rate of major complication. Also the work(12) done between January, 1997, and July, 2002, during which EUS-FNA of 77 liver lesions in 77 patients was performed, no complications were reported.

Conclusion

EUS and EUS-FNA is a useful diagnostic modality for the detecting small-sized liver metastasis that may be missed by other methods during TNM staging of pancreatic

and GI malignancy. Moreover, the sensitivity and specificity of EUS and EUS-FNA was higher than CT scan. Nevertheless, further large-scale studies are still needed to confirm these findings.

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