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ABOUT COVER

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AIMS AND SCOPE

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INDEXING/ABSTRACTING

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RESPONSIBLE EDITORS FOR THIS ISSUE

Prospective Study

Role of endoscopic ultrasound and endoscopic ultrasound-guided tissue acquisition in diagnosing hepatic focal lesions

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Abstract

BACKGROUND
Endoscopic ultrasonography (EUS) has become an established method in diagnostic and therapeutic procedures in gastroenterology; however, it has recently gained a growing role in hepatology.

AIM
To evaluate the role of EUS features, strain elastography (SE), and EUS-tissue acquisition in diagnosing hepatic focal lesions (HFLs) that could affect further management.

METHODS
This cross-sectional study included 215 patients with pancreatic, biliary, or

gastrointestinal malignancies referred for EUS examination. HFLs were identified in 43 patients (20%), and EUS-guided tissue acquisition was performed from these lesions.

RESULTS

EUS features were highly sensitive (100%) but much less specific (57%) in diagnosing HFLs; the overall accuracy was 94%. Real-time elastography was also very sensitive (97%) but less specific (67%) in diagnosing HFLs; however, the overall accuracy was 92%. EUS tissue acquisition was extremely sensitive (100%) and specific (100%), with a 100% overall diagnostic accuracy.

CONCLUSION

The diagnostic utility of EUS-guided tissue acquisition was extremely accurate in diagnosing HFLs. EUS characteristics and real-time SE accurately predicted the histological diagnosis of both benign and malignant HFLs.

Key Words: Endoscopic ultrasonography; Hepatic focal lesions; Fine needle aspiration; Fine needle biopsy; Elastography

Core Tip: This cross-sectional study included 43 patients with hepatic focal lesions among 215 pancreatic, biliary, or gastrointestinal malignant lesions referred for Endoscopic ultrasonography (EUS) examination. EUS tissue acquisition was highly sensitive (100%) and specific (100%), with an overall diagnostic accuracy of 100%.

INTRODUCTION

Endoscopic ultrasonography (EUS) is one of the main tools used to evaluate the upper and distal parts of the lower gastrointestinal tract and to define pancreatic and hepatobiliary features. The utility of EUS in diagnosing and managing hepatic focal lesions (HFLs) has gained special concern nowadays due to the proximity of the scope to the liver, and its excellent spatial resolution enables real-time images and guided intervention[1-4].

Liver diseases are among the most common worldwide and manifest as diffuse liver diseases and focal hepatic lesions, ranging from benign to malignant. To make a definitive diagnosis of liver diseases, biochemical and imaging investigations and, in some instances, liver biopsies are typically used[2]. The application of EUS in diagnosing liver diseases is a promising technique and should be considered a first-line therapeutic option in selected cases[4].

EUS-guided diagnosis of focal liver lesions by endosonographic features and cytological and histopathological examination of biopsies obtained *via* fine needle aspiration/biopsy (EUS-FNA/FNB) has been shown to significantly improve the diagnosis of solid liver lesions compared to traditional imaging tools[1].

US and computed tomography (CT)-guided FNA/FNB of focal liver lesions are safe and provide high diagnostic accuracy; however, it is sometimes challenging to access subdiaphragmatic and posteriorly located lesions.

Compared to percutaneous and transjugular routes, EUS-FNA/FNB may have better accessibility and diagnostic yield and may be superior for a targeted approach to focal lesions. It provides higher-quality images and allows for more patient comfort[3]. However, there is limited data regarding the accuracy of EUS-guided biopsy of HFLs[5].

Elastography is a US-based imaging modality that provides information about tissue stiffness and can be considered a virtual biopsy. Several elastographic approaches have been developed, such as transient elastography, strain elastography (SE), histograms, and shear wave imaging, which include point shear wave elastography and 2D shear wave elastography[6].

This study evaluated the diagnostic utility of EUS sonographic features, SE, and EUS-FNA/FNB in differentiating benign from malignant liver lesions, including primary and metastatic lesions that may affect further management.

MATERIALS AND METHODS

This cross-sectional study included 215 Egyptian patients who were referred to the internal medicine department, Kasr Al-Aini hospitals, Cairo University for EUS and EUS-FNA/FNB for an assessment of pancreatic or gastrointestinal tumors without or with HFLs detected by contrast abdominal CT or magnetic resonance imaging (MRI). After the EUS examination, 43 out of 215 (20%) patients had HFLs for which EUS-FNA/FNB was performed. All the required data is

collected from the hospital's medical record after ethical approval is obtained from our hospital's ethical committee.

Exclusion criteria include patients unfit for deep sedation and patients with bleeding disorders contraindicating EUS-FNA/FNB.

All patients were subjected to a thorough history taking, clinical examination, abdominal US, CT, or MRI abdomen, and routine laboratory investigations such as complete blood count, hepatic and renal function tests, and coagulation profile, in addition to virological tests for human immunodeficiency virus, hepatitis C virus, and hepatitis B virus and tumor markers including CA-19-9 and alpha-fetoproteins.

EUS and EUS-FNA/FNB were performed by a single endoscopist. It was conducted under deep sedation using a Pentax linear array echoendoscope type EG-3870UTK attached to a Hitachi ultrasound AVIUS machine. A detailed description of the primary tumor and the HFLs regarding their site, size, shape, and number was applied. Based on EUS features, we considered the mass as malignant if any one of the following criteria is present: (1) The presence of peripheral hypoechoic halo; and (2) The presence of mass effect as compression or interruption of the course of a blood vessel or a biliary radicle, or the presence of contour bulge.

Real-time SE scoring was done to all HFLs. We considered grades 1 and 2 as benign and grades 3 and 4 as malignant lesions. EUS-FNA was conducted with 22G Echotip needles from Cook Company; however, the FNB was conducted with 22G Acquire needles from Boston Scientific Company. All biopsies were done by high pressure technique and fanning, at least two passes, no Rapid On-Site evaluation (ROSE) was available in any of the cases. We have targeted the nearest mass to the Echoendoscope, with no intervening vessels along the needle tract and with the presence of a rim of normal liver tissue between the liver capsule and targeted mass to minimize bleeding. The material was spread over a glass slide and fixed by 95% alcohol, whereas formalin blocks were prepared and sent to a single experienced cytologist.

The gold standard of malignant lesions is the FNB as it has extremely high specificity, about 95%-100% in most articles in the literature. All benign-looking lesions were followed up with the disappearance of all cholangitis abscesses under antibiotic therapy, while the two benign liver nodules were constant in size over 6 mo.

The collected data from the 43 patients with HFLs was organized and statistically analyzed using appropriate methods.

RESULTS

The average age of the patients examined was 56, the majority were male (74.42%), and the most common co-morbidities were diabetes mellitus (10 patients; 23.25%), systemic hypertension (8 patients; 18.6%), and ischemic heart disease (6 patients; 13.95%). Most of the HFLs were present in the left lobe of the liver (67.44%).

The cytopathological confirmed malignant lesions were found in 35 (81.4%) of patients, while benign lesions were found in 8 (18.6%) of patients (Table 1). The eight benign lesions were six cholangitis abscesses and two benign liver lesions, likely areas of focal fat depletion. All benign lesions were followed up with the disappearance of all cholangitic abscesses under antibiotic therapy, while the two benign liver nodules were constant in size over 6 mo. The other 35 malignant lesions were five primary hepatocellular carcinomas, one neuroendocrine tumor, and 29 metastatic liver lesions (Figure 1) from malignant pancreatic masses, as proved by cytopathological and histopathological examination after EUS-FNA/FNB (Figure 2A). The mean size was 23.47 mm × 39.19 mm, with an average number of needles passing 1.49 (0.51).

EUS-FNA/FNB was accurate in diagnosing HFLs with 100% sensitivity, specificity, and diagnostic accuracy.

EUS features provisionally diagnosed 38 patients (88.37%) with malignant lesions and five patients (11.63%) with benign ones (Table 2). Thus, 5 out of 8 benign lesions could be correctly diagnosed based on EUS features. On the other hand, 38 cases were reported with malignant lesions, while the actual number evident by histopathology was only 35; thus, three benign cases were incorrectly diagnosed as malignant lesions (Table 3).

Based on Real-Time elastography scoring, 5 patients were suggested to have benign lesions while 38 lesions were suggested to have malignant lesions. Real-time elastography (Figures 2B and 3) was very sensitive (97%) but less specific (67%) in the diagnosis of HFLs; however, the overall accuracy was 92% (Tables 4 and 5).

EUS-FNA needles were used in 20 patients while EUS-FNB were used in 23 patients. No complications were reported in the study. EUS-FNA was done in 20 patients while EUS-FNB was done in 23 patients.

DISCUSSION

Percutaneous CT or US-guided biopsy is the classical diagnostic method for liver masses. However, it has shown some difficulties in diagnosing small liver lesions less than 2 cm, with common complications and many contraindications limiting its use[7,8].

EUS has been broadly used for identifying and managing GIT and pancreaticobiliary diseases[3]. It has become an excellent tool to confirm the pathological diagnosis in combination with EUS-FNA/FNB.

Compared to percutaneous liver biopsy (PC-LB), EUS-guided liver biopsy (ELB) is a new approach to liver parenchyma sampling that has shown promise for safety, patient comfort, and good tissue yield[9]. ELB also allows sampling from multiple sites in the liver, both in the right and left lobes[9,10].

Few studies have verified the efficacy and safety of ELB; however, the review of Sbeit reported a variable diagnostic yield for EUS-guided liver biopsy in focal liver lesions (91%-100%)[4].

Table 1 Cytopathological diagnosis of hepatic focal lesions

Variable	Total, *n* = 43	
	n	%
Cytopathological diagnosis		
Benign	8	18.60
Malignant	35	81.40
Inflammatory	8	18.60
Cholangitic abscess	6	13.94
Cirrhotic nodule	2	4.65
Primary	6	13.95
Hepatocellular carcinoma	5	11.63
Neuroendocrine tumor	1	2.32
Secondary	29	67.44

Table 2 Endoscopic ultrasonography finding of patients with hepatic focal lesions

Variable	Total, *n* = 43
No. of passes	1.49 (0.51)
Shortest diameter size in mm	19 ± 12.8/(3-67)
Longest diameter size in mm	26 ± 19.1/(4-109)
Diagnosis	
Benign	5 (11.63)
Malignant	38 (88.37)

Data are presented as *n* (%) or mean ± SD/(range).

Table 3 Comparison between endoscopic ultrasonography diagnosis and histopathology results

Variable	EUS, *n* = 43		Histopathology, *n* = 43	
	n	%	*n*	%
Benign	5	11.63	8	18.60
Malignant	38	88.37	35	81.40

EUS: Endoscopic ultrasonography.

Table 4 Diagnostic utility of elastography in predicting benign and malignant hepatic focal lesions

Elastography, *n* = 43	*n* (%)
Benign	
Grade 1	0
Grade 2	5 (11.6)
Malignant	38 (88.4)
Grade 3	10 (23.3)
Grade 4	28 (65.1)

Table 5 Comparison between different endoscopic ultrasonography tools regarding their utility in diagnosis of hepatic focal lesions
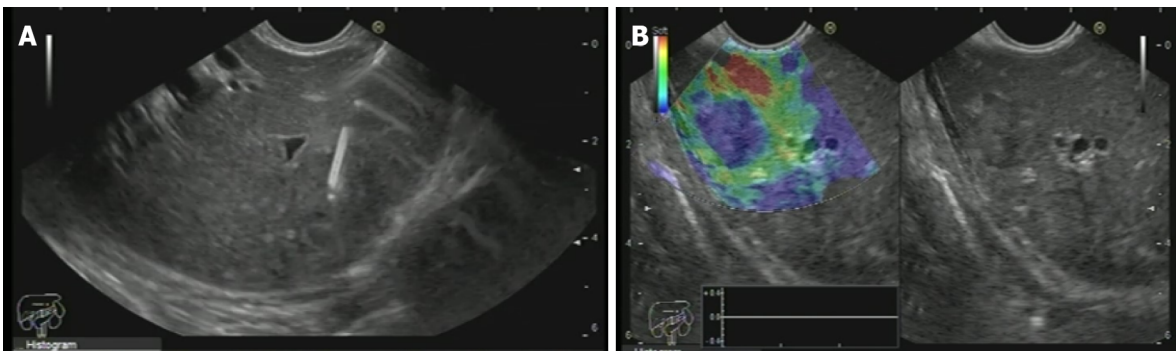
Tool	Sensitivity	Specificity	PPV	NPV	Overall accuracy
Elastography	97	67	94	80	92
EUS	100	57	94	100	94
FNA/FNB	100	100	100	100	100

EUS: Endoscopic ultrasonography; FNA/FNB: Fine needle aspiration/biopsy.

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**Figure 1 Multiple hepatic focal lesions due to liver metastasis.**

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Figure 2 A metastatic focal hepatic mass. A: Endoscopic ultrasound guided fine needle biopsy from hepatic focal lesion; B: A metastatic focal hepatic mass with grade 4 Elasticity score.

This study aimed to evaluate EUS and EUS-FNA/FNB's diagnostic efficacy in diagnosing liver lesions, whether benign or malignant, including primary and metastatic lesions.

In this study, EUS detected and sampled all HFLs, whereas 88.37% of patients had malignant lesions (liver metastasis) and 11.63% had benign ones. The mean elastographic strain ratio of the HFLs was 3.6 (0.7), and the mean size was 23.47 mm × 39.19 mm, with an average number of needles passing 1.49 (0.51). Finally, considering the cytopathological diagnosis of the biopsy, it proved malignant lesions in 81.4 percent of patients, while benign lesions were found in 18.6%. The eight benign lesions were six cholangitis abscesses and two benign-looking liver lesions. All benign-looking lesions were followed up with the disappearance of all cholangitis abscesses under antibiotic therapy, while the two benign liver nodules were constant in size over 6 mo. The other 35 malignant lesions were five primary hepatocellular carcinomas, one neuroendocrine tumor, and 29 liver metastatic lesions. This finding was consistent with Oh *et al*[11], who investigated the role of EUS-FNA in targeting right-sided liver masses and found that 39 (80.9%) of 47 patients were proven to have malignant lesions. The mean tumor size was 26 mm. The median number of needle passes was 3. On microscopic examination, tissue specimens obtained by EUS-FNA were determined to be adequate in 42 of 46 patients (91.3%). The pathological diagnosis was malignancy in 23 of 46 patients (50%), suspicious for malignancy in 6 patients (13%), atypical in 4 patients (8.7%), and negative for malignancy in 9 patients (19.6%).
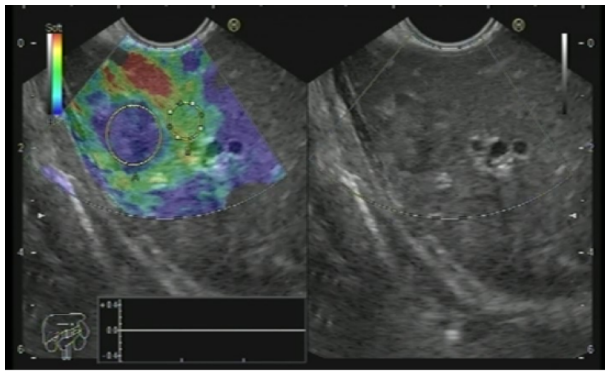
Figure 3 A metastatic focal hepatic mass with high Strain ratio.

Another study by Chon *et al*[12] discussed the role of ELB in diagnosing solid liver lesions. The study included 58 patients (35 males and 23 females) with a mean age (68.0 ± 10.6 years). The mean size of the mass was 21.4 ± 9.16 mm × 11.5 ± 8.15 mm. The biopsy target site was the left lobe in 39 patients, the right lobe in 16 patients, and the caudate lobe in 3 patients. The number of trans-gastric and trans-duodenal route procedures was 39 (67.2%) and 19 (32.8%), respectively. The mean needle pass number was 2.6 ± 0.8, ranging from 1-5 per lesion. The final diagnosis was performed in 52 cases out of 58; all were malignant, either HCC or metastatic.

Adler *et al*[13] performed a multicenter retrospective review of 200 patients, specifically looking at safety and performance when sampling solid lesions. They reported excellent diagnostic yield at 98.5%; however, 6.5% of the patients needed a repeat procedure at some point. No adverse events were identified in the population.

In our study, EUS features were highly sensitive (100%) and less specific (57%) in diagnosing HFL, with an overall accuracy of 94%. Real-time elastography was also highly sensitive (97%) and less specific (67%) for diagnosing HFL; overall accuracy was 92%. EUS tissue acquisition was extremely sensitive (100%) and specific (100%), with an overall diagnostic accuracy of 100%.

Similarly, in 2019, Chon *et al*[12] stated that the diagnostic accuracy for EUS-FNB was 89.7%, but both specimen adequacy for histology, and available immunohistochemistry stain were 91.4%. The sensitivity and specificity of EUS-FNB were 89.7% and 100%, respectively[12].

Two recent meta-analyses reported that ELB and PC-LB are comparable in terms of safety and diagnostic performance [14,15]; however, ELB was more cost-effective than PC-LB regarding lower costs per patient and higher quality-adjusted life years[15].

EUS has the advantage of sampling and evaluating both lobes of the liver and small liver lesions that may have been missed by other non-invasive imaging modalities[16]. This accurately depicts liver histology and potentially addresses concerns about sampling error[17].

A further advantage of ELB over PC-LB was that it permitted more straightforward access to the right and left regions of the liver, thereby reducing the variability in diagnosis. Furthermore, ELB provided a much shorter recovery period (around 4 h) than PC-LB (usually a minimum of 10 h)[18].

In the Oh study, there were no statistical differences in the diagnostic accuracy of ELB between right and left lobe sites (25/28, 89.3% *vs* 13/14, 92.9%, *P* = 0.86), and none of the patients experienced procedure-related adverse events[18]. Similarly, no significant adverse events had been encountered in our study. Liver biopsy is very safe as liver is very near to the Echoendoscope. Also, if intrahepatic hematoma occurred, the blood will trickle to one of the portal or hepatic vessels, so the patient will bleed into its own circulation.

More recently, the meta-analysis by Zeng *et al*[15] suggests that the use of Acquire Franseen-tip needles may increase the ability to obtain more diagnostic samples than Sharkcore Fork-tip needles and that the use of FNB needles may be associated with a higher risk of adverse events than FNA needles[15].

Cholongitas *et al*[19] conducted a systematic review and meta-analysis of over 10000 percutaneous liver biopsies and found that an average of 7.5 core biopsy passes (CPT) and a target specimen length (TSL) of 17.7 mm were necessary for adequate pathological evaluation. However, when the biopsy was obtained through the transjugular route, adequacy was defined as 6.5 CPT and a TSL of 12 mm. While there is no established optimal definition of specimen adequacy for endoscopic ultrasound-guided liver biopsy (EUSLB), the American Association for the Study of Liver Diseases (AASLD) recommends a minimum of 11 CPTs as the definition of adequacy, regardless of the sampling route[19-22]. Additionally, the AASLD guideline suggests a TSL greater than 15 mm to define adequacy, with an ideal size of 30 mm. In this study, all routes of tissue sampling achieved at least 11 CPTs and a TSL greater than 15 mm. However, only EUSLB achieved the ideal TSL of 30 mm or more, which is considered optimal[23].

The study conducted by Ching-Companioni *et al*[24] demonstrated that endoscopic ultrasound-guided liver biopsy (EUS-LB) using a novel 19G FNB needle produced longer and less fragmented biopsy specimens compared to the standard 19G FNA needle. Furthermore, there was a reduced occurrence of specimen fragmentation during post-processing, and the yield of CPT was higher. These findings suggest that utilizing a 19G FNB needle represents an advancement over the conventional 19G FNA needle for EUS-LB[24].

In a prospective crossover randomized controlled trial, which is an appropriate model for assessing two types of tools, the researchers reached the conclusion that EUS-FNB is highly effective for solid liver masses. The newly developed antegrade-bevel needle demonstrated comparable efficacy and incidence of adverse events to the original reverse-bevel needle. However, the antegrade-bevel needles were able to obtain a larger amount of biopsy tissue compared to the reverse-bevel needles[25].

In a systematic review and meta-analysis examining the feasibility, safety, and usefulness of EUS-LB in patients undergoing parenchymal liver biopsy, the researchers found that the combined analysis of multiple studies demonstrated a significant diagnostic success rate of over 90%. This rate is similar to the diagnostic yield achieved by traditional PC-LB [26].

In another meta-analysis study, a comprehensive analysis was conducted on published studies examining the effectiveness and safety of EUS-LB for liver parenchymal diseases and focal liver lesions. The study assessed various outcomes including diagnostic yield, specimen adequacy, qualified specimens with the assistance of ROSE, and adverse events. The pooled analysis revealed that EUS-LB proved to be a highly effective and safe technique, with a successful pathological diagnosis rate of 95%, an adequate specimen rate of 84%, and an adverse events rate of 3%. Subgroup analyses were also performed, which indicated that Acquire Franseen-tip needles exhibited a higher diagnostic yield compared to SharkCore Fork-tip needles (99% *vs* 88%, *P* = 0.047). Moreover, FNB needles showed a higher risk of adverse events in comparison to FNA needles (6% *vs* 1%, *P* = 0.028). Interestingly, no significant differences were observed between 19 G and 22 G needles. Additionally, no significant disparities were identified between FNB and FNA needles in relation to our primary outcomes[15].

In order to improve the quality and accuracy of EUS, elastography has been developed, which allows the assessment of liver tissue firmness and the characterization of HFL. Real-time elastography showed high sensitivity (92.5%) and specificity (88.8%) with reasonable accuracy (88.6%) in a study by Sandulescu *et al*[27].

Innovations in needle technology and new approaches using ELB are in development, with the possibility of concomitant procedures such as EUS portal pressure gradient measurement, another emerging area in the field of endo-hepatology, in the coming years[8].

CONCLUSION

The diagnostic utility of EUS-LB with FNA/FNB was perfect and the best diagnostic tool for the definitive diagnosis of the HFLs. Furthermore, EUS features during the procedures provided an excellent and accurate prediction of the histological diagnosis, determining whether the lesion was benign or malignant.

ARTICLE HIGHLIGHTS

Research background
Endoscopic ultrasonography (EUS) has become an established method in diagnostic and therapeutic procedures in gastroenterology; however, it has recently gained a growing role in hepatology.

Research motivation
EUS tissue acquisition was highly sensitive (100%) and specific (100%), with an overall diagnostic accuracy of 100%.

Research objectives
This study aimed to evaluate the role of EUS features, strain elastography (SE), and EUS-tissue acquisition in diagnosing hepatic focal lesions (HFLs) that could affect further management.

Research methods
This cross-sectional study included 215 patients with pancreatic, biliary, or gastrointestinal malignancies referred for EUS examination. HFLs were identified in 43 patients (20%), and EUS-guided tissue acquisition was performed from these lesions.

Research results
EUS features were highly sensitive (100%) but much less specific (57%) in diagnosing HFLs; the overall accuracy was 94%. Real-time elastography was also very sensitive (97%) but less specific (67%) in diagnosing HFLs; however, the overall accuracy was 92%. EUS tissue acquisition was extremely sensitive (100%) and specific (100%), with 100% overall diagnostic accuracy.

Research conclusions
The diagnostic utility of EUS-guided tissue acquisition was extremely accurate in diagnosing HFLs. EUS characteristics and real-time SE accurately predicted the histological diagnosis of both benign and malignant HFLs.

Research perspectives

This cross-sectional study included 43 patients with HFLs among 215 pancreatic, biliary, or gastrointestinal malignant lesions referred for EUS examination. EUS tissue acquisition was highly sensitive (100%) and specific (100%), with an overall diagnostic accuracy of 100%.

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