Role of Endoscopic Ultrasonography (EUS) in Diagnosis of Subepithelial Lesions (SELS)

By

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ABSTRACT

Background: *A subepithelial lesion of the gastrointestinal tract is an elevated lesion, mass or bulge within the lumen that is usually covered by normal-appearing mucosa. Subepithelial lesions were previously described as submucosal tumors.*

Aim and objectives: *This study aims to clarify the usefulness of the EUS in differential diagnosis of upper gastrointestinal sub epithelial lesions in Egyptian patients.*

Subjects and methods: *This prospective analytical study that was conducted at the gastroenterology department of Al-Azhar University Hospitals and Theodor Bilharz Research Institute on 60 cases with sub epithelial lesions that incidentally discovered during upper gastrointestinal endoscopy throughout the duration of the study, which was 6 months from march 2023 to September 2023,and those patients who met the inclusion criteria were biopsied by the endoscopist and the biopsies were sent for histopathology analysis, Later we compared the diagnosis reached by EUS and pathology to identify the diagnostic accuracy of EUS.*

Results: *showed that 40 out of 60 cases examined by EUS biopsy was done while the remaining 20 cases biopsy was not indicated with a diagnosis of lipoma (n=9), pancreatic rest (n=6), and duplication cyst (n=5). In the 40 biopsied cases, the EUS diagnosis was confirmed in all cases except 4 cases, three were diagnosed by EUS as Gastrointestinal stromal tumor (GIST) and turned to be Leiomyoma by pathology, and one case was diagnosed by EUS as Leiomyoma and turned to be GIST by pathology. So, a total GIST of 19 and a total Leiomyoma of 15 were finally diagnosed by pathology.*

Conclusion*: EUS is a very important modality in the diagnosis of various SELs. Its diagnostic accuracy has been proven by multiple studies including our study. However, it has its limitations, as it is mainly operator dependent and its relatively high cost and scarcity. The need for unifying EUS as a crucial step when confronting SEL since it can reveal critical data about the nature of SEL.*

Keywords: *Subepithelial Lesions; SELs; EUS*

INTRODUCTION

Subepithelial lesions of the gastrointestinal tract are elevated lesions, masses or bulges within the lumen that are usually covered by normal-appearing mucosa. Subepithelial lesions have previously been described as submucosal tumors. However, subepithelial lesions can occur in any layer of the gastrointestinal wall, sometimes even imprinting extramural surrounding structures; therefore, the term "subepithelial lesions" is more commonly used. Subepithelial lesions are usually asymptomatic and discovered incidentally during endoscopy **(Gong & Kim, 2016)**.

Initial treatment of SEL focuses on correct diagnosis and determination of the malignant potential of the lesion. Most of these tumors are benign, with less than 15% found to be malignant at presentation. Tumors with a lower malignant potential may resemble tumors with a higher risk of malignant transformation endoscopically. Because of its subepithelial location, biopsies using endoscopic forceps often do not provide diagnostic tissue. Therefore, additional imaging and sampling techniques, often using EUS, are needed to characterize these lesions **(Faulx et al., 2017)**.

When a SEL is suspected, after an upper gastrointestinal endoscopy EUS is the second step in assessing SEL to guide further treatment and to provide valuable information. EUS is the diagnostic test to differentiate between intramural and extramural lesions, to assess the size, margins, and layer of origin, echotexture of the lesion and presence of adjacent lymph nodes. Based on EUS a decision can be made to decide between no further exams, follow up with EUS or additional diagnostic or therapeutic strategy with resection when the lesion is likely to be malignant. **(Dias de Castro et al., 2016).**

Whenever EUS is performed to examine a subepithelial lesion, the operator should try to address the following points: Location of the lesion (esophagus, stomach, small intestine, colon), The general endoscopic appearance (presence of ulcerated mass, umbilicated mass, yellowish appearance, and so forth), Whether the mass is intramural or extramural, Layer of origin, Echogenicity of the mass by comparing the mass to the spleen or 3rd and 4th layer of the gastrointestinal wall, Define internal structures; for example presence of calcifications, tubular structures or cystic changes, Size of the lesion, Extent of the mass, Presence of vessels around or within the lesion, Relationship to surrounding structure and Presence of lymphadenopathy **(Vasilakis et al., 2023)**.

Once we have determined that the lesion is intrinsic to the wall, and is not an extrinsic compression, we must evaluate to which wall Layer it corresponds **(Ye et al., 2022).**

Gastrointestinal wall is detected as a five-layer structure with lower frequency (7.5–12 MHz) and a nine-layer structure with higher frequency (12–20 MHz). Then, using EUS, it has become possible to diagnose subepithelial lesions by evaluating its originating layer, its echo level, and its internal echo pattern etc. **(Kida et al., 2017)**.

AIM OF THE WORK

This study aims to clarify the usefulness of the EUS in differential diagnosis of upper gastrointestinal sub epithelial lesions in Egyptian patients.

PATIENTS AND METHODS

Study design and setting

This prospective analytical study was conducted at the gastroenterology department of Al-Azhar University Hospitals and Theodor Bilharz Research Institute during the period from march 2023 to September 2023.

Target Population

This study was conducted on a number of cases with sub epithelial lesions incidentally discovered during upper gastrointestinal endoscopy throughout the duration of the study, which was 6 months.

Ethical Considerations

1.The study was conducted after approval of the protocol by The Research Committee local and The Studies Committee well as the Research Ethics Committee.

2.An informed written consent was obtained from all study population and it will contain the following: The aim and methods of the study in simple way.

3.The patients have the right to refuse participation or withdraw without affecting medical care at any time without any penalty.

4.Confidentiality of all data and results of all study population was preserved.

5.declaire: there is no conflict of interest or funding for the study and publication.

Sample Size

The sample size is calculated according to the following equation:

$$\text{Necessary Sample Size} = \frac{(\text{Z-score})2 \times \text{StdDev} \times (1\text{-StdDev})}{(\text{margin of error})2}$$

(Keogh et al., 2020)

The sample was 56 patients with 90% prediction & 16% standard deviation alpha error of 0.10.

Inclusion Criteria:

Age>18 years, both sexes. Any patient indicated for upper GIT endoscopy either diagnostic or therapeutic with subsequent incidentally discovered sub epithelial lesions.

Exclusion criteria:

An un-cooperative patient. Lack of informed consent by patients. patients who developed complications during endoscopy as: Gastrointestinal perforation. Bleeding. Difficult sedation and intubation. Patient with critical illness or pregnant female who underwent endoscopy for emergency.

Study procedures:

All the participants were subjected to the following:

i. Medical history including demographics, anthropometrics,age, comorbidities and smoking.

ii. Clinical examination including general, systemic and local examination.

iii. Routine investigations: CBC, CRP, ESR, Tumor markers as (CEA and CA 19-9), Renal function tests (creatinine, urea and uric acid), Liver function tests (AST, ALT and ALP) and Viral markers (HCV, HBV and HIV).

iv. Radiological investigations: Pelvi-abdominal ultrasonography and Chest X-ray

v. Endoscopic examination (Gastroduodenoscopy and Endoscopic ultrasonography).

All our subjects underwent upper endoscopy. If SELs were found, they were biopsied by the endoscopist and the biopsy was sent for analysis. Later we compared the diagnosis reached by EUS and pathology to identify the diagnostic accuracy of EUS.

Endoscopic ultrasonography:

The following EUS features were analyzed: site and size of the lesion, wall layer involved, echogenicity, heterogeneity, outer margins, presence of calcifications or cystic component and regional adenopathies.

EUS features, presumptive diagnosis assessed by EUS and management decision after EUS (either no follow-up, surveillance with EUS or additional tissue sampling with EUS-FNA or endoscopic or surgical resection).

In all patients, careful EUS was performed using radial echoendoscopes at a scanning frequency of 5-10 MHz**.** High-frequency catheter probes were not available. All procedures were performed on an outpatient basis, by one of two experienced endosonographers using intravenous propofol sedation. Written informed consent for EUS was obtained for all patients. All EUS-FNA were performed by experienced endosonographers.

After eight hours of fasting before the procedure and obtaining written informed consent, oral gel was applied for local anesthesia and intravenous propofol was administered for sedation. A mini-probe (20 MHz) or linear array ultrasound probe (6.0–7.5 MHz) was selectively used according to the findings of the routine endoscopy. The lumen was filled with water for scanning. Once the position of the lesion was identified, the size was measured, and the origin and echo characteristics of the lesion were determined (heterogeneity, whether the boundary was clear, etc.). The ultrasound device was then used in Doppler mode to detect blood flow, velocity, and direction.

Ultrasound video sequences were recorded and analyzed using the software of the ultrasound processor. Analysis of the recorded video data was simple.

Statistical analysis of the data

Statistical analysis was done by SPSS v28 (IBM Inc., Armonk, NY, USA). Quantitative variables were presented as mean and standard deviation (SD). Qualitative variables were presented as frequency and percentage (%). Evaluation of diagnostic performance was performed by evaluation of the following: The diagnostic sensitivity: It measures the incidence of true positive results in patients' groups. Diagnostic specificity: It measures the incidence of true negative results in a non-diseased group. Positive predictive value (PPV): It is the percentage of true positive results among total positive results. Negative predictive value (NPV): It is the percentage of true negative results among total negative results. Spearman correlation was done to estimate the degree of correlation between two variables.

RESULTS

Table 1:

Demographic and Clinical characteristics.		
Age (years)	Range	59-71
	Median	65
Sex	Male	(28) 46.7 %
	Female	(32) 53.3 %
BMI (kg\m)	Range	24.2-27.2
	Median	25.6
Comorbidities and risk factors	Hypertension	29 (48.3 %)
	Diabetes	28 (43.3 %)
	Dyslipidemia	14 (23.3 %)
	Current smoking	16(26.7 %)

This table shows the demographic and clinical data of the studied patients.

Table 2:

Laboratory characteristic		**Median**	**Range**
Hemoglobin(gm/dl)		12.05	10.7-12.8
WBC count per (µL)		7.7	6.9-10.7
Platelet count per (µL)		267.5	234.5-309
CRP (mg/l)		4.5	1-9
ESR (mm/hour)		10	5.3-15
Serum creatinine (mg/dl)		1.1	0.9-1.3
Blood urea (mg/dl)		13	7.3-17
AST (IU/L)		20	15-29
ALT (IU/L)		30.5	19.3-45.3
Alkaline phosphatase (IU/L)		86.5	59-116
Tumer markers	CEA (ng/ml)	1.8	0.6-2.4
	CA19-9 (U/ml)	17	7-30

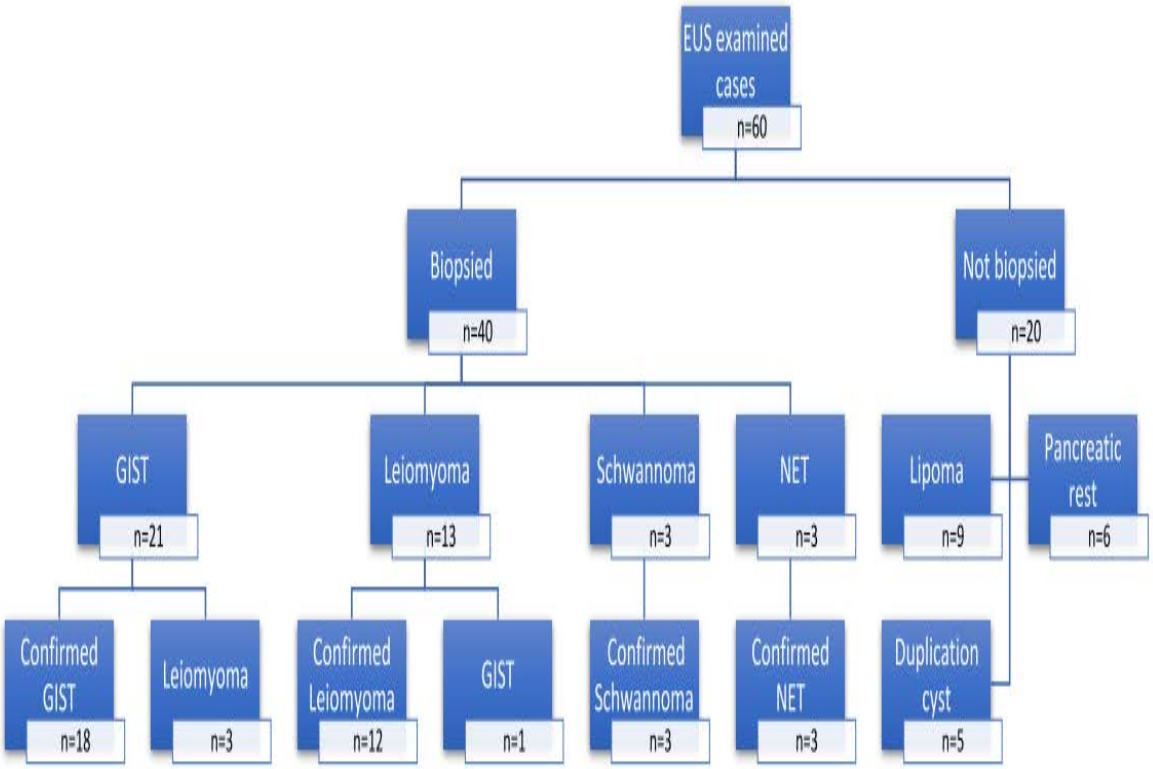
This table shows laboratory characteristics of the studied patients.

Table 3:

Finding	**Number**	**Percentage** (%)
Lesion size (mm)		
≤20 mm	21	35
>20 mm	39	65
Size of puncture needle (G)		
19	6	10
22	54	90
Lesion location		
Esophageal	21	35
Gastric	31	51.7
Duodenal	8	13.3
EUS Diagnosis (n=60)		
Leiomyoma	13	21.7
GIST	21	35
Schwannoma	3	5
NET	3	5
Lipoma	9	15
Duplication cyst	5	8.3
Pancreatic rest	6	10
Pathological Diagnosis (n=40)		
Leiomyoma	15	37.5
GIST	19	47.5
Schwannoma	3	7.5
NET	3	7.5

This table shows the characteristics of the studied lesions and the Eus and pathological findings.

flow chart for EUS and pathologic diagnosis



This flow chart showed that in 40 out of the 60 cases examined by EUS required biopsy (66.7%) while in the remaining 20 cases biopsy was not required (33.3%) with a diagnosis of lipoma (n=9), pancreatic rest (n=6), and duplication cyst (n=5).

In the 40 biopsied cases, the EUS diagnosis was confirmed in all cases except 4 (three were diagnosed by EUS as GIST and turned to be Leiomyoma by pathology, and one case was diagnosed by EUS as Leiomyoma and turned to be GIST by pathology. So, a total GIST of 19 and a total Leiomyoma of 15 were finally diagnosed by pathology.

Table 4: Comparison between EUS and pathology for diagnosis of biopsied SELs

Cohen's Kappa (*k*)		Total	Pathological diagnosis				diagnosis	
Sig.	*k*		NET	Schwannoma	GIST	Leiomyoma		
<.001	0.838	13	0	0	1	12	Leiomyoma	EUS diagnosis
		21	0	0	18	3	GIST	
		3	0	3	0	0	Schwannoma	
		3	3	0	0	0	NET	
		40	3	3	19	15	Total	

Notes: Data is N.

The test of significance is Cohen's kappa. This table shows an almost perfect agreement between EUS and pathology for diagnosing SELs (k = 0.81 – 1.0). There was a 90% agreement between the two modalities (36 out of 40 cases), and they disagree for the diagnosis of 4 cases.

Table 5: Diagnostic accuracy of EUS for the diagnosis of tumors

	Diagnostic accuracy	Sensitivity	Specificity	PPV	NPV
Leiomyoma	93 %	80 %	97.8 %	92 %	91 %
Gastrointestinal stromal tumor	93 %	95 %	93 %	86 %	97 %
Schwannoma	100 %	100 %	100 %	100 %	100 %
NET	100 %	100 %	100 %	100 %	100 %

NET: Neuroendocrine tumor, PPV: positive predictive value, NPV: negative predictive value

The diagnostic accuracy of EUS for diagnosis of leiomyoma was 93%, with 80% sensitivity, 97.8% specificity, 92% PPV and 91% NPV. The diagnostic accuracy of EUS for diagnosis of gastrointestinal stromal tumor was 93%, with 95% sensitivity, 93% specificity, 86% PPV and 97% NPV. The diagnostic accuracy of EUS for diagnosis of schwannoma was 100%. The diagnostic accuracy of EUS for diagnosis of NET was 100%.

Table 6: Correlation between size of lesion and different parameters

	Size of lesion	
	R	P
Hb (g/dL)	-0.314	0.015*
BMI (Kg/m^2)	-0.351	0.006*
Bleeding	0.449	<0.001*
Weight loss	0.675	<0.001*

Hb: hemoglobin, BMI: body mass index, r: correlation coefficient, *: statistically significant as P value<0.05.

There were significant negative correlations between size of lesions and Hb level (r= -0.314, P= 0.015) and BMI (r= -0.351, P= 0.006). There were significant positive correlations between size of lesions and bleeding (r= 0.449, P<0.001) and weight loss (r= 0.675, P <0.001).

Since large size lesions are positively related to malignancy, so there were significant negative correlations between malignancy and Hb level and BMI and significant positive correlations between malignancy and both bleeding and weight loss.

DISCUSSION

This is a prospective analytical study that was conducted to clarify the usefulness of EUS in the differential diagnosis of sub epithelial lesions (SEL) found during upper GI endoscospy. The study was conducted at the gastroenterology department of Al-Azhar university hospitals and Theodor Bilharz Research Institute. The study involved 60 cases with sub-epithelial lesions that incidentally discovered during upper gastrointestinal endoscopy during the duration of the study which was 6 months from March 2023 to September 2023.

Regarding demographic data of the studied patients, age ranged from 59 to 71 years with a median of 65 years. 46.7% were males and 53.3% were females. BMI ranged from 24.2-27.2 kg/m^2 with a median of 25.6 kg/m^2.

As to the history of comorbidities in the studied patients, 48.3% of the patients had HTN, 43.3% patients had DM, 26.7% were smokers and 23.3% had dyslipidemia.

Considering the laboratory findings, Hemoglobin ranged from 10.7-12.8 g/dL with a median of 12.05 g/dL. WBCs ranged 6.9-10.7× 10^9/L with a median of 7.7× 10^9/L. Platelets ranged from 234.5-309× 10^9/L with a median of 267.5× 10^9/L. CRP ranged from 22.6-30.3 mg/dL with a median of 27.5 mg/dL. ESR ranged from 5.3-15 mm/hr. with a median of 10 mm/hr. Creatinine ranged from 0.9-1.3 mg/dL with a median of 1.1mg/dL. Urea ranged from 7.3-17 mg/dL with a median of 13 mg/dL. ALT ranged from 19.3-45.3 U/L with a median of 30.5 U/L. AST ranged from 15-29U/L with a median of 20 U/L. ALP ranged from 59-116 IU/L with a median of 86.5 IU/L. In addition, CEA ranged from 0.6-2.4 µg/L with a median of 1.8 µg/L. CA 19-9 ranged from 7-30 U/mL with a median of 17 U/mL.

As to the nature of the studied lesions, (35%) were esophageal, (51.7%) were gastric, and (13.33%) were duodenal. Concerning their size, (65%) were >20 mm, and 35% were <20 mm. In 10% of those a 19G puncture needle was used and in the other 90% a 22G puncture needle was used.

Regarding EUS findings, 13 (21.7%) patients had leiomyoma (mostly found in the esophagus and stomach respectively) seen by EUS, on confirming those with pathology, 12 of them were true leiomyoma and 1 was a GIST. 21 (35%) patients were seen by EUS having GIST, on confirming that with pathology, 18 only were true GIST and 3 were leiomyoma. 3 (5%) patients had Schwanoma and other 3 (5%) patients had NET seen by EUS and both were confirmed 100% of them as true Schwanoma and NET by pathology respectively. There were other lesions detected by EUS including lipoma (9 cases) 15%, pancreatic rest (6 cases) 10%, duplication cyst (5 cases) 8.3%.

As to the pathological findings, pathological study of the biopsied obtained by EUS detected 15 (37.5%) cases of leiomyoma, of these 15, 12 were seen originally by EUS alone as leiomyoma and 3 were seen as GIST. 19 (47.5%) had GIST, 18 of them were originally seen by EUS alone as GIST and 1 was seen as leiomyoma. 3 (7.5%) had Schwanoma and other 3 (7.5%) had NET. Both were originally seen by EUS alone as Schwanoma and NET respectively.

These findings indicate that the diagnostic accuracy of EUS alone is not so far behind that of pathology especially when it comes to Schwanoma and NET with an accuracy of 100%. The accuracy of EUS alone in the diagnosis of leiomyoma was 92.3% and that for GIST was 85.7%.

The accuracy of Endoscopic Ultrasound (EUS) in diagnosing gastric subepithelial lesions (SELs) varies depending on the type of lesion. According to a study, the diagnostic accuracy of EUS for stromal tumors and leiomyomas was 80.4% and 68.0%, respectively (Vasilakis et al. 2023).

In a study performed to assess the accuracy of EUS in the evaluation of gastric sub epithelial lesions , EUS alone had an accuracy of 66.7% for non-neoplastic lesions and an accuracy of 30.8% for neoplastic lesions **(Sadeghi et al., 2023)**.

Another study reported that the overall accuracy of EUS-FNA for the diagnosis of malignancy was 89% **(Chen et al., 2022)**.

A study was conducted about EUS reliabity for gastric sub epithelial lesions. Using histopathology as the gold standard, the overall diagnostic accuracy of EUS imaging was 49% **(Vaicekauskas et al., 2020)**.

The accuracy of EUS varied among different studies probably due to the fact that EUS is mainly operator dependent and the sampling techniques also varied in multiple studies as well. In addition, the variance in sample size between the studies also affects the accuracy of EUS. Where we tried to include as much subjects as feasible.

The difference in the methodology of various studies suggests that a unified multicenter prospective cohort study should be done on a relatively large sample following certain criteria for tissue sampling and examination to provide reliable data about the use of EUS in the diagnosis of SEL.

CONCLUSION

EUS is a very important modality in the diagnosis of various lesions. Its diagnostic accuracy has been proven by multiple studies including ours. However, it has its limitations, as it mainly is operator dependent, its relative high cost and scarcity. The need for unifying EUS as a crucial step when confronting SEL since it can reveal critical data about the nature of SEL.

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