Lesion size determines diagnostic yield of EUS-FNA with onsite cytopathologic evaluation for upper gastrointestinal subepithelial lesions

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ABSTRACT

Background/Aims: *The aim of this study was to determine the diagnostic yield and factors influencing the diagnostic yield of endoscopic ultrasound-guided fine-needle aspiration (EUS-FNA) for upper gastrointestinal (GI) subepithelial lesions (SELs) with rapid onsite cytopathologic evaluation.*

Materials and Methods: *This is a single-center, retrospective study.*

Results: *Among 22 patients who underwent EUS-FNA, a cytopathological diagnosis was reached in 16 (72.7%) patients. The EUS-FNA results were as follows: seven GISTs (31.8%), six leiomyomas (27.2%), four non-diagnostics (18%), two duplication cysts (9%), two spindle cell tumor (9%), and one ectopic pancreas (4.5%). The long-axis size was >20 mm in 12 patients (average size: 31.3 ±9.3 mm) and <20 mm (average size: 16.6 ±2.5 mm) in 10 patients. Diagnostic accuracy of EUS-FNA from lesions <20 mm was 50% (5/10 lesions), and of lesions >20 mm was 91.6% (11/12 lesions) (Fisher's exact test; p=0.028). Six patients underwent surgical resection. Surgical pathology results of five lesions (four GIST, one leiomyoma) were consistent with cytopathology results (83.3%).*

Conclusion: *The diagnostic yield of EUS-FNA of the upper GI SELs with an onsite cytopathologic interpretation was 72.7%. Lesion size <2 cm significantly reduces the diagnostic yield of EUS-FNA for the upper GI SELs.*

Keywords: *Endoscopic ultrasound, subepithelial lesions, fine-needle aspiration*

INTRODUCTION

Gastrointestinal (GI) luminal protuberances encountered in endoscopic examinations are referred to as subepithelial lesions (SELs). As the name implies, they are located beneath the epithelium and originate from any layer of the gastrointestinal wall. Although the true incidence of gastrointestinal SELs is unknown, they are roughly encountered in one out of every 300 upper endoscopies (1). An overwhelming majority of SELs are diagnosed incidentally (2). Since the differential diagnosis of SELs includes a wide range of benign, malignant, and potentially malignant growths, as well as mural lesions and extramural compressions, tissue sampling to diagnose the underlying etiology is an important diagnostic challenge that will guide appropriate management and follow-up. Routine imaging, such as transabdominal ultrasound, computed tomography (CT), and magnetic resonance (MR) imaging, has limited value in the evaluation of SELs. However, endoscopic ultrasound plays a pivotal role in the diagnosis and management of lesions originating from the gastrointestinal wall owing to its unique ability to differentiate between gastrointestinal histological wall layers via high-resolution imaging (3).

Familiarity with the histologic layers of the gastrointestinal wall and their sonographic correlates is essential in the endosonographic evaluation of SELs. Interpretation of endosonographic images is operator dependent. Although an overall agreement for the endosonographic evaluation of SELs is good (κ=0.63), the interobserver agreement depends on the lesion type [excellent for extrinsic compressions (κ=0.94) and cystic lesions (κ=0.80); good for lipoma (κ=0.65); fair for leiomyoma (κ=0.53) and vascular lesions (κ=0.54); and poor for other submucosal lesions (κ=0.34)], and correct diagnoses correlate with the operator experience (4).

Although the tumor size, extraluminal border irregularity, echogenic foci, cystic spaces, and presence of lymph

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nodes have been found to differentiate benign from malignant mesenchymal tumors, more recent studies have shown that the accuracy of endosonographic imaging features for differentiating benign from malignant or potentially malignant lesions is suboptimal (5-7). Therefore, a cytologic confirmation is necessary to determine the etiology and behavior pattern of SELs. Various endoscopic tissue acquisition methods, including the endoscopic ultrasound-guided fine-needle aspiration (EUS-FNA), endoscopic ultrasound-guided trucut biopsy, cold forceps or jumbo forceps bite-on-bite biopsies, unroofing techniques, endoscopic submucosal resection or dissection, and submucosal tunneling, have been used for cytohistopathological diagnosis (8). EUS-FNA has been the preferred method by many gastroenterologists in the evaluation of SELs. A rapid onsite evaluation (ROSE) by a cytopathologist allows an immediate assessment and feedback about the adequacy of the material obtained from EUS-FNA. This potentially improves the diagnostic yield, reduces the number of FNA passes, and decreases the incidence of repeat procedures. However, given the considerable resource implications, the access to ROSE is not available in all units.

The aim of this study is to determine the diagnostic yield as well as factors influencing the diagnostic yield of EUS-FNA for the upper GI SELs by ROSE.

MATERIALS AND METHODS

Patients

The institutional review boards of Koç University School of Medicine approved this study. All consecutive patients who underwent endosonographic evaluation for upper gastrointestinal SELs at a referral institution from 2010 to 2016 were identified. Patients with extramural lesions/compressions and epithelial infiltrative lesions were excluded. All procedures were performed by a single operator (TA). Medical charts, procedures and cytopathology reports were retrospectively reviewed. The demographics, clinical presentation, procedural information (instruments and sedation), endoscopic and endosonographic characteristics [endoscopic mucosal features, lesion location within the gastrointestinal tract, layer of origin, size (long and short axis in millimeters), contour, echogenicity (as compared with muscularis propria), echo-pattern (homogeneous, heterogeneous, anechoic areas, and calcifications), and vascular pattern (color Doppler)], gauge of FNA needle and number of passes, cytopathology results, and, in case of availability, cross-sectional (CT or MR) imaging characteristics were retrospectively analyzed. In patients who underwent serial EUS evaluations, only the first examination was included. ROSE was available for each case of EUS-FNA. An annual follow-up was recommended for all patients with SELs that did not undergo EUS-FNA, except for patients with endosonographic features consistent with lipoma, duplication cyst, or vascular structure.

Equipment and procedure

Informed consent was obtained from each patient prior to the procedures. All procedures were performed in the endoscopy suite with patients in the left lateral decubitus position. Patients were on conscious sedation (midazolam and pethidine) or deep sedation (fentanyl, midazolam, and propofol) under supervision by an anesthesiologist. Each lesion was examined by a single endosonographer. All patients had a radial endosonographic evaluation (GF-UE 260, Olympus, Japan). Curvilinear echoendoscopes (GF-UC 240 P, Olympus, Japan) were used after the radial endosonographic examination when it was clinically appropriate and endoscopically feasible to perform EUS-FNA. A 22-gauge needle occluded with a stylet (Olympus, Japan) was used for EUS-FNA. An Aloka Prosound α5SV processor was used. An attempt was defined as one or multiple punctures of a lesion with the same needle; one puncture comprised many back-and-forth motions of the needle. The lesions were sampled until the cellularity was assessed as adequate by a cytopathologist. In case of inadequate sampling, a total of 4-6 FNA passes were performed. The day after the procedures, patients were routinely called by a nurse. Any post-procedure complaints were reported to the physician. The physicians performing the procedure called patients within a week to share the cytopathologic diagnosis with them. Any procedure-related complications were documented in the chart.

Cytopathologic evaluation

Cytopathologic evaluation was performed by an experienced pathologist (OA) with a cytopathology fellowship training. The sample from the needle was expressed onto the glass slides by advancing the stylet into the needle followed by forcing air into the needle through an attached air-filled syringe. The slides were air-dried, and two of them were stained with the Romanowsky stain (Quick Giemsa) for a ROSE of obtained samples for adequacy, as well as preliminary diagnosis. The needle was then rinsed in saline solution to prepare cytospin slides, and particles were fixed in a 10% formaldehyde solution for cell blocks. In the presence of spindle cell tumor, cytochemical staining was performed on cellblocks with c-kit (CD117), CD34, DOG1, actin, and S100 antibodies. The aspirates were cytologically categorized as non-diagnostic, benign, atypical, suspicious for malignancy, and malignant. Non-diagnostic aspirates were characterized

by a scant or acellular material. A result was considered as diagnostic when cytologic and immunohistochemical evaluations yielded a pathologic diagnosis. Non-diagnostic cytology specimens were characterized by scant or acellular material. Suspicious or atypical results were considered non-diagnostic.

Statistical analysis

Statistical analysis was performed using STATA (Data Analysis and Statistical Software; StataCorp LLC; College Station, Texas, USA).

RESULTS

During the study period, 64 patients underwent the endosonographic evaluation for SELs. Characteristics of patients with SELs are presented in Table 1. Thirty-nine patients (60.9 %) were male and 25 patients (39.1 %) were female. Forty-two patients underwent EUS (65.7 %), and 22 patients (34.3 %) underwent EUS-FNA. The mean age of the patients who underwent EUS and EUS-FNA was 51.2 and 50.8 years, respectively. All patients had endoscopically visible SELs except two, whose exophytically growing tumors were identified in CT imaging. One of these patients was diagnosed with GIST in the duodenum, employing the EUS-FNA; the other with SEL in the stomach underwent EUS without the FNA owing to the small size of the lesion. The mean long- and short-axis tumor size in patients who underwent EUS were 11.3 (4.4) mm {[mean [standard deviation (SD)]] and 6 (3.2) mm respectively, and of those patients who underwent EUS-FNA were 24.5 (10.5) mm and 16.5 (8) mm, respectively. The tumor locations in patients who underwent EUS were as follows: 27 (64.2%) in the stomach, eight (19%) in the duodenum, seven (16.6%) in the esophagus; the tumor locations in patients who underwent EUS-FNA were as follows: 12 (54.5%) in the stomach, six (27.2%) in the esophagus, and four (18%) in the duodenum.

Among 22 patients who underwent EUS-FNA, a cytopathological diagnosis was reached in 16 (72.7%) patients (Table 2). The EUS-FNA results were as follows: seven GISTs (27.2%), six leiomyomas (27.2%), four non-diagnostics (18%), two duplication cysts (9%), two spindle cell tumor (9%), and one ectopic pancreas (4.5%). The preliminary ROSE analysis was consistent with the cytopathological diagnosis. The long-axis size was >20 mm in 12 patients (average size: 31.3±9.3 mm) and <20 mm in 10 patients (average size: 16.6±2.5 mm). The diagnostic accuracy of EUS-FNA from lesions <20 mm was 50% (5/10 lesions) and of lesions >20 mm was 91.6 % (11/12 lesions; Fisher's exact test, p=0.028). The average number of the FNA passes was 3.4 with a SD of 1.6. In lesions >20 mm in size, the average number of FNA passes in diagnostic cases was 3.2 and in non-diagnostic cases was five. In lesions <20 mm in size, the average number of FNA passes in diagnostic cases was 3.1 and non-diagnostic cases was 3.7. The tumor locations of patients with a lesion <20 mm were as follows: four in the stomach, three in the duodenum, and three in the esophagus. Among lesions <20 mm in size, 75% (3/4) of gastric lesions and 66% (2/3) of duodenal lesions had non-diagnostic EUS-FNA, but all of the esophageal lesions had a diagnostic EUS-FNA. Among the lesions >20 mm in size, one out of eight (12.5%) gastric lesions had a non-diagnostic EUS-FNA, and all esophageal (3/3) and duodenal (1/1) lesions

Table 1. Patient characteristics

	EUS	EUS-FNA
Patients	42	22
Age (SD)	51.2 (12.3)	50.8 (17.8)
Sex (%)		
Male	26 (62%)	13 (59%)
Female	16 (38%)	9 (41%)
Tumor Location		
Esophagus	7 (16.6%)	6 (27.2%)
Stomach	27 (64.2%)	12 (54.5%)
Duodenum	8 (19%)	4 (18%)
Mean Size (SD; mm)		
Long axis	11.3 (4.4)	24.5 (10.5)
Short axis	6 (3.2)	16.5 (8)

EUS: Endoscopic ultrasound; EUS-FNA: Endoscopic ultrasound-guided fine needle aspiration; SD: Standard deviation

Table 2. Cytopathology results

	Lesion Size	
	<2 cm	>2 cm
Number of patients (%)	10 (45.5%)	12 (54.5%)
Mean Size (mm)		
Long axis	16.6±2.5	31.3±9.3
Diagnostic accuracy	5/10 (50%)	11/12 (91.6%)
Cytology results (%)		
GIST	3	4
Leiomyoma	2	4
Non-diagnostic	3	1
Spindle cell tumor	2	
Duplication cyst		2
Ectopic pancreas		1

GIST: Gastrointestinal stromal tumor

had a diagnostic EUS-FNA.

The layer of origin for the lesions was as follows: muscularis propria in 16 patients, muscularis mucosa in four patients, and submucosa in two patients. Twenty lesions had hypoechoic, homogeneous echo features. One lesion had heterogeneous mixed echogenicity, and a cytologic examination of this lesion revealed ectopic pancreas. One patient had an iso-hyperechoic lesion; the EUS-FNA results were non-diagnostic. A follow-up MR imaging was consistent with lipoma. One lesion had lobulated borders, and the EUS-FNA results of this lesion were consistent with GIST. Two lesions had a small cystic space, and the EUS-FNA results were consistent with a leiomyoma in one patient and non-diagnostic in the other. Two lesions diagnosed as duplication cysts had homogeneous, hypoechoic echo texture, rather than anechoic echo texture. The entrance of the needle caused twirling of the material within the lesions. Both patients did not receive antibiotics during or after the procedure. Only one post-EUS-FNA-related complication occurred in a patient with an esophageal duplication cyst (4.5%). This patient received antibiotics during the procedure. The patient was hospitalized for fever and chest pain. The patient was treated with antibiotics and pain medications and discharged within 3 days. No procedure-related mortality occurred.

Follow-up

Four patients with GIST >2 cm underwent surgical resection. All surgical pathology results were consistent with the cytopathologic diagnosis. Two patients with GIST <2 cm elected to have an endoscopic follow-up rather than surgical resection due to an advanced age and comorbidities. In both the cases, the endoscopic follow-up for 2 years did not reveal any changes in the lesion size. We lost the follow-up of the other patient with a GIST lesion <2 cm in size.

A patient with a symptomatic leiomyoma (16 mm) at cardia region had surgical resection. Surgical pathology results were consistent with the cytopathologic diagnosis. The other five patients with leiomyoma did not have any endoscopic follow-up at our institution.

Four patients had non-diagnostic EUS-FNA results. The MR findings with a gastric lesion >2 cm was consistent with lipoma. This lesion endosonographically appeared iso- to hyperechoic. A <2 cm gastric lesion originating from muscularis propria with a non-diagnostic EUS-FNA underwent surgical resection. Surgical pathology was consistent with GIST. The other non-diagnostic lesion has been stable over a 3-year endosonographic follow-up. The other patient with a non-diagnostic EUS-FNA elected to be followed by referring a gastroenterologist.

The follow-up of two patients with lesions (<2 cm) with spindle cells on EUS-FNA was lost. Patients with ectopic pancreas and duplication cysts were not followed endoscopically.

Six patients had surgical resection. The surgical pathology results of five lesions were consistent with the cytopathology results (83.3%). One patient with surgically removed GIST had non-diagnostic EUS-FNA results.

DISCUSSION

SELs are relatively uncommon tumors of the gastrointestinal tract. An endosonographic evaluation allows differentiation of extrinsic lesions from intramural lesions, identification of the originating layer, characterization of echo features, and tissue acquisition to reach an accurate diagnosis. In clinical practice, cytological and immunocytochemical results determine the final diagnosis. Resection of a lesion is indicated when malignant or potentially malignant endosonographic and cytologic findings are identified. Identification of typical endosonographic benign features (e.g., vascular structures, cysts, and lipoma) obviates the need for tissue acquisition, follow-up, and resection.

GISTs are the most common mesenchymal tumors of the gastrointestinal tract. They are encountered throughout the gastrointestinal tract, the stomach being the most common location (9). Autopsy and post-gastrectomy series for gastric cancer revealed a high frequency (22.5%-35%) of subcentimeter GISTs in the stomach (10-11). Although all GISTs are considered to have some degree of malignant potential, approximately 20%-25% of gastric and 40%-50% of small intestinal stromal tumors are clinically malignant (12). The annual incidence of new cases of GIST is roughly 10-20 cases per million persons; however, most small gastric stromal tumors are likely clinically silent (13-15).

The management of SELs and GISTs is evolving. The AGA Institute technical review recommended a follow-up by EUS or endoscopy at regular intervals for gastric SELs <3 cm without concerning endosonographic features (3). More recently, the national comprehensive cancer network recommended surgical resection of GISTs >2 cm because of their malignant potential (16). According to recent guidelines, small gastric SELs without high-risk features can be periodically followed by endosonography (16-19).

Endosonographic imaging features have been evaluated

to predict the malignant potential. The predictive value of endosonographic features for malignancy were assessed in 56 histologically proven cases; irregular extraluminal margins, cystic spaces, and lymph nodes with a malignant pattern were found to be predictive of malignancy (20). The presence of at least one of these criteria had 91% sensitivity, 88% specificity, and 83% positive predictive value. In another study, GISTs with mucosal ulceration, irregular borders, non-oval shape, and tumor size >3 cm were identified as high-risk features for malignancy (21). Even though echo features, as well as the cytological examination of the EUS-FNA samples, provide important diagnostic and prognostic information, reliable categorization of GISTs for malignant potential requires histologic evaluation of a resected specimen to determine the mitotic index.

Although EUS has a pivotal role in the evaluation of SELs, its diagnostic accuracy is not perfect. The sensitivity of EUS-FNA to diagnose GIST was found to be 78.4%, which was influenced by the size, location, shape, and layer of origin (22). A recent meta-analysis on diagnostic efficacy of EUS-FNA sampling for upper gastrointestinal SELs revealed a diagnostic rate of 59.9 % (ranging from 43% to 91%) (23). In a meta-analysis, a review of 978 EUS tissue sampling attempts did not show any difference in the diagnostic rate among fine needle aspiration, trucut needle biopsy, and fine needle biopsy or among different needle sizes (23). In our study, the diagnostic yield of EUS-FNA of the upper GI SELs with onsite cytopathologic interpretation was 72.7%. Diagnostic accuracy was 91.6% for lesions >20 mm in size and 50% for lesions <20 mm in size (Fisher's exact test, p=0.028). In the setting of similar procedure standards (single operator, the same FNA needle size, ROSE for each case), the lesion size was the only determinant of the EUS-FNA diagnostic accuracy. Given that the majority of the lesions were located in the stomach and originated from the muscularis propria, the location and layer of origin were not associated with an increased diagnostic yield. As in our study, Akahoshi et al. have also shown that the diagnostic accuracy of EUS-FNA for SELs was size dependent; the diagnostic rate of lesion <20 mm, between 20 mm and 40 mm, and >40 mm was 71 %, 86 %, and 100%, respectively (24). A recent study on EUS-FNA of gastric SELs <2 cm with ROSE revealed a diagnostic rate of 62% at the first session. Additional sessions have improved the diagnostic rate to 73% (25). A better diagnostic rate of 81.5% of EUS-FNA using a forward-viewing echoendoscope and 19 G needle for SELs <2 cm in size was reported in 27 patients (26). In a recent study, eight patients with small SELs (mean diameter, 10.6 mm) had EUS-FNA with a forward-viewing curved linear array echoendoscope with a cap device attached to the tip (27). Although adequate samples were obtained in seven (87.5%) patients, only four patients (50%) had adequate sampling for histological examination with immunohistochemical staining (27). It is challenging to puncture and obtain adequate sampling from small SELs with a needle advanced through a conventional oblique-viewing curved linear array echoendoscopes owing to the mobility of the lesion. For example, when the gastric wall bends or the lesion slips under the needle, the needle cannot enter into the lesion. Furthermore, in some cases the needle enters the lesion, but subsequent in-and-out stabbing motions of the needle simply drag the lesion back-and-forth rather than digging needle sampling tracts into the lesion. Therefore, the placement of a cap on a forward-viewing curved linear array echoendoscope is recommended to stabilize small SELs and perform FNA without escape of the lesion (27). In our study, given the low yield of EUS-FNA in small lesions, 42 out of 64 patients (65.6 %) referred for EUS did not undergo EUS-FNA (average lesion size, 11.3×6 mm). Two of these lesions underwent endoscopic mucosal resection for hypoechoic lesions at the submucosal layer; cytopathological evaluation revealed neuroendocrine tumors in both of them. The remaining patients who did not undergo EUS-FNA were recommended an endosonographic follow-up.

Non-diagnostic cases had a higher number of total EUS-FNA passes during the case, regardless of the lesion size. This is an expected finding since an immediate feedback by the onsite cytopathologist triggers further passes until adequacy is reached or the case is abandoned. However, our study is underpowered to pick up a statistically significant difference in the number of EUS-FNA passes in diagnostic and non-diagnostic ROSE. On the other hand, ROSE may potentially decrease EUS-FNA-related complications by allowing an earlier termination of successful diagnostic procedures. However, we found that this is already a low-morbidity procedure, with the only complication in this study predisposed by lesion biology (duplication cyst) rather than the number of FNA passes. Anechoic SELs suggestive of duplication cyst should not be sampled to prevent infectious complications. In our patient, the duplication cyst had a hypoechoic echotexture, which is likely secondary to the heavy protein content of the cyst.

There are several limitations to the current study that are inherent to a retrospective study design. The main limitation of this study was its retrospective nature, lack of predefined algorithm, reliance on data that were not designed for the study, and relatively small sample size. Since benign lesions are not routinely resected, cyto-

pathologic diagnosis of each SEL was not confirmed pathologically.

In conclusion, the lesion size determines the yield of EUS-FNA with ROSE to diagnose upper GI SELs. While lesions >20 mm in size can be definitely diagnosed using EUS-FNA with ROSE, the yield drops to 50% in smaller lesions. Further studies should optimize EUS and EUS-FNA for small SELs, as well as chronicle the natural course and clinical impact of endoscopy for these lesions. Finally, in an era of cost-containment, a cost-benefit analysis of EUS-FNA with and without ROSE is warranted for both large and small SELs.

Ethics Committee Approval: Ethics committee approval was received for this study from the Institutional Review Board of Koç School of Medicine (No: 2016.298.IRB2.153).

Informed Consent: Written informed consent was obtained from all the patients who participated in this study.

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