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ORIGINAL ARTICLE

Yield and Performance Characteristics of Endoscopic Ultrasound-Guided Fine Needle Aspiration for Diagnosing Upper GI Tract Stromal Tumors

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Abstract
Background and Aims EUS-FNA is a means of sampling suspected GI stromal tumors (GIST). However, there are limited published data on factors influencing the sampling yield, and on the performance characteristics of this technique in comparison with resection pathology. We analyzed the yield of EUS-FNA for submucosal lesions of the upper GI tract, and determined the performance characteristics of EUS-FNA for diagnosing GISTs.
Methods We retrospectively reviewed procedural and pathology data from consecutive patients undergoing EUS-FNA of submucosal lesions from two medical centers over a 4-year period. We analyzed the yield of EUS-FNA, and calculated performance characteristics of EUS-FNA for GIST based on resection pathology.
Results A total of 65 patients underwent EUS-FNA of 66 submucosal lesions during the study period. EUS-FNA was either diagnostic (68%) or suspicious (12%) in a total of 80%. EUS-FNA yielded the following diagnoses: GIST based on cytology and immunohistochemistry (56%), suspected GIST (12%), leiomyoma (9%), other neoplasm (3%), and non-diagnostic (20%). Larger lesion size, gastric location, and presence of on-site cytopathology were associated with higher yield in univariate analysis. Larger needle size and number of FNA passes were not associated with improved yield. Based on resection pathology from 28 specimens, the EUS-FNA performance characteristics for diagnosing GISTs included a sensitivity of 82%, a specificity of 100%, and an overall accuracy of 86%.
Conclusions EUS-FNA provides a high yield for sampling submucosal lesions and is highly accurate for diagnosing GISTs. EUS-FNA has an important role in the evaluation of suspected GISTs.

Keywords Gastrointestinal stromal tumors · Endoscopy · Endoscopic ultrasound · Fine needle aspiration · Gastrointestinal neoplasms

Introduction

Although gastrointestinal stromal tumors (GISTs) may be found anywhere in the GI tract, they are most commonly encountered in the stomach [1]. It is believed that GISTs originate from stem cell precursors to the interstitial cells of Cajal, which are involved in the regulation of gastrointestinal motility [2]. GISTs express the *c-kit* proto-oncogene, a transmembrane tyrosine kinase receptor. The presence of this receptor may be used to help distinguish GISTs from other submucosal tumors of the GI tract [1, 3, 4].

All GISTs harbor malignant potential. While small lesions may behave in an indolent manner during short-term interval follow-up, larger lesions are thought to have a higher risk for malignant potential and aggressive behavior [1, 5]. Although close imaging follow-up of small suspected GISTs may be possible, the only definitive treatment option for localized GISTs is resection; thus, distinguishing GISTs from other submucosal lesions preoperatively would be useful.

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Endoscopic ultrasound (EUS) has become a helpful tool in evaluating submucosal lesions of the GI tract. Sonographic features may easily allow one to differentiate certain types of submucosal lesions (e.g. lipoma vs. potential GIST) [6]. But other lesions that exhibit similar EUS characteristics are managed quite differently (e.g. leiomyoma vs. GIST). Thus, sonographic characteristics alone may be insufficient to distinguish submucosal lesions, and tissue sampling is ideal for a definitive diagnosis.

EUS-guided fine needle aspiration (FNA) has emerged as a means of sampling potential GISTs. In addition to providing specimens for cytology, EUS-FNA with immunohistochemistry studies assists in differentiating various submucosal tumors due to the preferential staining for several antigens including, *c-kit* for GISTs, smooth muscle actin for leiomyomas, and S-100 for schwannomas [1, 7]. Data from large series, however, are lacking. Prior studies have been limited by either small sample size or lack of a surgical reference standard. We report a large experience with EUS-FNA for suspected GISTs in the upper GI tract with a high proportion of resected specimens on which to base the performance characteristics of EUS-FNA.

Methods

Approval was obtained from the California Pacific Medical Center (CPMC) and the San Francisco Veterans Affairs Medical Center (SFVAMC) institutional review boards for this dual center retrospective study. Consecutive patients undergoing EUS-FNA of submucosal, intramural solid lesions of the upper gastrointestinal tract were identified from the electronic medical records of our two medical centers from July 2003 to November 2007. The following data were collected: patient demographics, location of lesion, endoscopic and EUS characteristics of the lesion (size, echogenecity, wall layer of origin), size of EUS-FNA needle, number of FNA passes, presence or absence of an on-site cytopathologist, final diagnosis from FNA, and final pathology based on resection specimen, when available.

All EUS examinations were performed using curvilinear array echoendoscopes (GFUC-140 or GFUCT-140; Olympus America, Center Valley, PA, USA) by experienced endosonographers (Fig. 1). FNA was performed with either 22-gauge or 19-gauge needles (Echotip, Cook Medical, Winston-Salem, NC, USA). The choice of FNA needle size was at the discretion of the endosonographer.

When a cytopathologist was available, the EUS-FNA specimen was expressed onto one or two slides for direct smears and rapid on-site evaluation. Air dried smears were prepared with Diff-Quick stain (Siemens, Newark DE); alcohol-fixed smears were prepared with toluidine blue followed by Papanicolau staining. Additional material was expressed into a 30-cc formalin container for cell block preparation (with hematoxylin and eosin stain), and subsequent immunohistochemical (IHC) staining. Additional FNA passes were performed based on the cytopathologist's

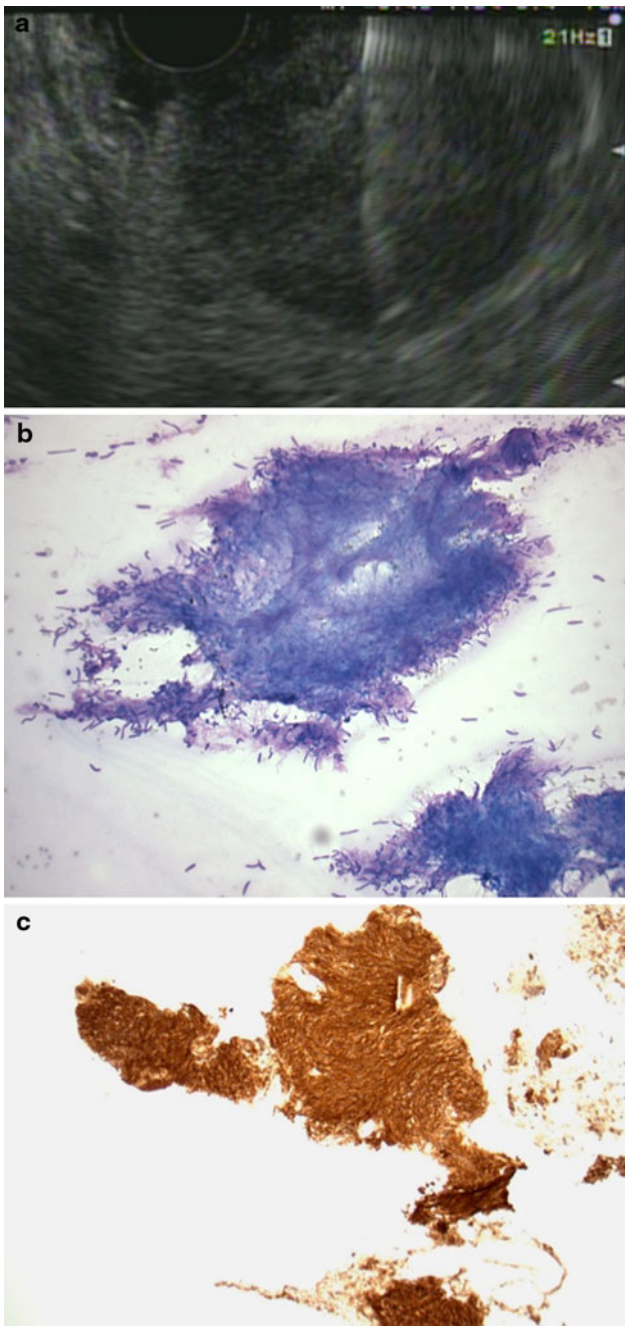

Fig. 1 **a** Endoscopic ultrasound (EUS) image showing fine needle aspiration (FNA) of a 2-cm hypoechoic lesion in the muscularis propria layer of the stomach. **b** Direct smear cytologic specimen from EUS-FNA revealing a spindled cell neoplasm (Diff Quik stain; original magnification ×20). **c** Formalin-fixed cell block preparation from aspirate with positive immunohistochemical stain for *c-kit* (immunoperoxidase stain; original magnification ×20)

immediate microscopic assessment of the slide and gross assessment of sample adequacy for the cell block and subsequent IHC analysis. When an on-site cytopathologist was not available, the FNA sample was placed directly into a container for subsequent cell block preparation. Additional FNA passes were performed based on the endoscopist's gross assessment of sample adequacy in the cell block.

Cytology results from EUS-FNA were categorized as *diagnostic, suspicious* or *non-diagnostic*. A *diagnostic* specimen was defined as: (1) sufficient sample for cytopathologic evaluation and IHC analysis, if needed, and (2) a specific diagnosis was provided by the cytopathologist. A *suspicious* specimen was defined as an FNA sample from which suspicious cellular material was obtained on direct smears, but there was insufficient sample in cell block for confirmatory IHC analysis. A *non-diagnostic* specimen was defined as a sample from which the cytopathologist could not make a diagnosis from the direct smears or the cell block. The EUS-FNA diagnosis of GIST was based on the presence of spindle-type cells that stained positive for *c-kit*. Leiomyomas were defined by the presence of smooth muscle or spindle cells that stained positive for actin or desmin, and negative for *c-kit*. Performance characteristics of EUS-FNA for GISTs were calculated based upon pathology from resection specimens as the reference standard.

Continuous variables are displayed as means and standard deviations. Categorical variables are displayed as percentages. Comparisons of continuous variables were done using the Student's *t* test and categorical variables were compared using chi-square analysis or Fisher's exact test where appropriate. Multivariate logistic regression was used to determine the unique association of patient and procedural factors with cytology results (diagnostic versus non-diagnostic yield). A P value of <0.05 was used to determine statistical significance for all tests.

Results

A total of 65 patients underwent EUS-FNA of 66 solid-appearing submucosal, intramural upper GI tract lesions during the 4-year study period at our two centers. The mean patient age was 66 years, and 51% were male. Endoscopic and EUS characteristics of the submucosal lesions are summarized in Table 1.

EUS-FNA was *diagnostic* in 45 of 66 lesions (68%), *suspicious* in 8 (12%), and *non-diagnostic* in 13 (20%). The mean number of FNA passes was 2.3 (range 1–5); this included 2.2 passes in patients with *diagnostic* cytology versus 2.9 passes in patients with *suspicious* or *non-diagnostic* cytology ($P = 0.267$) (Table 2). A *diagnostic* sample was achieved in 64% with use of a 22-gauge needle, and in 79% with a 19-gauge needle ($P = 0.345$; NS). An on-site cytopathologist was present for 65% of procedures. A definite EUS-FNA diagnosis was achieved in 74% (31/42) with the presence of on-site cytology versus 58% (14/24) without a cytopathologist present during the procedure ($P = 0.023$). The diagnostic yield of EUS-FNA was higher for gastric lesions (75%), as compared to esophageal or duodenal lesions (43 and 25%, respectively; $P = 0.002$). A definite diagnosis was achieved in 80% for lesions $\geq$20 mm compared with 45% for those measuring $<$20 mm ($P = 0.001$). However, none of the higher yields found with the presence of on-site cytopathology, gastric lesions, and larger-sized lesions were significant in multivariate analysis.

Table 1 Endoscopic and endoscopic ultrasound (EUS) characteristics of 66 submucosal lesions

Characteristic	*n* (%)
Lesion location	
Esophagus	7 (11%)
Stomach	55 (83%)
Duodenum	4 (6%)
Endoscopic appearance	
Smooth overlying mucosa	58 (88%)
Ulcerated	5 (7%)
Umbilicated or dimpled	3 (5%)
Size on EUS	
≤20 mm	22 (33%)
21–30 mm	16 (24%)
31–40 mm	18 (27%)
>40 mm	10 (15%)
Echocharacteristics of lesions	
Hypoechoic	61 (92%)
Isoechoic	5 (8%)
Hyperechoic or anechoic	None
Wall layer origin on EUS	
Muscularis propria	56 (85%)
Submucosa	4 (6%)
Deep mucosa	6 (9%)
Lesion borders on EUS	
Smooth	62 (94%)
Irregular	4 (6%)

The final cytology results from EUS-FNA are summarized in Fig. 2. Of the 13 lesions with a *non-diagnostic* initial FNA attempt, a repeat FNA was attempted in three cases. This resulted in a new cytologic diagnosis of lymphoma in one patient, while the other two remained *non-diagnostic*.

Among the 66 lesions, a definitive pathologic diagnosis was available for 28 lesions (24 surgical resections,

Table 2 Factors influencing diagnostic yield of endoscopic ultrasound fine needle aspiration (EUS-FNA) for submucosal lesions

Factors	Diagnostic EUS-FNA	*P* value
19G versus 22G needle	79% vs 64%	0.345
On-site cytopathologist present versus absent	74% vs 58%	0.023[a]
Lesion location		
Gastric versus esophageal	75% vs 43%	0.07[a]
Gastric versus duodenal	75% vs 25%	0.001[a]
Lesion size ≥20 mm versus <20 mm	80% vs 45%	0.001[a]
Number of needle passes for diagnostic versus non-diagnostic FNA	2.2 vs 2.9	0.267

[a] Not significant in multivariate analysis

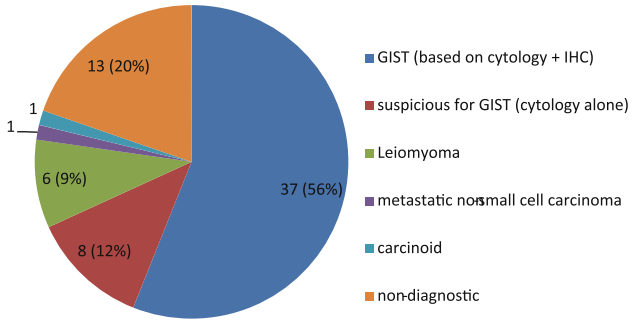

Fig. 2 Cytologic diagnoses from endoscopic ultrasound fine needle aspiration (EUS-FNA)

4 endoscopic resections). EUS-FNA provided a correct diagnosis in 21 of 28 (overall accuracy 75% for all submucosal lesions). Of the 22 resection-confirmed GISTs, EUS-FNA was *diagnostic* in 18 (82%), *suspicious* in two, and *non-diagnostic* in two (Table 3). Performance characteristics for the EUS-FNA diagnosis of GIST based on cytology and IHC are summarized in Table 3. There were no resection-proven, false positive EUS-FNA diagnoses of GIST. Of the remaining six resected lesions, EUS-FNA sampling correctly identified three leiomyomas, while failing to obtain adequate cytology to identify three tumors (one granular cell tumor, one leiomyoma, one carcinoid).

One minor EUS-FNA associated complication occurred in which mild hemorrhage (oozing) was noted at the FNA puncture site. This was immediately recognized and successfully treated endoscopically with a hemoclip. The patient required no further interventions.

Table 3 Endoscopic ultrasound fine needle aspiration (EUS-FNA) performance for diagnosis of gastrointestinal stromal tumor (GIST) based on cytology and immunohistochemical (IHC) staining compared to surgical pathology from 28 resected specimens

Approach	Type	Resection pathology	
		GIST	Other lesion
EUS-FNA	GIST	18	0
	Non-diagnostic or other lesion	4	6

Performance characteristics: sensitivity 82%, specificity 100%, positive predictive value 100%, negative predictive value 60%, overall accuracy 86%

Discussion

We report a yield of 80% for the EUS-FNA sampling of submucosal lesions in the upper GI tract. This includes 68% with a definite EUS-FNA diagnosis based on cytology and IHC, and an additional 12% with suspicious cytology. Although our overall yield was similar to that found in other recent studies, the proportion based on cytology and IHC was higher. Hoda et al. reported a diagnostic yield of 84%, but included 22% deemed "suspicious" by the presence of spindle cells but without confirmatory IHC staining [8]. Sepe et al. demonstrated a diagnostic yield of 78% in 37 surgically-resected, *c-kit* positive GISTs that were subjected to EUS-FNA preoperatively [9]. However, a positive *c-kit* stain was not necessary for the EUS-FNA sample to be considered diagnostic, and cell blocks for IHC were performed in only 35%. A third study from Japan reported a sample adequacy rate of 83% for gastric submucosal tumors [10]. But, this included 39% that met suggestive cytologic criteria without IHC staining.

A gastric location, increased lesion size, and the presence of an on-site cytopathologist were associated with improved diagnostic yield in our study. A higher yield for gastric lesions was described in a prior report by Sepe et al. but others have not shown a difference in yield with anatomic location [8–10]. Technical issues with needle trajectory and echoendoscope position likely account for the lower yield in the small intestine as compared to the stomach. However, this should not be a problem in the esophagus. We wonder if a higher proportion of non-GIST lesions in the esophagus may account for a lower yield; but we had low numbers of esophageal lesions and even lower with corresponding resection pathology on which to substantiate or refute this notion.

Diagnostic yield improved with increasing lesion size. We differentiated size into two categories: <20 mm or ≥20 mm. We believe this was an appropriate demarcation with respect to potential difficulties with targeting lesions and aspirating contents during the to-and-fro movements with the FNA needle. Conceptually, a higher diagnostic yield with EUS-FNA of larger lesions seems reasonable, and has been suggested in other reports [9–11].

An on-site cytopathologist was present for about two-thirds of procedures, and we found a significantly greater

yield with their presence during sampling. On-site cytology is associated with higher yield of EUS-FNA for various other GI and mediastinal lesions [12, 13]. Although one may question the need for on-site cytology for suspected GISTs in which definitive diagnosis is dependent on the IHC staining from cell block, we believe the immediate review of direct smears is helpful to confirm an adequate lesional aspirate. Prior reports on EUS-FNA for submucosal lesions have either been unable to assess this due to the universal use of on-site cytology [8, 10], or have only revealed a trend towards higher yield with an on-site cytopathologist [9]. Our findings support the role for on-site cytology for sampling suspected GISTs.

Scant data exist comparing the yield of EUS-FNA for submucosal lesions using different FNA needle sizes. In the present study in which choice of needle-size was at the discretion of the endosonographer, there was a non-significant, higher diagnostic yield with the use of the larger-bore 19-gauge needle. Although we did not record the specific rationale for needle choice during each procedure, our general experience has been that the larger 19-gauge needle can be difficult to use in angulated echoendoscope positions. This is reflected in the current series in which 65% of samples were obtained with a 22-gauge device. Prospective trials with larger sample sizes would be needed to validate a true difference in yield between 19-gauge and 22-gauge FNA needles.

An increased number of needle passes was not associated with a higher diagnostic yield. In contrast, patients with diagnostic EUS-FNA required on average fewer passes compared to non-diagnostic cases, but this was not statistically significant. We suspect that this is related to the use of on-site cytopathology for the majority of our cases. The actual number of passes needed for diagnosis may be less relevant when an on-site cytopathologist confirms specimen adequacy. Other reports have also found no association of higher yield with increased needle passes [8–10].

Using resection pathology from 28 lesions (42%) as the criterion standard for measuring the performance characteristics of EUS-FNA for GISTs, we found a sensitivity of 82% and overall accuracy of 86%. Few studies have been able to provide these types of data. Akahoshi et al. found an accuracy of 97% for EUS-FNA characterization of GIST versus non-GIST among 29 surgically resected cases [14]. Mekky et al. calculated an accuracy of 94% from 69 cases in their series with a definite follow-up diagnosis [10]. However, they evaluated performance of EUS-FNA for differentiating benign from malignant submucosal lesions (not GIST from non-GIST), and their 69 cases included seven gastric wall carcinomas and six extragastric lesions. Sepe et al. found a 79% sensitivity of EUS-FNA for diagnosing GISTs, but could not assess other performance characteristics as the entire cohort was comprised of surgically resected GISTs [9]. Our results, in combination with other limited available data, suggest that performance characteristics of EUS-FNA for diagnosing GISTs are comparable to those of EUS-FNA of other sites [15].

Our study is limited by several factors. The retrospective nature makes it difficult to assess the decisions behind using a certain needle size or requesting on-site cytopathology. That issue combined with the size of our patient cohort (albeit on par with other studies), do not allow for analyzing our results independent of other findings. Thus, we were unable to confirm the factors that were associated with higher diagnostic yield in multivariate analysis. However, we believe that our findings of improved yield with gastric location, increased lesion size, and the presence of on-site cytology seem rational. Larger prospective studies that are adequately powered to detect differences independently are needed to validate our findings.

As demonstrated from a recent survey on practice patterns of endosonographers, there is no standardized or widely accepted method for evaluating and managing suspected GISTs [16]. Our results support the routine role of EUS-FNA in the evaluation of suspected GISTs. The technique appears to be a safe and effective method for characterizing these lesions, with accuracy rates resembling those of other sites in which EUS-FNA is routinely used for diagnosis. A higher diagnostic yield of EUS-FNA is seen in association with larger sized lesions, tumors in the stomach, and with the presence of an on-site cytopathologist.

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