Diagnostic utility of EUS-guided FNA in patients with gastric submucosal tumors CME

Mohamed A. Mekky, MD, Kenji Yamao, MD, Akira Sawaki, MD, Nobumasa Mizuno, MD, Kazuo Hara, MD, Mohamed A. Nafeh, MD, Ashraf M. Osman, MD, Takashi Koshikawa, MD, Yasushi Yatabe, MD, Vikram Bhatia, MD

Nagoya, Japan

Background: Submucosal tumors (SMTs) comprise both benign and malignant lesions, and most of the gastric lesions tend to be malignant. The addition of EUS-guided FNA (EUS-FNA) has the potential to improve this distinction, but published series are limited.

Objective: To evaluate the yield of EUS-FNA in gastric SMTs with referral to a criterion standard final diagnosis.

Design: Retrospective study.

Setting: Tertiary-care referral center.

Patients: This study involved 141 consecutive patients with gastric SMTs, who underwent EUS-FNA from January 2000 to December 2008. Immunohistochemical staining with c-kit, CD34, actin, and S-100 antibodies was done if a spindle cell tumor was found. Based on FNA sample adequacy, and whether a specific diagnosis could be established, EUS-FNA results were categorized as diagnostic, suggestive, or nondiagnostic. The criterion standards for final diagnosis were the surgical histopathological results or the follow-up course for malignant, inoperable cases.

Intervention: EUS-FNA.

Main Outcome Measurements: Diagnostic yield of EUS-FNA and factors related to sampling adequacy for cytological and immunohistochemical evaluation.

Results: A total of 141 patients (52% female, mean age 56.7 years) underwent EUS-FNA (range 1-5 passes). The overall results of EUS-FNA were diagnostic, suggestive, and nondiagnostic in 43.3%, 39%, and 17.7% of cases, respectively. Adequate specimens were obtained in 83% of cases, and 69 cases (48.9%) had a definitive final diagnosis. The most common gastric SMT was GI stromal tumor (59.5%). EUS-FNA results were 95.6% accurate (95% confidence interval [CI], 87.5%-99%) for the final diagnosis and 94.2% (95% CI, 85.6%-98.1%) accurate for differentiating potentially malignant lesions. A heterogeneous echo pattern was the only independent predictor for sampling adequacy (adjusted odds ratio 6.15; $P = .002$). There were no procedure-related complications.

Limitations: Possibility of selection bias.

Conclusion: EUS-FNA is an accurate method for diagnosis of gastric SMTs and for differentiating malignant lesions. (Gastrointest Endosc 2010;71:913-9.)

Abbreviations: EUS-FNA, EUS-guided FNA; GIST, GI stromal tumor; IHC, immunohistochemical; SMT, submucosal tumor.

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Current affiliations: Department of Gastroenterology (M.A.M., K.Y., A.S., N.M., K.H.), Aichi Cancer Center Hospital, Nagoya, Japan, Department of Tropical Medicine and Gastroenterology (M.A.M., M.A.N., A.M.O.), Assiut University, Egypt, Aichi Prefectural College of Nursing and Health (T.K.), Nagoya, Japan, Department of Pathology and Molecular Diagnostics (Y.Y.), Aichi Cancer Center Hospital, Nagoya, Japan, Department of Medical Hepatology (V.B.), Institute of Liver and Biliary Sciences, New Delhi, India.

Reprint requests: Mohamed A. Mekky, MD, Department of Gastroenterology, Aichi Cancer Center Hospital, 1-1 Kanokoden, Chikusa-ku, Nagoya, Aichi 464-8681 Japan.

If you would like to chat with an author of this article, you may contact Dr. Mekky at doc_mekky0000@yahoo.com.

Gastric submucosal tumors (SMTs) include a diverse array of benign, potentially malignant, and malignant lesions. These lesions are being increasingly recognized during routine endoscopies, with a reported frequency of 1 in every 100 to 300 gastroscopic examinations.[1,2] Polkowski[2] estimated that about 13% of GI SMTs were malignant, with the highest risk of malignancy in the stomach. EUS imaging features alone cannot substitute for a pathological diagnosis of SMT subtype, and EUS is an imperfect tool for assessing the malignancy risk for these lesions. Hence, EUS-assisted tissue sampling modalities have been increasingly incorporated for evaluation of SMTs.[2-11]

Cytomorphologically, spindle cell tumors are the most commonly encountered SMTs. The most common subtype is GI stromal tumor (GIST), which needs to be distinguished from its benign spindle cell counterparts like leiomyomas and schwannomas.[2-7] This distinction is difficult on cytology smears alone and requires immunohistochemical (IHC) staining and ultrastructure studies.[4-9] EUS-assisted sampling by both EUS-guided FNA (EUS-FNA) and EUS-guided Trucut Biopsy (EUS-TCB) can provide cytological material as well as tissue cores for histological evaluation.[4-5] The use of the latter has been limited because of its potential complications and difficulty of use.[2,10-12] On the other hand, EUS-FNA makes it possible to obtain an adequate cell block specimen, which then can be examined histologically and immunohistochemically. Most previous reports of EUS-FNA studies in SMTs have been limited to GISTs or mesenchymal tumors, rather than encompassing the entire spectrum of lesions encountered in practice.[4,11-16] The reported accuracy rates in these studies have varied widely between 19% and 100%, with most studies lacking a final surgical diagnosis for reference.[4,5,11-17] Hence, the aim of this study was to evaluate the diagnostic yield of EUS-FNA with the addition of IHC staining for gastric SMTs with reference to a criterion standard final diagnosis.

Capsule Summary

What is already known on this topic

- Variable accuracy rates have been reported with the use of EUS-guided FNA in submucosal tumors, a large proportion of which tend to be malignant.

What this study adds to our knowledge

- In a retrospective study of 141 consecutive patients with gastric submucosal tumors who underwent EUS-guided FNA, adequate tissue sampling was obtained in 83%, a concordant diagnosis was reached in 95.6%, and malignant lesions were diagnosed in 94.2%.

PATIENTS AND METHODS

Consecutive patients with gastric SMTs, who had undergone EUS-FNA at Aichi Cancer Center Hospital, Nagoya, Japan between January 2000 and December 2008, were retrospectively selected. Informed consent was given by each patient prior to the procedure as a part of their clinical management. Those patients who had undergone EUS-FNA in some other institution and patients in whom on-site cytological evaluation was unavailable during the EUS-FNA procedures were excluded. The objective and outcome measurements were the diagnostic yield of EUS-FNA and factors related to sampling adequacy for cytological and IHC evaluation.

Study procedures

All patients underwent an upper endoscopic examination prior to EUS-FNA. The procedures were performed with the patients under conscious sedation (using intravenous Pentzaocine 15mg; Pentagin, Daiichi-sankyo Corp., Tokyo, Japan, and intravenous midazolam 5-10mg; Dormicum, Astellas Corp., Tokyo, Japan). EUS-FNA was performed by using a convex array echoendoscope (GF–UCT240; Olympus Optical Corp Ltd, Tokyo, Japan) connected to a US scanning system (SSD 5500; Aloka, Tokyo, Japan). All FNA procedures were performed by using 22-gauge needles (eg, NA-10J-1, NA-10J-KB, NA-11J-KB, or NA-200H-8022; Olympus Medical System Corp Ltd, Tokyo, Japan). Patients were followed-up after the procedure for 48 hours for any procedure-related complications. Cytological samples were processed by the same experienced cytopathologist (T.K.). For all samples, one slide was fixed by air drying and then stained with modified Giemsa stain (Diff-Quik; Kokusai Shiyaku, International Reagents, Kobe, Japan) and reviewed immediately (on-site examination) by the cytopathologist (or cytotechnician) to ensure specimen adequacy. The other slides were fixed by immediate immersion in 95% alcohol and then stained with the Papanicolaou stain. The cell-block material was processed by fixation in 10% neutral buffered formalin solution and then embedded in paraffin to be handled as a routine tissue block. Thin sections from paraffin-embedded cell blocks were cut and then stained with hematoxylin and eosin. A provisional diagnosis was first assigned with the cytology smear, and then cell blocks were stained by IHC staining if indicated.

For lesions diagnosed with EUS-FNA cytology as spindle cell tumors, IHC stain preparations were assembled in cell-block specimens. The Avidin Biotin Complex (ABC; VECTASTAIN, Vector Laboratories Ltd, California, USA) was used with the following antibodies: c-kit (Dako Inc., California, USA), CD34 (Novocastra, Leica Microsystems Ltd., Newcastle Upon Tyne, UK), S-100 (Mie University laboratories, Aichi, Japan; noncommercial), and Actin (Nichirei Bioscience Inc., Tokyo, Japan). The results of IHC staining were described as positive or negative. Positive IHC staining was defined as staining of >50% of the tumor cells. Negative IHC staining was defined as either focal positivity or staining of <50% of the tumor cells. A

diagnosis of GIST was made by positive c-kit staining, with or without positive CD34 IHC staining. Leiomyoma and leiomyosarcoma were diagnosed by positive actin staining and schwannomas by positive S-100 staining.

Study definitions

For the overall diagnostic yield, the procedure results were categorized as the following: (1) diagnostic, if sufficient samples were obtained for cytology, cell-block preparation, and IHC staining, if needed, and a specific diagnosis could be established, (2) suggestive, if sufficient samples were obtained for cytology, and a suggestive primary diagnosis was assigned, but samples were inadequate for IHC staining, and/or a definitive final diagnosis was not achieved, and (3) nondiagnostic, if samples were primarily insufficient, and/or the results were discordant with the criterion standard.

The results of EUS-FNA and the final diagnosis were categorized into 2 groups: (1) malignant or potentially malignant group, including all GISTs, malignant lymphomas, and gastric wall carcinomas, and (2) benign group, including leiomyomas, schwannomas, gastric desmoid tumors, ectopic pancreatic tissues, benign inflammatory granulomas, glomus tumors, and lipomas. We considered all GISTs as potentially malignant, in accordance with the National Institutes of Health consensus statement.[8,9]

The criterion standard for final diagnosis was either the surgical histopathological results for resected specimens or the clinical management and follow-up course for malignant, inoperable cases.

Statistical analysis

Frequencies, percentages, and means were used, as appropriate, for descriptive analysis. Univariate and a multivariate logistic regression analysis were performed to assess the significant predictors of obtaining sufficient specimens (insufficient versus sufficient samples). All statistical analysis was conducted by using SPSS software for Windows, release 11 (SPSS Inc, Chicago, Ill). A P value of $< .05$ was considered significant.

RESULTS

A total of 141 consecutive patients with SMTs of the stomach, who fulfilled our inclusion criteria, were identified. Fifty-two percent were women, and the mean (± SD) age of the patients was 56.7 years ± 14.4 years. Over 87.8% of the patients were asymptomatic, and the SMTs were discovered incidentally. The mean (± SD) diameter of the SMTs was 29.9 mm (± 16.0 mm; range 6-90 mm). The characteristics of the 141 gastric SMTs, including their locations, endoscopic characteristics, sizes, layers of origin, and echo patterns, are summarized in Table 1.

Among the 141 cases, 69 (48.9%) had a definitive final diagnosis (67 cases were surgically resected, and 2 cases were proved on follow-up to be malignant lymphomas).

TABLE 1. Endoscopic and EUS characteristics of gastric submucosal lesions (n = 141)

Characteristic	No. (%)
Location within the stomach	
Cardia	30 (21.3)
Fundus	45 (31.9)
Body	29 (20.6)
Antrum	31 (22)
Pyloric canal	6 (4.3)
Endoscopic characteristics	
Smooth mucosa	92 (65.2)
Mucosal ulceration	11 (7.8)
Umbilication	10 (7.1)
Multinodular lesion	24 (17)
Multiple lesions*	4 (2.8)
Size	
<20 mm	34 (24.1)
20-50 mm	90 (63.8)
>50 mm	17 (12.1)
EUS layer of origin	
Third layer (submucosa)	21 (14.9)
Fourth layer (muscle)	108 (76.6)
Extragastric	5 (3.5)
Undetermined	7 (5)
Echo pattern	
Homogeneous-hypoechoic	65 (46.1)
Homogeneous-hyperechoic	3 (2.1)
Heterogeneous	73 (51.8)
Other characteristics	
Presence of cystic spaces	20 (14.1)
Adjacent lymphadenopathy	5 (3.5)
Irregular border	31 (22)

*Only the largest lesion was included in the analysis.

Of the remaining cases, 63 (44.6%) were followed-up without surgical resection for at least 12 months, and 9 cases (6.5%) were lost to follow-up. The mean number of FNA passes was 2.5 (SD:0.7; range 1-5). The overall rate of sample adequacy was 83% (117 cases). Adequate samples were obtained in 67.6% of lesions with size <20 mm, 86.6% of lesions with size between 20 and 50 mm, and 94.1% of lesions with size >50 mm ($P = .01$). IHC staining

TABLE 2. Diagnostic yield of EUS-FNA and its presumptive pathological diagnosis in patients with gastric submucosal tumors (n = 141)

	Sufficient samples (n = 117; 83%)					Insufficient samples (n = 24; 17%)	
	IHC stained (n = 64)			IHC not stained (n = 53)			
Diagnostic category	GIST	Leiomyoma	Schwannoma	Spindle cell tumor	Misc	Unknown	Total, no. (%)
Diagnostic	37	9	2	0	13	0	61 (43.3)
Suggestive	9	7	0	29	10	0	55 (39)
Nondiagnostic	0	0	0	0	1	24	25 (17.7)
Total, no. (%)	46 (32.6)	16 (11.3)	2 (1.4)	29 (20.6)	24 (17)	24 (17)	141 (100)

EUS-FNA, EUS-guided FNA; *IHC,* immunohistochemical; *GIST,* GI stromal tumor; *misc,* miscellaneous tumor; *CI,* confidence interval.
EUS-FNA was classified as *diagnostic* in 61 cases (43.3%; 95% CI, 35%-51%), *suggestive* in 55 cases (39%; 95% CI, 31%-47%), and *nondiagnostic* in 25 cases (17.7%; 95% CI, 12.5%-25%).

with c-kit, CD34, actin, and S-100 antibodies were done on cell-block samples in 64 of 141 cases (45.6%) in which cytological evaluation showed a spindle cell tumor. There were no serious procedure-related complications.

Diagnostic yield of EUS-FNA

The EUS-FNA diagnosis was classified as *nondiagnostic, suggestive*, or *diagnostic* in 25 (17.7%), 55 (39%), and 61 (43.3%) cases, respectively.

Of the 25 cases classified as *nondiagnostic*, EUS-FNA failed to provide adequate samples in 24 cases (1 each of lipoma and desmoid tumor, which were resected, 13 that were followed-up, and 9 that were lost to follow-up). One GIST case, which was eventually resected, was misdiagnosed as benign inflammatory granuloma by EUS-FNA.

All of the 55 cases classified as *suggestive* had adequate FNA sampling but a lack of criterion standard diagnosis for final reference. In 16 of the 55 cases, the specimens were adequate for IHC staining and were given a diagnosis of GIST (9 cases) and leiomyoma (7 cases) after EUS-FNA. However, because these patients did not undergo surgical resection, we conservatively classified them as *suggestive*. In the remaining 39 cases, IHC staining was not done. In 29 of these cases, spindle cell tumor was found on cytology, but the cell-block specimens were inadequate for IHC staining. Three of these 29 lesions were resected because of an increase in size on follow-up and were found to be GISTs. The remaining 10 of the 39 cases were presumptively diagnosed after EUS-FNA as 6 ectopic pancreatic tissues, 3 benign epithelioid cells suggestive of glomus or carcinoid tumors (2 of them were resected), and 1 inflammatory granuloma.

For the remaining 61 cases, EUS-FNA specimens were adequate, and a definitive final diagnosis was achieved either by surgery (59 cases) or the follow-up course for malignant, inoperable cases (2 cases of lymphoma), and the EUS-FNA results were classified as *diagnostic*. The detailed summary is shown in Table 2.

Performance characteristics of EUS-FNA

Of the 69 cases with a definite final diagnosis, 41 (59.4%) were GISTs, 9 (13%) were leiomyomas, 7 were gastric wall carcinomas, 6 were extragastric lesions (3 pancreatic tumors, 2 abdominal lymph nodes, and 1 peritoneal desmoid tumor), 2 were glomus tumors, 2 were schwannomas, 1 was a gastric inflammatory granuloma, and 1 was a lipoma. Fifty-three of the 69 SMTs (76.8%) were proven finally to be malignant lesions or potentially malignant lesions.

EUS-FNA results were concordant with the final diagnosis in 66 of 69 lesions (accuracy rate 95.6%; 95% CI, 87.5%-99%), as shown in Table 3. For the differentiation of benign from potentially malignant lesions, EUS-FNA had a sensitivity of 92.4% (95% CI, 82%-98%), specificity of 100% (95% CI, 79%-100%), positive predictive value of 100% (95% CI, 92.5%-100%), negative predictive value of 80% (95% CI, 56.3%-94%), and accuracy rate of 94.2% (95% CI, 85.6%-98.1%) (Table 4).

Factors related to sampling adequacy

Logistic regression analysis showed that a heterogeneous echo pattern of the lesion was the only independent predictor for obtaining a sufficient sample by EUS-FNA (adjusted odds ratio 0.1; 95% CI, 0.02-0.4; $P = .002$). Other factors such as the size of the mass, the long axis location within the stomach, the number of needle passes, and EUS layer of origin were not significant (Table 5).

DISCUSSION

Gastric SMT is an umbrella term that encompasses both neoplastic and nonneoplastic lesions.[1-3] Once the lesions are viewed endoscopically, the main challenge is to distinguish the potentially malignant SMTs from their benign counterparts.[3,8] The reported yield of EUS-FNA cytology for the diagnosis of SMTs is less than that

TABLE 3. Comparison of EUS-FNA diagnosis with the final diagnosis of gastric submucosal tumors (n = 69)

	EUS-FNA diagnosis no. (%)	Final diagnosis no. (%)
GIST*	37 (53.6)	41 (59.4)
Leiomyoma	9 (13)	9 (13)
Spindle cell tumor	3 (4.3)	0
Schwannoma	2 (2.9)	2 (2.9)
Gastric carcinoma	7	7
Pancreatic tumor	3	3
Desmoid tumor	0	1
Extragastric lymphoma	2	2
Glomus tumor†	2	2
Lipoma	0	1
Inflammatory granuloma	2	1
Unknown (insufficient)‡	2	0

EUS-FNA, EUS-guided FNA; *GIST,* GI stromal tumor.
The final diagnosis was achieved by surgery (67 cases) and follow-up for inoperable cases (2 extragastric malignant lymphomas). The diagnosis was concordant in 66 lesions or 95.6%. Sixty-one were diagnostic, and 5 were suggestive diagnoses. The diagnosis was discordant (nondiagnostic) in 3 lesions or 4.3%.
*GIST cases (n = 41): 37 correctly diagnosed; 1 lesion was a primary inflammatory granuloma (nondiagnostic), and 3 were benign spindle cell tumors (suggestive).
†Two glomus tumors were suspected in FNA specimens as benign vascular epithelioid cell tumors (suggestive).
‡There were 2 nondiagnostic (insufficient) FNA specimens; 1 was a lipoma and the other a desmoid tumor.

TABLE 4. Performance characteristics of EUS-FNA for differentiating benign from malignant (or potentially malignant) gastric submucosal tumors

	Final diagnosis	
EUS-FNA diagnosis	Benign	Malignant
Benign	16 (TN)*	4 (FN)†
Malignant	0 (FP)	49 (TP)

EUS-FNA, EUS-guided FNA; *TN,* true negative; *FN,* false negative; *FP,* false positive; *TP,* true positive.
*The 2 insufficient cases and the 2 cases of glomus tumor were treated as TN cases.
†Of the 4 FN cases, the EUS-FNA diagnosis was spindle cell tumor in 3 cases and benign inflammatory granuloma in 1 case; all proved to be GI stromal tumors after resection.

for other targets, and previous studies have been limited by small patient numbers, lack of a defined criterion standard, and a limited spectrum of lesions.[2,5-7,11-18] Ando et al[4] examined 49 submucosal tumors, with 91.8% adequate samples. Twenty-three lesions were surgically resected (20 were GISTs), and their accuracy rate was 95%. Arantes et al[17] studied 10 SMTs with 80% sampling adequacy, and GIST was suggested in 6 cases (60%). Vander Noot et al[18] also reported a 94.4% sampling adequacy rate with 18 GISTs, but it was unclear whether or not these results were confirmed surgically. Recently, Hoda et al[16] described the yield of EUS-FNA in 112 upper GI SMTs as diagnostic, suspicious (spindle cells), and nondiagnostic in 61.6%, 22.3%, and 16.1% of cases, respectively, with an overall accuracy rate of 84%. However, their study also lacked the final criterion standard reference. Accordingly, it may be difficult to calculate a weighted average accuracy for EUS-FNA in these studies because of their varied inclusions and designs. Some reviews mentioned a weighted average accuracy rate of EUS-FNA as 60% to 80%, but their pooled studies were concerned mainly with GISTs.[2,4,12]

In our study, we reported an accuracy rate of 95.6% in achievement of a concordant diagnosis and 94% in detecting malignant lesions, with a sensitivity and specificity of 92.4% and 100%, respectively. On-site cytological analysis as well as our recruiting design may have contributed to these relatively high figures. We not only reported a high rate of sampling adequacy (83%), with a mean number of 2.5 passes, but also we demonstrated that both cytology and cell-block processing were possible with the use of standard, 22-gauge, FNA needles. As expected, there was an increase in sampling adequacy with increasing size of the SMT, with a 95% yield with lesion size of >50 mm. Similar findings were reported by Akahoshi et al,[15] who had a 100% yield of EUS-FNA with lesion size of >40 mm. For SMTs, a 22-gauge, FNA needle is thought to be enough to obtain sufficient samples for cell-block preparations and then IHC staining, which is very useful for diagnosing the SMT subtypes and, hence, should become routine practice in sampling these lesions.

A large proportion of our gastric SMTs were found to be malignant (76.8%). This high percentage may be an overrepresentation, likely because our design may have led to a selection bias of higher-risk cases referred for surgery. In agreement with numerous previous reports, we found that GISTs were the most common SMT in the stomach, and only 40% of the gastric SMTs were not GISTs.[2-5,11-19] GISTs have a wide spectrum of risk behavior—from small, indolent tumors to overt sarcomas.[2,3,7-9] Nevertheless, it is this unpredictable behavior that leads many experts to recommend that every GIST should be considered as potentially malignant and therefore be resected.[2,3,8,9] Hence, it is very important to apply tools that help in differentiating GISTs from other benign SMTs, such as the implementation of IHC staining panels.[4,6,7] In our study, spindle cell tumors comprise the vast majority of our EUS-FNA diagnoses (93 of 141 lesions).[4,6,7] We used a directed IHC staining panel with c-kit, CD34, actin, and S-100 antibodies for differentiating spindle cell tumors into leiomyoma, schwan-

TABLE 5. Summary of univariate and multivariate analyses of factors associated with EUS-FNA sampling adequacy

Variable	Univariate analysis* *P* value	Multivariate analysis† *P* value (adjusted OR; 95% CI)
SMT location within the stomach	.572 NS	–
Tumor size on EUS (<20 mm vs ≥20 mm)	.022	.14 (0.46; 95% CI, 0.16-1.3)
EUS layer of origin	.489 NS	–
EUS echo pattern (homogenous vs heterogeneous)	.001	.002 (0.1; 95% CI, 0.02-0.4)
No. needle passes (≤2 vs >2)	.427 NS	–

EUS-FNA, EUS-guided FNA; *OR,* odds ratio; *CI,* confidence interval; *SMT,* submucosal tumor; *NS,* not significant.
*Chi-square test.
†Multivariate logistic regression analysis (insufficient vs sufficient sample).

noma, and GIST. Sixty-four spindle cell lesions were adequately stained for these antibodies, and of them, only 48 cases were counted for accuracy calculations because they had a definitive final diagnosis. Other IHC stains may be needed in selected cases, such as chromogranin, synaptophysin, and keratin in carcinoid tumors and calponin in glomus lesions.[6,7]

On evaluating the predictors for sampling adequacy, only a heterogeneous echo pattern was found significant in a multivariate analysis. It may be possible that the higher cellularity and proliferation rate are related to a more heterogeneous echo pattern. In contrast, Hoda et al[16] have previously reported that there were no identifiable factors that affected the yield of EUS-FNA.

We categorized our results into *diagnostic*, *suggestive*, and *nondiagnostic*, because previous reports have variably interpreted positive IHC staining results, especially for GISTs. Some authors are conservative, considering them as suggestive tools only, and their rationale is the presence of staining heterogeneity.[17,20,21] Others trust IHC results and rely upon them for treatment decision making.[5-7] We followed the former conservative approach and used a well-characterized criterion standard for final diagnosis to allow for robust conclusions. Because the cases used to calculate the performance characteristics of EUS-FNA in the present series were definitively diagnosed, our results may serve as a benchmark for future interventions. The main shortcoming of the present study is its retrospective nature and the potential for bias in selecting patients who were referred for surgery or chemotherapy. The strength of this study is the large number of gastric SMTs with EUS-FNA sampling and a well-defined criterion standard.

Based our results, we recommend a short algorithmic approach for the diagnosis of gastric SMTs. An initial EUS can rule out extraluminal, hyperechoic, and third-layer (submucosal) lesions. For hypoechoic lesions that originate from the fourth (muscle) layers, EUS-FNA should be performed even for small lesions, and IHC stains with a panel of CD34, c-kit, actin, and S-100 should be done if spindle cells are found.

In conclusion, EUS-FNA with 22-gauge needles is an accurate and safe method for diagnosing gastric SMTs and for delineating malignant lesions with the adjunctive and selective use of a limited panel of IHC stains.

REFERENCES

1. Hedenbro JL, Ekelund M, Wetterberg P. Endoscopic diagnosis of submucosal gastric lesions: the results after routine endoscopy. Surg Endosc 1991;5:20-3.
2. Polkowski M. Endoscopic ultrasound and endoscopic ultrasound guided fine-needle biopsy for the diagnosis of malignant submucosal tumors. Endoscopy 2005;37:635-45.
3. Miettinen M, Lasota J. Gastrointestinal stromal tumors: definition, clinical, histological, immunohistochemical, and molecular genetic features and differential diagnosis. Virchows Arch 2001;438:1-12.
4. Ando N, Goto H, Niwa Y, et al. The diagnosis of GI stromal tumors with EUS-guided fine needle aspiration with immunohistochemical analysis. Gastrointest Endosc 2002;55:37-43.
5. Matsui M, Goto H, Niwa Y, et al. Preliminary results of fine needle aspiration biopsy histology in upper gastrointestinal submucosal tumors. Endoscopy 1998;30:750-5.
6. Yamaguchi U, Hasegawa T, Masuda T, et al. Differential diagnosis of gastrointestinal stromal tumor and other spindle cell tumors in the gastrointestinal tract based on immunohistochemical analysis. Virchows Arch 2004;445:142-50.
7. Stelow EB, Murad FM, Debol SM, et al. A limited immunocytochemical panel for the distinction of subepithelial gastrointestinal mesenchymal neoplasms sampled by endoscopic ultrasound–guided fine-needle aspiration. Am J Clin Pathol 2008;129:219-25.
8. Fletcher CD, Berman JJ, Corless C, et al. Diagnosis of gastrointestinal stromal tumors: a consensus approach. Hum Pathol 2002;33:459-65.
9. Joensuu H. Risk stratification of patients diagnosed with gastrointestinal stromal tumor. Hum Pathol 2008;39:1411-9.
10. Chak A. EUS in submucosal tumors. Gastrointest Endosc 2002;56:S43-S48.
11. Hunt GC, Smith PP, Faigel DO. Yield of tissue sampling for submucosal lesions evaluated by EUS. Gastrointest Endosc 2003;57:68-72.
12. Polkowski M, Gerke W, Jarosz D, et al. Diagnostic yield and safety of endoscopic ultrasound guided trucut biopsy in patients with gastric submucosal tumors: a prospective study. Endoscopy 2009;41:329-34.
13. Okubo K, Yamao K, Nakamura T, et al. Endoscopic ultrasound guided fine-needle aspiration biopsy for the diagnosis of gastrointestinal stromal tumors in the stomach. J Gastroenterol 2004;39:747-53.

14. Chen VK, Eloubeidi MA. Endoscopic ultrasound-guided fine-needle aspiration of intramural and extraintestinal mass lesions: diagnostic accuracy, complication assessment, and impact on management. Endoscopy 2005;37:984-9.
15. Akahoshi K, Sumida Y, Matsui N, et al. Preoperative diagnosis of gastrointestinal stromal tumor by endoscopic ultrasound-guided fine needle aspiration. World J Gastroenterol 2007;13:2077-82.
16. Hoda KM, Rodriguez SA, Faigel DO. EUS-guided sampling of suspected GI stromal tumors. Gastrointest Endosc 2009;69:1218-23.
17. Arantes V, Logrono R, Faruqi S, et al. Endoscopic sonographically guided fine-needle aspiration yield in submucosal tumors of the gastrointestinal tract. J Ultrasound Med 2004;23:1141-50.
18. Vander Noot MR III, Eloubeidi MA, Chen VK, et al. Diagnosis of gastrointestinal tract lesions by endoscopic ultrasound-guided fine-needle aspiration biopsy. Cancer 2004;102:157-63.
19. Chatzipantelis P, Salla C, Karoumpalis I, et al. Endoscopic ultrasound-guided fine needle aspiration biopsy in the diagnosis of gastrointestinal stromal tumors of the stomach: a study of 17 cases. J Gastrointest Liver Dis 2008;17:15-20.
20. Liegl B, Kepten I, Le C, et al. Heterogeneity of kinase inhibitor resistance mechanisms in GIST. J Pathol 2008;216:64-74.
21. Medeiros F, Corless CL, Duensing A, et al. KIT-negative gastrointestinal stromal tumors: proof of concept and therapeutic implications. Am J Surg Pathol 2004;28:889-94.