

# Evaluation of Gastrointestinal Subepithelial Lesions Examined Using Endoscopic Ultrasonography: A Single-Center Experience

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## Abstract

**Objective:** Diagnosing and managing the treatment of gastrointestinal subepithelial lesions are often difficult for the clinician. The study aimed to investigate the contribution of endoscopic ultrasonography to the diagnosis of gastrointestinal subepithelial lesions and determine their potential for malignancy.

**Methods:** A total of 170 patients who underwent endoscopic ultrasonography with the suspicion of subepithelial lesions after upper gastrointestinal endoscopy or abdominal imaging between March 2009 and December 2019 were included in the study.

**Results:** In 170 patients who underwent endoscopic ultrasonography for gastrointestinal subepithelial lesions, the preliminary diagnosis was leiomyoma in 87 (51.2%) patients, gastrointestinal stromal tumor in 32 (18.8%), lipoma in 27 (15.9%), ectopic pancreas in 13 (7.6%), neuroendocrine tumor in 10 (5.8%), and cyst in 1 (0.6%) patient. The most common location of subepithelial lesions was the stomach (67.1%), and the most common origin of these lesions was the muscularis propria (47.1%). Among patients with pathological biopsy samples, 71.1% were accurately diagnosed using endoscopic ultrasonography. The percentages of an accurate diagnosis for different diseases were 94.4% for gastrointestinal stromal tumors, 81.8% for leiomyoma, and 75% for neuroendocrine tumors. Among the criteria used for establishing the preliminary diagnosis of gastrointestinal stromal tumor using endoscopic ultrasonography and determining the possibility of lesion malignancy, the most frequently used criteria with the highest sensitivity were lesion size >3 cm and the presence of cystic space. However, the specificity of the combination of the criteria that were less frequently used, such as irregular borders, ulceration, and the presence of necrotic focus, was 100%.

**Conclusion:** Endoscopic ultrasonography and endoscopic ultrasonography-fine-needle aspiration biopsy are the still most sensitive methods for the diagnosis of subepithelial lesions.

**Keywords:** Endoscopic Ultrasonography, Gastrointestinal Stromal Tumors, Gastrointestinal Subepithelial Lesions

## INTRODUCTION

The term “subepithelial lesion” (SEL) is often used to describe lesions covered with normal mucosa, which are incidentally detected during upper gastrointestinal endoscopy.<sup>1,2</sup> Most patients with gastrointestinal SEL are asymptomatic and are often incidentally diagnosed via imaging techniques that are performed for other reasons.<sup>3</sup> The characterization and management of gastrointestinal SEL are difficult, and treatment options range from surgical resection of malignant lesions to follow-up of benign lesions.<sup>1,4</sup> Therefore, the accurate classification of gastrointestinal SEL is crucial. To choose the appropriate treatment, it is extremely important to identify suspicious characteristics that indicate malignancy.<sup>1</sup>

Except for the cases of large lipoma or gastrointestinal stromal tumors (GIST) and tumors with metastatic spread, several non-invasive imaging modalities, such as transabdominal ultrasonography (USG), computed tomography (CT), and magnetic resonance imaging, are generally inadequate to characterize lesions.<sup>5,6</sup> Endoscopic ultrasonography (EUS) distinguishes SEL from the extramural structures, which are often confused with SEL in gastrointestinal endoscopy, by clearly showing the layers of the gastrointestinal tract. Moreover, it determines the layers from which these lesions originate as well as their endosonographic properties.<sup>1,7</sup> Further, EUS suggests the malignancy potential of these lesions by

providing some typical appearance characteristics.<sup>6,7</sup> Endoscopic ultrasonography studies that were successful in predicting the pathological diagnosis of SELs have reported a diagnostic accuracy ranging from 50% to 79%.<sup>5,8-11</sup>

The current follow-up and management algorithm of upper gastrointestinal tract SELs are based on the pathology results of the operations conducted on patients due to the risk of malignancy. As per these findings, it was determined that EUS/EUS-fine-needle aspiration biopsy (FNAB) alone is not sufficient for the diagnosis of upper gastrointestinal tract SELs, and further auxiliary imaging methods are needed.

The study aimed to detect gastrointestinal SELs using EUS and to evaluate the correlation between the EUS/EUS-FNAB and pathology results of the patients who were operated on, thus demonstrating the reliability of EUS both in diagnosis and determination of the malignancy potential of gastrointestinal SELs.

## METHODS

Patients aged  $\geq 18$  years who underwent endoscopic USG with suspected SEL after upper GIS endoscopy or abdominal imaging between March 2009 and December 2019 at the Department of Gastroenterology in Dokuz Eylul University Medical Faculty Hospital were included in the study. Sample size was not calculated. All patients who were diagnosed with SEL using EUS were included in the study. Approval for the study was obtained from the ethics committee of Dokuz Eylul University Faculty of Medicine Non-Invasive Clinical Studies (Date: January 28, 2019, Decision No: 2019/01-142). All patient information was kept confidential, and the study was conducted according to the principles of the Declaration of Helsinki. Figure 1 shows the inclusion algorithm of patients.

The demographic characteristics of the patients, radiological or EUS appearance reports of SELs, cytopathological diagnoses of patients who underwent EUS-FNAB/endoscopic biopsy, type of surgical operation, and postoperative pathological results of patients operated for SEL were analyzed retrospectively in Probel, the hospital registry system. The ability of CT to detect SEL and diagnostically distinguish between surgical pathology diagnoses and its ability to evaluate recurrence in operated patients were examined.

All EUS/EUS-FNAB evaluations were performed by 2 experienced gastroenterologists in Dokuz Eylul University Faculty Hospital of Medicine Internal Medicine Gastroenterology Department using Fujinon radial echoendoscope. The size, localization, number, layer of origin, echogenicity, and malignancy markers (border regularity, cystic space, calcification, size assessment, presence of adjacent lymph node, heterogeneity, mucosal ulceration, and presence of necrotic focus) of the SELs detected during EUS were investigated, and the lesions were accurately defined. A linear EUS (Fujinon EG-53UT) device was used for biopsy. Fine-needle aspiration biopsy was performed using needles of 19 or 22 Gy. Endoscopic ultrasonography-fine-needle aspiration biopsy was performed in 39 (22.9%) patients in the study group, and the samples were sent to the pathology laboratory. The biopsy materials were placed on slides, air-dried or fixed with alcohol, stained with May–Grunwald Giemsa or Papanicolaou, and evaluated. Lesions obtained using forceps biopsy and endoscopic mucosal resection (EMR) were stored in formol for 6 hours and then processed and kept in the tracing device. Sections were obtained from the samples and stained with hematoxylin–eosin. Immunohistochemical staining was also performed when necessary.

## Statistical Analysis

Statistical Package for the Social Sciences version 22.0. (IBM SPSS Corp.; Armonk, NY, USA) was used for data analysis. Categorical data were presented as numbers and percentages, whereas numerical data were presented as mean  $\pm$  standard deviation (minimum value–maximum value). The distribution of numerical variables was evaluated using Kolmogorov–Smirnov test and Kurtosis and Skewness coefficients. The data were assumed to be normally distributed if the coefficients were between  $-1.5$  and  $+1.5$ . The change in lesion size was evaluated using the dependent samples *t* test and Wilcoxon signed-rank test. To identify lesions, diagnostic tests were used to compare EUS and pathology results, and the sensitivity, specificity, positive predictive value, negative predictive value, false-positive rate, and false-negative rate were calculated.

## RESULTS

Of the 170 patients who underwent EUS due to gastrointestinal SELs, 59.4% were females ( $n=101$ ), 40.6% were males ( $n=69$ ), and the mean age was  $55.7 \pm 12.4$  years (26-91). Mean SEL size was  $1.6 \pm 1.3$  cm (0.4-10). In 170 patients who underwent EUS for gastrointestinal SELs, the preliminary diagnosis was leiomyoma in 87 (51.2%) patients, GIST in 32 (18.8%), lipoma in 27 (15.9%), ectopic pancreas in 13 (7.6%), neuroendocrine tumor in 10 (5.8%), and cyst in 1 (0.6%) patient. The localization, mean size, and the most common types of SELs are summarized in Table 1. The most common localization of SELs was the corpus. The most common layer of origin was the fourth layer, muscularis propria (47.1%), followed by the second layer, muscularis mucosa (24.7%), and the third layer, submucosa (18.8%).

Overall, 34.1% of the cases underwent FNAB using endoscopic methods, forceps biopsy, or EMR. In patients who underwent biopsy via endoscopic method, pathological sampling was performed using EUS-FNAB in 67.2%, forceps in 20.7%, and endomucosal resection in 10% of the patients. No complications were observed during the procedures. According to these results, the most common diagnoses in endoscopic biopsy pathology were GIST and leiomyoma. The distribution of other pathological diagnoses is presented in Table 2.

In cases with consistent EUS prediagnosis and pathology results, EUS led to accurate diagnosis in 71.1% of the patients. Overall, 12.4% ( $n=21$ ) of all cases were operated. Two of the 21 patients who were operated on did not undergo endoscopic biopsy. In 19 patients with both endoscopic and excisional biopsy, the consistency between endoscopic biopsy and excisional biopsy was 100%.

Endoscopy and/or CT imaging was performed in 41.1% of 170 patients with SEL. Both endoscopy and CT follow-up were performed in

**Table 1. Localization of Lesions in the Gastrointestinal Tract, Lesion Size, and the Most Common Subepithelial Lesion Types**

Lesion Localization	n (%)	Size, cm (mean)	Most Commonly Encountered SEL (%)
Corpus	54 (31.8)	$1.95 \pm 0.25$	Leiomyoma (51.0)
Antrum	43 (25.3)	$1.40 \pm 0.14$	Lipoma (34.8)
Esophagus	38 (22.4)	$1.40 \pm 0.19$	Leiomyoma (89.4)
Duodenum	13 (7.6)	$1.69 \pm 0.30$	Lipoma (46.1)
Cardiac	9 (5.3)	$1.88 \pm 0.30$	Leiomyoma (77.7)
Fundus	6 (3.5)	$0.90 \pm 0.20$	Leiomyoma (100.0)
Bulbus	5 (2.9)	$1.10 \pm 0.10$	Leiomyoma (60.0)
Pylorus	2 (1.2)	$1.50 \pm 0.50$	Ectopic pancreas (50.0)

SEL, subepithelial lesions.

**Table 2. Results of Biopsies Obtained Using Endoscopic Methods**

Biopsy Type	Pathological Diagnosis	n (%)
Lesions detected using EUS-FNAB	GIST	16 (41)
	Insufficient	7 (17.9)
	Leiomyoma	11 (28.2)
	Malignancy, metastasis	4 (10.2)
	Schwannoma	1 (2.9)
	Total	39 (100.0)
Lesions detected using forceps biopsy	GIST	1 (8.3)
	Insufficient	8 (66.6)
	Granular cell tm	1 (8.3)
	NET	2 (16.8)
	Total	12 (100.0)
Lesions detected using EMR	NET	2 (33.6)
	Insufficient	1 (16.6)
	Inflammatory fibroid polyp	1 (16.6)
	Lipoma	1 (16.6)
	Adenomatous polyp	1 (16.6)
	Total	6 (100.0)

EUS-FNAB, endoscopic ultrasonography-fine-needle aspiration biopsy; GIST, gastrointestinal stromal tumors; NET, neuroendocrine tumor; EMR, endoscopic mucosal resection.

13 of these patients. Twenty-two patients (12.9%) were followed up only using CT, and 61 patients (35.9%) were followed up only using endoscopy.

Patients who underwent endoscopic mucosal resection, polypectomy, or surgery were followed up for an average of  $10.4 \pm 3.8$  months. Recurrence was detected in only 1 patient. This patient with a neuroendocrine tumor (0.4-cm lesion with corpus localization) had previously undergone EMR. A total of 43 patients who were not operated on and monitored with a preliminary diagnosis of benign lesions were followed up for an average of  $14.9 \pm 3$  months. The average initial size of the lesions was  $1.15 \pm 0.6$  cm, whereas the average final size was  $1.2 \pm 0.6$  cm ( $P < .05$ ). The size did not change in 60% of the lesions and increased in 30% of the lesions. Nine of the 13 lesions that showed an increase in size were cases of leiomyoma (69.2%).

#### Results of Patients with Gastrointestinal Stromal Tumor Prediagnosis Performed Using Endoscopic Ultrasonography

Overall, 43.8% of patients with the prediagnosis of GIST performed using EUS ( $n = 32$ ) were females and the mean age was 60.9 (31-91)

**Table 3. Localization and Size of Lesions in Patients Diagnosed with GIST Using EUS**

Lesion Localization	n (%)	Size (cm) (mean)
Corpus	17 (53.1)	$1.95 \pm 0.25$
Antrum	7 (21.9)	$1.40 \pm 0.14$
Esophagus	4 (12.5)	$1.40 \pm 0.19$
Duodenum	3 (9.4)	$1.69 \pm 0.30$
Cardiac	1 (3.1)	$1.88 \pm 0.30$

EUS, endoscopic ultrasonography; GIST, gastrointestinal stromal tumors.

**Table 4. Diagnostic Value of EUS in the Diagnosis of GIST**

	Sensitivity	Specificity	False-Positive	False-Negative	Positive Predictive Value	Negative Predictive Values
Detection of GIST using EUS	94.4%	66.7%	34.6%	5.3%	65.4%	94.7%

EUS, endoscopic ultrasonography; GIST, gastrointestinal stromal tumors.

years. The average lesion size was  $3.5 \pm 0.3$  cm (1.5-10). The localization of the lesions in the gastrointestinal system is shown in Table 3.

Biopsy was performed using endoscopic method (FNAB+forceps+EMR) in 28 of 32 patients with the prediagnosis of GIST performed using EUS. Biopsy samples obtained from 4 patients were insufficient. Endoscopic biopsy results indicated GIST in 16 (57.1%) of the total patients with the prediagnosis of GIST. Two patients without endoscopic biopsy samples were operated on because EUS images were consistent with typical GIST and showed malignant characteristics. Gastrointestinal stromal tumor was detected in one patient and gangliocytic paraganglioma was detected in the other patient. Therefore, in 17 (56.6%) of the 30 patients with the prediagnosis of GIST performed using EUS, where the pathology results were obtained using sufficient biopsy samples, the diagnosis was found to be GIST. Of the 19 lesions that were suspected to be SELs using EUS and subsequently sampled, only 1 was diagnosed with GIST. In other words, GIST was accurately diagnosed using EUS at a rate of 94.4% compared with pathology results, which is the definitive diagnostic method. Furthermore, the absence of GIST was accurately diagnosed using EUS at a rate of 66.7% compared with pathology results (Table 4).

The most common feature detected during the preliminary diagnosis of GIST using EUS was lesion size  $>3$  cm. Other EUS characteristics are presented in Table 5. In lesions exhibiting multiple criteria for GIST diagnosis using EUS, the most common combination was lesion size  $>3$  cm and the presence of cystic space (21.8%). This was followed by the combination of calcification and lesion size  $>3$  cm (Table 6).

#### Results of Patients with the Prediagnosis of Leiomyoma Performed Using Endoscopic Ultrasonography

Of the patients with the prediagnosis of leiomyoma performed using EUS, 64.4% ( $n = 87$ ) were females, and the mean age was 55.2 (32.79) years. The mean lesion size was  $1.15 \pm 0.6$  cm (0.44-3). Lesions were localized in the esophagus in 36.7% and gastric corpus in 32.1% of the patients. Overall, 58.6% of the lesions diagnosed with leiomyoma using EUS originated from the muscularis propria and 41.4% from the muscularis mucosa. Of the 32 lesions originating from the esophagus,

**Table 5. Incidence of GIST Diagnosis Parameters Detected in EUS**

GIST Diagnosis Parameters Detected in EUS	(%)
Lesion $>3$ cm	56.2
Irregular borders	6.2
Calcification	25
Heterogeneity	25
Cystic space	43.7
Extraluminal spread	6.2
Ulceration	3.1
Necrotic focus	3.1
Lymph node	0

EUS, endoscopic ultrasonography; GIST, gastrointestinal stromal tumors.

**Table 6. Diagnostic Power of Combination of GIST Detection Parameters in EUS**

GIST Detection Parameters in EUS	Co-occurrence, %	Sensitivity (N, %)	Specificity (N, %)	Positive Predictive Value (N, %)	Negative Predictive Value (N, %)
Lesion > 3 cm +cystic space	21.8	27.7	92.5	71.4	65.7
Calcification+lesion > 3cm	15.6	22.2	96.2	80	65
Cystic space+calcification	12.5	20	100	100	64
Lesion > 3 cm+heterogeneity	12.5	20	100	100	64
Calcification+heterogeneity	6.25	5.5	96.2	50	60.4
Cystic space+heterogeneity	12.5	16.6	96.2	75	63.4

EUS, endoscopic ultrasonography; GIST, gastrointestinal stromal tumors.

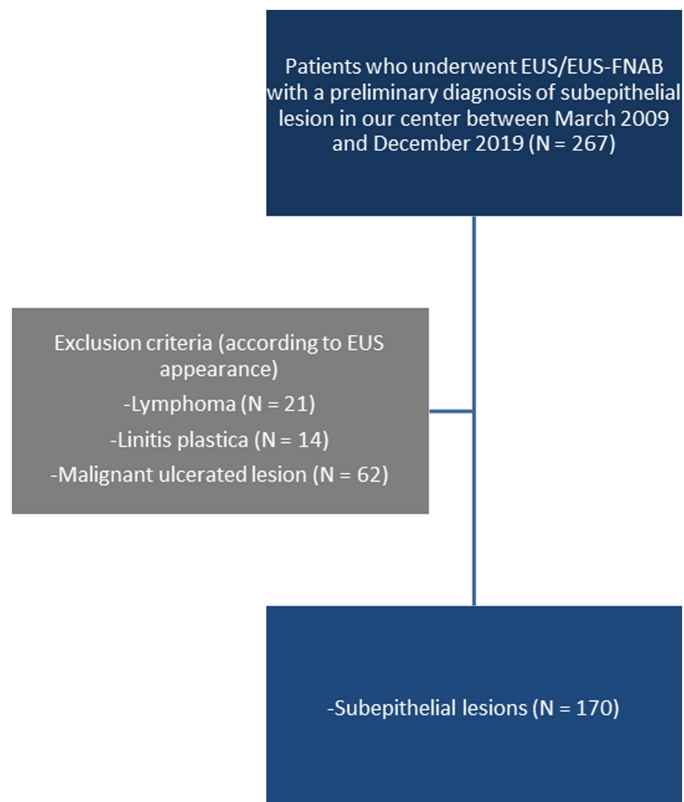
65.4% originated from the muscularis mucosa and 73.4% of gastric leiomyomas originated from the muscularis propria.

Endoscopic biopsy was performed in 18 of the 87 patients with the prediagnosis of leiomyoma performed using EUS. In 50% of these patients, pathology results were confirmed as leiomyoma according to the EUS prediagnosis. Of the 34 lesions with the prediagnosis of non-leiomyoma SEL performed using EUS, only 2 were diagnosed with leiomyoma according to the pathology results. In other words, leiomyoma was accurately diagnosed using EUS at a rate of 81.8% compared with pathology results, which is the definitive diagnostic method. Furthermore, the absence of leiomyoma was accurately diagnosed at a rate of 94.1% compared with pathology results. In 29 patients, leiomyoma was followed up with endoscopy/EUS for an average of  $16.9 \pm 3$  months. The average initial size of the lesions was  $1 \pm 0.1$  cm, whereas the average final size was  $1.1 \pm 0.1$  cm. As the number of patients was insufficient, no significant results could be obtained for the evaluation of size change ( $P > .05$ ).

## DISCUSSION

In the management of gastrointestinal SELs, it is important to determine the type of lesion and whether the lesions have malignancy potential. To assess this, clinical, radiological, and endosonographic examinations and pathology results are used. Standardization of treatment plan, cost-effective disease management, avoiding unnecessary invasive procedures, and standardization of effective follow-up of lesions are extremely important for SELs. From this perspective, when we reviewed the data of the patients with the prediagnosis of SEL performed using EUS, it was observed that the diagnostic accuracy of EUS was 71.1%. Additionally, it was found that common appearance characteristics for GIST diagnosis using EUS had higher sensitivity than the less common characteristics. Although there are no studies on this subject in the literature, the combination of less common parameters showed high specificity.

When SELs were examined in terms of mean age of onset and gender, it was found that lesions were more common in women, contrary



**Figure 1.** Algorithm of patient inclusion.

to previous studies in the literature reporting an equal distribution between men and women.<sup>3,12</sup> However, there is no step in the mechanism of SEL formation that can explain this difference. In contrast, GISTs were equally distributed between male and female patients, which is consistent with the literature.<sup>13</sup> The mean age of the patients was  $55.7 \pm 12.4$  years, which is between the fifth and sixth decades of an individual's life when SELs and their subtypes are most commonly detected.<sup>2,3,12-17</sup> The organ where SELs were most commonly located was the stomach with 67.1%, consistent with other studies.<sup>2</sup> Similar to the results in the literature, leiomyomas are the most common lesions in the esophagus; however, in contrast with the literature, the lesion that was most commonly detected in the stomach was identified as GIST.<sup>2,18,19</sup> This may be due to the small number of patients included in the present study. In contrast with the literature, the most common SEL detected using EUS in our clinic was leiomyoma with a rate of 51.2%, and the most common prediagnosis was GIST with a rate of 18.8%.<sup>20</sup> This may again be due to the small number of patients included in the study. The most common layer of origin of the SELs was the muscularis propria (47.1%). This is consistent with the literature as the muscularis propria is the layer of origin of GIST and leiomyoma, the most common types of SELs.<sup>16,20,21</sup> It was found that 65.4% of esophageal leiomyomas originated from the muscularis mucosa, 73.4% of gastric leiomyomas originated from the muscularis propria, and duodenal lesions originated from these 2 layers equally. These results were consistent with a previous study conducted in 2003, which stated that esophageal leiomyomas predominantly originated from the muscularis mucosa and gastric and duodenal lesions predominantly originated from the muscularis propria. Further, a 2017 study reported that 62.9% of esophageal leiomyomas originated from the second layer.<sup>22,23</sup>

When patients with sufficient biopsy material obtained using endoscopic methods and/or excisional biopsy were evaluated, EUS led to accurate diagnosis in 71.1% of the patients with SELs. The diagnostic accuracy of EUS was 94.4% for GISTs, 81.8% for leiomyomas, and 75% for neuroendocrine tumors. Several studies have stated that the accuracy of EUS is between 50% and 79% for predicting the pathological diagnosis of SELs.<sup>8-11</sup> As per the study results, the accuracy of EUS performed in the present study for identifying lesions was highly similar to that of other studies.

When establishing a prediagnosis of GIST using EUS, various appearance characteristics are examined to identify the lesion and determine whether it is malignant. The sensitivity and specificity of the most common parameters in lesions, which were lesion size  $>3$  cm and the presence of cystic space, evaluated using EUS with the prediagnosis of GIST were 55%-50% and 74%-88%, respectively. The combination of less common parameters, including irregular borders, ulceration, and the presence of necrotic focus, had a sensitivity and specificity of 5.5% and 100%, respectively. The sensitivity of the extraluminal spread was 5.5% with a specificity of 96%. Based on this analysis, it was concluded that the sensitivity of the most common parameters was higher than the less common ones; however, the rare parameters were more specific. The combination of multiple parameters in some lesions helped us to evaluate the diagnostic power of different combinations. The diagnostic sensitivity of the combination of parameters was lower than that of a single parameter. However, these combinations were successful in diagnosis because of their high specificity. The combination of irregular borders, ulceration, and the presence of necrotic focus, as well as cystic space-calcification and lesion size  $>3$  cm heterogeneity, showed 100% specificity.

Only a patient who underwent EMR and polypectomy (patient underwent EMR due to neuroendocrine tumor) showed recurrence, whereas

no recurrence was observed in the remaining 20 patients (95.2%). In 3 studies that reported EMR results on neuroendocrine tumors, no recurrence was observed in any patient during their follow-up.<sup>24-26</sup> In other studies, the resection success rates were  $>90\%$  in patients with neuroendocrine tumors<sup>27</sup> and granular cell tumors.<sup>28,29</sup> For all patients who underwent EMR, lesion size  $>2$  cm, invasion, and the presence of lymphadenopathy in the surrounding area are the most important factors in treatment failure; however, these criteria were not present in our study patients.<sup>24,30-32</sup> In the lesion of the patient with recurrence, the grade of the neuroendocrine tumor was G1. Furthermore, the pathology reports did not mention tumor positivity in any resection border related to the material. Endoscopic/EUS and CT follow-ups revealed no recurrence in patients with GIST who were operated on and regularly followed up. In the literature, the incidence of recurrence varies between 39% and 63% in high-risk groups,<sup>16,33,35</sup> and between 2% and 4.5% in moderate- and low-risk groups.<sup>16,34</sup> As the location of recurrence for GIST is usually the peritoneum and/or liver, CT was also used in the follow-up of patients.<sup>35</sup>

In this study, 43 patients did not undergo surgery, polypectomy, or EMR and were regularly followed up. The average follow-up period was  $14.9 \pm 3$  months for these patients. In the literature, if the SEL is  $<2$  cm with no evidence of malignancy, regular follow-up once or twice a year using endoscopy or EUS is recommended.<sup>36,37</sup> In the present study, only 3 lesions were  $>2$  cm and EUS-FNAB results of these lesions were consistent with leiomyoma. Of the patients who needed follow-up, only 30.2% were regularly followed up. The low rate of regular follow-up was mostly due to the difficulties in applying to the hospital, reaching the health center, and patients not paying the necessary attention to the subject. Another important factor is the limited number of centers in Turkey where EUS can be performed. In the patients who were followed up, the lesion size did not change in 60% of the cases and increased in 30% of the cases ( $P < .05$ ). Of the 13 lesions that increased in size, 9 were leiomyoma cases (69.2%). The size changes in lesion subtypes could not be examined due to the small number of patients ( $P > .05$ ). No additional treatment was performed and follow-up was continued when the growth of lesions was not  $>1$  cm, no evidence of further malignancy was detected in EUS, and the patients did not develop symptoms.<sup>38</sup> Repeated endoscopic ultrasound (EUS) examinations every 6-12 months are recommended for small asymptomatic leiomyoma lesions that do not exhibit properties indicating malignancy. If there is no change within a year, follow-up intervals can be extended.<sup>39</sup>

The main limitations of the present study include the retrospective design, small number of patients, and consequently, the lack of homogeneity in the lesion subtypes to conduct a subtype analysis and measure the EUS accuracy. The most important limitations during follow-up were the difficulties that patients experienced in reaching the hospital and/or understanding the importance of follow-up and the fact that endoscopic and cross-sectional imaging studies were often not used together during follow-up.

In conclusion, EUS and EUS-FNAB are the methods with the highest sensitivity in the diagnosis of SELs in terms of evaluating the layers from which lesions originate, establishing a preliminary diagnosis and predicting malignancy. The patients should be followed up based on the biopsy results by taking into account the appearance characteristics and lesion size that were examined using EUS, or if necessary, they should be referred for surgery. The parameters with the highest sensitivity among the diagnostic criteria for predicting GIST diagnosis were lesion size  $>3$  cm and the presence of cystic space, the 2 most common parameters, whereas irregular borders, ulceration, and the presence of necrotic focus are the less common parameters but their specificity is 100%. The

combination of these parameters has lower diagnostic sensitivity than a single parameter; however, they are successful in diagnosis due to their high specificity. Regular follow-up of patients who are operated on or followed-up is crucial for detecting any recurrence, examination of changes in appearance characteristics of the lesions, and treatment planning. Further comprehensive studies can be conducted on these lesions with an increase in the number of experienced medical personnel who can perform EUS in Turkey as well as centers where EUS is available.

**Ethics Committee Approval:** Ethics committee approval was received for this study from the ethics committee of Dokuz Eylul University Hospital (Date: January 28, 2019, Decision No: 2019/01-142)

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## REFERENCES

- Eun K. Subepithelial lesions. In: Feckens P, Robert H, Shiyam V, eds. *Endosonography*. 3th ed. China: Elsevier Saunders; 2015:112-129.
- Nishida T, Kawai N, Yamaguchi S, Nishida Y. Submucosal tumors: comprehensive guide for the diagnosis and therapy of gastrointestinal submucosal tumors. *Dig Endosc*. 2013;25(5):479-489. [\[CrossRef\]](#)
- Hedenbro JL, Ekelund M, Wetterberg P. Endoscopic diagnosis of submucosal gastric lesions. The results after routine endoscopy. *Surg Endosc*. 1991;5(1):20-23. [\[CrossRef\]](#)
- Chak A. EUS in submucosal tumors. *Gastrointest Endosc*. 2002;56(4):S43-S48. [\[CrossRef\]](#)
- Thompson WM, Kende AI, Levy AD. Imaging characteristics of gastric lipomas in 16 adult and pediatric patients. *AJR Am J Roentgenol*. 2003;181(4):981-985. [\[CrossRef\]](#)
- Scatarige JC, Fishman EK, Jones B, Cameron JL, Sanders RC, Siegelman SS. Gastric leiomyosarcoma: CT observations. *J Comput Assist Tomogr*. 1985;9(2):320-327. [\[CrossRef\]](#)
- Caletti G, Zani L, Bolondi L, Brocchi E, Rollo V, Barbara L. Endoscopic ultrasonography in the diagnosis of gastric submucosal tumor. *Gastrointest Endosc*. 1989;35(5):413-418. [\[CrossRef\]](#)
- Kojima T, Takahashi H, Parra-Blanco A, Kohsen K, Fujita R. Diagnosis of submucosal tumor of the upper GI tract by endoscopic resection. *Gastrointest Endosc*. 1999;50(4):516-522. [\[CrossRef\]](#)
- Kwon JG, Kim EY, Kim YS, et al. Accuracy of endoscopic ultrasonographic impression compared with pathologic diagnosis in gastrointestinal submucosal tumors. *Korean J Gastroenterol*. 2005;45(2):88-96.
- Karaca C, Turner BG, Cizginer S, Forcione D, Brugge W. Accuracy of EUS in the evaluation of small gastric subepithelial lesions. *Gastrointest Endosc*. 2010;71(4):722-727. [\[CrossRef\]](#)
- Hwang JH, Saunders MD, Rulyak SJ, Shaw S, Nietsch H, Kimmey MB. A prospective study comparing endoscopy and EUS in the evaluation of GI subepithelial masses. *Gastrointest Endosc*. 2005;62(2):202-208. [\[CrossRef\]](#)
- Nowain A, Bhakta H, Pais S, Kanel G, Verma S. Gastrointestinal stromal tumors: clinical profile, pathogenesis, treatment strategies and prognosis. *J Gastroenterol Hepatol*. 2005;20(6):818-824. [\[CrossRef\]](#)
- Ma GL, Murphy JD, Martinez ME, Sicklick JK. Epidemiology of gastrointestinal stromal tumors in the era of histology codes: results of a population-based study. *Cancer Epidemiol Biomarkers Prev*. 2015;24(1):298-302. [\[CrossRef\]](#)
- Kadkhodayan K, Rafiq E, Hawes RH. Endoscopic evaluation and management of gastric stromal tumors. *Curr Treat Options Gastroenterol*. 2017;15(4):691-700. [\[CrossRef\]](#)
- DeMatteo RP, Lewis JJ, Leung D, Mudan SS, Woodruff JM, Brennan MF. Two hundred gastrointestinal stromal tumors: recurrence patterns and prognostic factors for survival. *Ann Surg*. 2000;231(1):51-58. [\[CrossRef\]](#)
- Nilsson B, Bümbling P, Meis-Kindblom JM, et al. Gastrointestinal stromal tumors: the incidence, prevalence, clinical course, and prognostication in the preimatinib mesylate era – a population-based study in western Sweden. *Cancer*. 2005;103(4):821-829. [\[CrossRef\]](#)
- Seremetis MG, Lyons WS, DeGuzman VC, Peabody JW, Jr. Leiomyomata of the esophagus. An analysis of 838 cases. *Cancer*. 1976;38(5):2166-2177. [\[CrossRef\]](#)
- Mathew G, Carter YM. *Esophageal leiomyoma*. StatPearls [internet]; Treasure Island (FL): StatPearls Publishing; 2018-2019.
- Willmore-Payne C, Layfield LJ, Holden JA. c-KIT mutation analysis for diagnosis of gastrointestinal stromal tumors in fine needle aspiration specimens. *Cancer*. 2005;105(3):165-170. [\[CrossRef\]](#)
- Fletcher CD, Berman JJ, Corless C, et al. Diagnosis of gastrointestinal stromal tumors: a consensus approach. *Hum Pathol*. 2002;33(5):459-465. [\[CrossRef\]](#)
- Tran T, Davila JA, El-Serag HB. The epidemiology of malignant gastrointestinal stromal tumors: an analysis of 1,458 cases from 1992 to 2000. *Am J Gastroenterol*. 2005;100(1):162-168. [\[CrossRef\]](#)
- Sun LJ, Chen X, Dai YN, et al. Endoscopic ultrasonography in the diagnosis and treatment strategy choice of Esophageal Leiomyoma. *Send to Clinics (Sao Paulo)*. 2017;72(4):197-201. [\[CrossRef\]](#)
- Xu GQ, Zhang BL, Li YM, et al. Diagnostic value of endoscopic ultrasonography for gastrointestinal leiomyoma. *World J Gastroenterol*. 2003;9(9):2088-2091. [\[CrossRef\]](#)
- Ichikawa J, Tanabe S, Koizumi W, et al. Endoscopic mucosal resection in the management of gastric carcinoid tumors. *Endoscopy*. 2003;35(3):203-206. [\[CrossRef\]](#)
- Saund MS, Al Natour RH, Sharma AM, Huang Q, Boosalis VA, Gold JS. Tumor size and depth predict rate of lymph node metastasis and utilization of lymph node sampling in surgically managed gastric carcinoids. *Ann Surg Oncol*. 2011;18(10):2826-2832. [\[CrossRef\]](#)
- Sun W, Wu S, Han X, Yang C. Effectiveness of endoscopic treatment for gastrointestinal neuroendocrine tumors: a retrospective study. *Med (Baltimore)*. 2016;95(15):e3308. [\[CrossRef\]](#)
- Kim HH, Kim GH, Kim JH, Choi MG, Song GA, Kim SE. The efficacy of endoscopic submucosal dissection of type I gastric carcinoid tumors compared with conventional endoscopic mucosal resection. *Gastroenterol Res Pract*. 2014;2014:253860. [\[CrossRef\]](#)
- Lu W, Xu MD, Zhou PH, et al. Endoscopic submucosal dissection of esophageal granular cell tumor. *World J Surg Oncol*. 2014;12:221. [\[CrossRef\]](#)
- He Z, Sun C, Wang J, et al. Efficacy and safety of endoscopic submucosal dissection in treating gastric subepithelial tumors originating in the muscularis propria layer: a single-center study of 144 cases. *Scand J Gastroenterol*. 2013;48(12):1466-1473. [\[CrossRef\]](#)
- Hoteya S, Iizuka T, Kikuchi D, Yahagi N. Endoscopic submucosal dissection for gastric submucosal tumor, endoscopic sub-tumoral dissection. *Dig Endosc*. 2009;21(4):266-269. [\[CrossRef\]](#)
- Matsumoto T, Iida M, Suekane H, Tominaga M, Yao T, Fujishima M. Endoscopic ultrasonography in rectal carcinoid tumors: contribution to selection of therapy. *Gastrointest Endosc*. 1991;37(5):539-542. [\[CrossRef\]](#)
- Yazıcı C, Boulay BR. Evolving role of the endoscopist in management of gastrointestinal tumors. *World J Gastroenterol*. 2017;23(27):4847-4855. [\[CrossRef\]](#)
- Menge F, Jakob J, Kasper B, Smakic A, Gaiser T, Hohenberger P. Clinical presentation of gastrointestinal stromal tumors. *Visc Med*. 2018;34(5):335-340. [\[CrossRef\]](#)
- Shepherd BD, Merchant N, Fasig J, Schwartz DA. Endoscopic ultrasound diagnosis of pelvic lipoma causing neurologic symptoms. *Dig Dis Sci*. 2006;51(8):1364-1366. [\[CrossRef\]](#)
- Gold JS, van der Zwan SM, Gönen M, et al. Outcome of metastatic GIST in the era before tyrosine kinase inhibitors. *Ann Surg Oncol*. 2007;14(1):134-142. [\[CrossRef\]](#)
- Matsushita M, Hajiro K, Okazaki K, Takakuwa H. Gastric aberrant pancreas: EUS analysis in comparison with the histology. *Gastrointest Endosc*. 1999;49(4 Pt 1):493-497. [\[CrossRef\]](#)
- Shah P, Gao F, Edmundowicz SA, Azar RR, Early DS. Predicting malignant potential of gastrointestinal stromal tumors using endoscopic ultrasound. *Dig Dis Sci*. 2009;54(6):1265-1269. [\[CrossRef\]](#)
- Humphris JL, Jones DB. Subepithelial mass lesions in the upper gastrointestinal tract. *J Gastroenterol Hepatol*. 2008;23(4):556-566. [\[CrossRef\]](#)
- Pavić T, Hrabar D, Duvnjak M. The role of endoscopic ultrasound in evaluation of gastric subepithelial lesions. *Coll Antropol*. 2010;34(2):757-762.