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Correlation of Endoscopic Ultrasonography Features with the Mitotic Index in 2- to 5-cm Gastric Gastrointestinal Stromal Tumors

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Keywords
Endoscopic ultrasound · Gastrointestinal stromal tumors · Mitotic index · Stomach

Abstract
Background: Predicting the malignancy potential of gastrointestinal stromal tumor (GIST) before resection could improve patient management strategies as gastric GISTs with a low malignancy potential can be safely treated endoscopically, but surgical resection is required for those tumors with a high malignancy potential. This study aimed to evaluate endoscopic ultrasound (EUS) features of 2- to 5-cm gastric GISTs that might be used to predict their mitotic index using surgical specimens as the gold standard. ***Patients and Methods:*** Forty-nine patients (30 females and 19 males; mean age 55.1 ± 12.7 years) who underwent EUS examinations, followed by surgical resections of 2- to 5-cm gastric GISTs, were retrospectively reviewed. ***Results:*** The mean tumor size was 3.44 ± 0.97 (range 2.1–5.0) cm. A univariate analysis revealed no significant differences in age, sex, and tumor location in the low mitotic index and high mitotic index groups (all $p > 0.05$). In terms of EUS features, there were no significant differences in the mitotic indexes with respect to the shape, surface lobulation, border regularity, echogenicity, homogeneity, growth patterns, presence of mucosal ulceration, hyperechogenic foci, anechoic spaces, and hypoechoic halos (all $p > 0.05$). However, the tumor size was larger in the high mitotic index group than that in the low mitotic index group (3.97 ± 1.05 vs. 3.27 ± 0.9 cm, $p = 0.03$). ***Conclusion:*** Conventional EUS features are not reliable for predicting the mitotic index of 2- to 5-cm gastric GISTs. Further modalities for predicting the mitotic index are needed to prevent unnecessary surgical resections in patients with a low risk of malignancy.

Introduction

Gastrointestinal stromal tumors (GISTs) are the most common mesenchymal tumors in the gastrointestinal (GI) tract, and gastric GISTs account for 60–70% of all GISTs [1]. No GISTs can be definitively deemed benign because all GISTs have a theoretical potential for malignant behavior, even those smaller than 2 cm. The current classification systems stratify GISTs according to their progression risk [1–3]. A widely used risk classification

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system proposed by the Armed Forces Institute of Pathology (AFIP) incorporates the tumor size and location and the mitotic count of resected tumors [1]. The National Comprehensive Cancer Network (NCCN) guidelines recommend that gastric GISTs larger than 2 cm or smaller lesions with high-risk endoscopic ultrasound (EUS) features such as irregular border, cystic spaces, ulceration, echogenic foci, and heterogeneity, should be referred for surgical resection, but GISTs smaller than 2 cm without high-risk EUS features may be monitored conservatively [4].

Recently, minimally invasive therapies have gained increasing interest. Some studies have demonstrated the feasibility and effectiveness of endoscopic excision as an alternative to the surgical resection for gastric GISTs smaller than 5 cm [5, 6]. However, the risk of local recurrence associated with endoscopic resections is a significant concern, and the topic remains especially controversial for 2- to 5-cm gastric GISTs. According to the AFIP criteria (or Miettinen's criteria), the risk of recurrence or metastasis for 2- to 5-cm gastric GISTs depends mainly on their mitotic activity, and there is a 10-fold increase in the risk between tumors with a low mitotic index (≤5/50 high-power fields [HPFs]) and those with a high mitotic index (>5/50 HPFs) [1]. Therefore, for 2- to 5-cm gastric GISTs, the ability to ascertain a tumor's mitotic activity would help guide clinicians to better manage the course of treatment. However, the limited amount of tissue obtained by EUS-guided fine-needle aspirations or biopsies (EUS-FNAs/Bs) precludes a reliable mitotic index determination; therefore, these procedures are not routinely performed [7, 8]. In this study, we investigated whether the conventional EUS features of 2- to 5-cm gastric GISTs are correlated with the mitotic index and could, therefore, help in the management of these GISTs.

Patients and Methods

This study was approved by the Institutional Review Board of Bezmialem Vakif University Hospital. A flowchart of the inclusion process is outlined in Figure 1. From October 2010 to August 2020, the medical records of patients with surgically proven gastric GISTs who had previously undergone EUS examinations were retrospectively reviewed. Patients with surgically resected gastric GISTs and a tumor size of 2–5 cm confirmed by pathologic measurements were included in the study. Each pathology report was re-evaluated by a single pathologist on the basis of the main prognostic factors (mitotic count and tumor size) to confirm the risk of metastasis or recurrence according to the AFIP criteria (or Miettinen's criteria) [1]. The mitotic index was defined as the mitosis count per 50 HPFs, and the tumor sizes were measured at the largest diameter of the tumors. For the statistical analysis, the patients were divided into low mitotic index (≤5/50 HPFs) and high mitotic index (>5/50 HPFs) groups (Fig. 2).

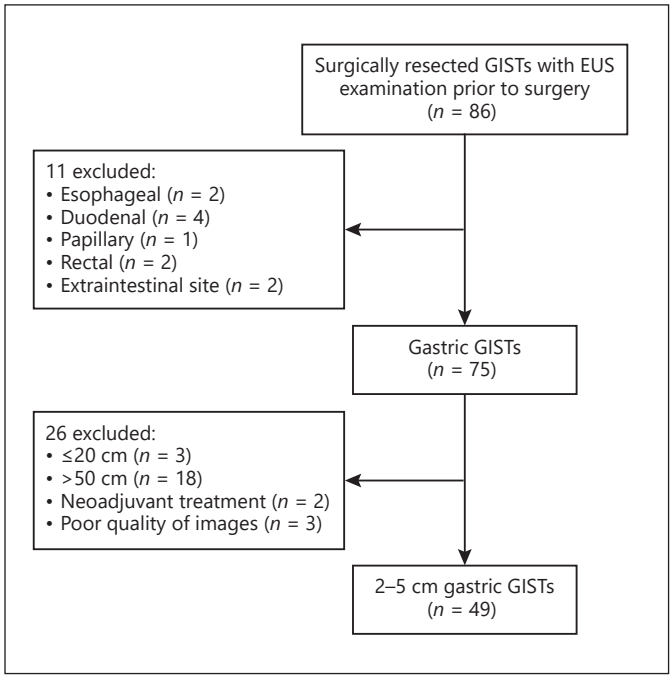

Fig. 1. Flowchart of patient enrollment.

Analysis of EUS Features

All EUS examinations were performed using a linear echoendoscope (Pentax Europe GmbH, Hamburg, Germany) by a single expert with more than 10 years of experience in EUS procedures (H.S.). The EUS images and reports were obtained from an endoscopy database and reviewed by the same endosonographer who knew the lesions were GISTs but was blinded to the surgical pathology results. The median number of EUS images evaluated per patient was 17 (range 9–34). In some patients, recorded videos were also evaluated. The following EUS features were recorded for each lesion: the longest diameter of tumors (mm), border regularity (regular or irregular), shape (oval/round or distorted), echogenicity compared with the surrounding muscular layer (iso-/hypoechoic or hyperechoic), homogeneity (homogeneous or heterogeneous), the presence of mucosal ulceration, surface lobulation, hyperechogenic foci, cystic spaces, hypoechoic halos, and growth patterns (exophytic or intraluminal) (Fig. 3).

Statistical Analysis

The data are presented as mean ± standard deviation for the continuous variables and as the number of cases with the frequency (%) for the categorical variables. The distributions of the continuous variables were evaluated using the Shapiro-Wilk test. The different characteristics were compared between the groups using the χ^2 test, Fisher's exact test, *t* test, or Mann-Whitney U test. Multiple logistic regression analyses were conducted to assess the differences in the EUS features between the 2 groups. Any variable that had a p value <0.25 was accepted as a candidate for the multi-

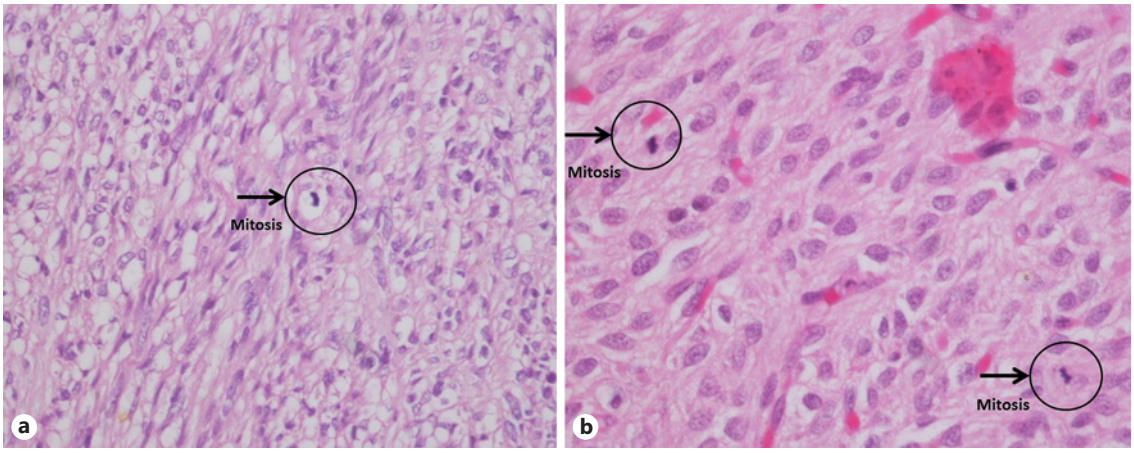

Fig. 2. a Histopathological evaluation showing mitotic count = 1/HPF, resulting in a mitotic index/50 HPFs <5. **b** Histopathological evaluation showing mitotic count = 2/HPF, resulting in a mitotic index/50 HPFs >5. HE. ×400. HPF, high-power field.

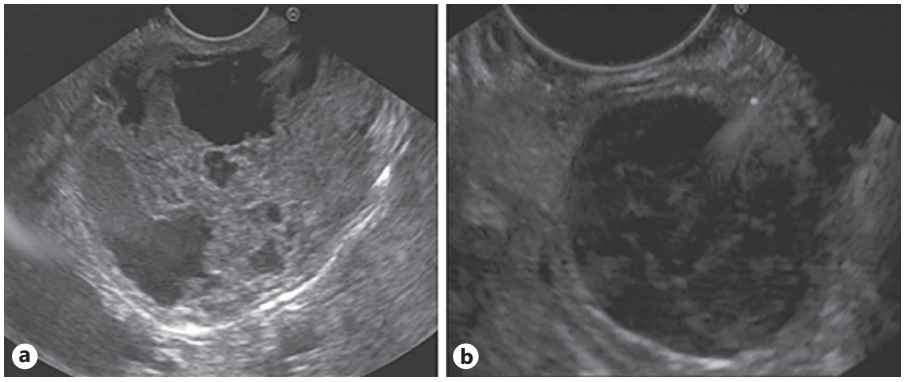

Fig. 3. a Endosonographic image of a 5-cm gastric GIST with a low mitotic index. The lesion has large anechoic spaces, irregular border, and hyperechogenic echo. **b** Endosonographic image of a 2.5-cm lesion with a high mitotic index. The lesion has marked heterogeneity without anechoic space or echogenic foci. GIST, gastrointestinal stromal tumor.

variable model along with the variables of known clinical importance. The odds ratios, 95% confidence intervals, and Wald statistics for each independent variable were also calculated. A receiver operating characteristic curve was applied to determine the optimal tumor size cutoff point that correlates with a high mitotic index. The sensitivity, specificity, positive predictive value, negative predictive value, and accuracy of the tumor size were also calculated. SPSS version 17.0 (IBM Corporation, Armonk, NY, USA) was used for the statistical analysis. A p value <0.05 was considered significant.

Results

The baseline characteristics of the patients and the EUS features of the tumors are presented in Table 1. A total of 49 patients with a mean age of 55.1 ± 12.7 (range 22–78) years were enrolled. Thirty of the patients were female and 19 were male. The mean tumor size was 3.44 ± 0.97 (range 2.1–5.0) cm. The tumors were located in the cardia or fundus in 14 patients (28.6%), the body in 19 (38.8%) patients, and the antrum in 16 (32.6%) patients. Forty-seven of the tumors originated from the fourth layer of the gastric wall (the muscularis propria) and 2 from the second layer (the muscularis mucosa). The mitotic index was ≤5/50 HPFs in 37 patients (75.5%), which were categorized as having a very low malignancy potential, and >5/50 HPF in 12 patients (24.5%), which were categorized as having a moderate malignancy potential.

Since tumor size is already a parameter in the AFIP risk classification system, we aimed to predict the mitotic count and compare the low and high mitotic index groups. A univariate analysis showed no significant differences between the 2 groups with regard to age, sex, or tumor location ($p > 0.05$). However, the tumor size was larger in the high mitotic index group than that in the low mitotic index group (3.97 ± 1.05 vs. 3.27 ± 0.9 cm, $p = 0.03$). None

Table 1. Comparison of baseline characteristics and EUS features according to the mitotic index in patients with gastric GISTs

Characteristic	Overall (n = 49)	Low mitotic index (≤5/50 HPFs) (n = 37)	High mitotic index (>5/50 HPFs) (n = 12)	p value
Age (±SD), years	55.1±12.7	56.0±11.9	52.3±15.2	0.391
Sex, n (%)				
Male	19 (38.8)	16 (43.2)	3 (25.0)	0.323
Female	30 (61.2)	21 (56.8)	9 (75.0)	
Location, n (%)				
Cardia/fundus	14 (28.6)	9 (24.4)	5 (41.7)	
Body	19 (38.8)	14 (37.8)	5 (41.7)	0.377
Antrum	16 (32.6)	14 (37.8)	2 (16.6)	
Tumor size, cm	3.44±0.97	3.27±0.90	3.97±1.05	0.030
Shape, n (%)				
Oval to round	33 (67.3)	23 (62.2)	10 (83.3)	0.290
Distorted	16 (32.7)	14 (37.8)	2 (16.7)	
Surface lobulation, n (%)				
No	31 (63.3)	24 (64.9)	7 (58.3)	0.738
Yes	18 (36.7)	13 (35.1)	5 (41.7)	
Extraluminal border, n (%)				
Regular	17 (34.7)	12 (32.4)	5 (41.7)	0.729
Irregular	32 (65.3)	25 (67.6)	7 (58.3)	
Intraluminal border, n (%)				
Regular	30 (61.2)	21 (56.8)	9 (75.0)	0.323
Irregular	19 (38.8)	16 (43.2)	3 (25.0)	
Ulceration, n (%)				
No	33 (68.7)	24 (66.7)	9 (75.0)	0.728
Yes	15 (31.3)	12 (33.3)	3 (25.0)	
Echogenicity, n (%)				
Hyperechogenic	21 (42.9)	16 (43.2)	5 (41.7)	>0.999
Iso-/hypoechogenic	28 (57.1)	21 (56.8)	7 (58.3)	
Homogeneity, n (%)				
Homogeneous	18 (36.7)	15 (40.5)	3 (25.0)	0.494
Heterogeneous	31 (63.3)	22 (59.5)	9 (75.0)	
Anechoic area, n (%)				
No	24 (49.0)	19 (51.4)	5 (41.7)	0.802
Yes	25 (51.0)	18 (48.6)	7 (58.3)	
Hyperechoic foci, n (%)				
No	27 (55.1)	21 (56.8)	6 (50.0)	0.940
Yes	22 (44.9)	16 (43.2)	6 (50.0)	
Hypoechoic halo, n (%)				
No	22 (44.9)	15 (40.5)	7 (58.3)	0.458
Yes	27 (55.1)	22 (59.5)	5 (41.7)	
Growth pattern, n (%)				
Intraluminal	30 (61.2)	25 (67.6)	5 (41.7)	0.173
Extraluminal/exophytic	19 (38.8)	12 (32.4)	7 (58.3)	

EUS, endoscopic ultrasonography; HPF, high-power field; SD, standard deviation; GISTs, gastrointestinal stromal tumors.

of the studied EUS features, namely, tumor shape, surface lobulation, border regularity, echogenicity, homogeneity, growth patterns, presence of mucosal ulceration, hyperechogenic foci, anechoic spaces, and hypoechoic halos appeared to be predictive for the mitotic index in the resected tumors.

Because only the tumor size was found to be a significant factor in the univariate analysis and the p values were influenced by the sample, we introduced factors with a p value <0.25 in the multivariate analysis. A stepwise logistic regression analysis showed that tumor size was the only independent predictor of a high mitotic index. No

combination of features, such as sex, age, and extraluminal growth pattern, significantly improved the prediction of the mitotic index better than the tumor size. A receiver operating characteristic curve was constructed to identify the discriminating value of the size for predicting the mitotic index of the GISTs. The optimal cutoff value for the tumor size was determined to be 4.1 cm, with a sensitivity of 58.3%, a specificity of 83.8%, a positive predictive value of 53.8%, a negative predictive value of 86.1%, and an accuracy of 77.6% (Table 2). Seven of 13 patients (54%) with a tumor size ≥4.1 cm were in the high mitotic index group, and 31 out of 36 patients (86%) with a tumor size ≤4.0 cm were in the low mitotic index group.

Table 2. Tumor size according to the mitotic index

	Results
Area under the curve	0.703
95% CI	0.517–0.889
p value	0.036
The optimal cutoff point	4.1 cm
Sensitivity	58.3%
Specificity	83.8%
Positive predictive value	53.8%
Negative predictive value	86.1%
Accuracy	77.6%

CI, confidence interval.

Discussion

Currently, there are no established effective methods for the risk stratification of GISTs prior to resection, although the NCCN guidelines provide treatment recommendations based on size and high-risk EUS features such as irregular border, cystic spaces, ulceration, echogenic foci, and heterogeneity [4]. EUS allows for the evaluation of tumor size, invasion depth, border regularity, echogenicity, determination of the GI wall layer from which tumors arise, and other tumor morphological characteristics as well as tissue sampling. On EUS, GISTs are typically well-defined, hypoechoic, homogeneous lesions arising from the fourth layer of the GI wall or rarely from the second layer. More robust criteria are needed, however, to guide physicians in making clinical decisions regarding the management of patients with gastric GISTs. At present, the reliability of mitotic index assessments of EUS-FNA/B samples and their prognostic importance has yet to be defined [7, 9–11]. The mitotic count yield of tissue obtained from EUS-FNAs/Bs was found to be significantly lower than that of resected specimens. Moreover, it has been claimed that even if a count of 50 HPFs was reached in EUS-FNB specimens, the mitotic index values were still lower than those of the surgical specimens [8, 11]. The Ki67 protein, a nuclear marker expressed in all phases of the cell cycle, has been suggested as an alternative parameter to the mitotic index on EUS-FNAB samples [12]. However, the results have remained inconclusive [8, 13]. If low-risk GISTs are preoperatively distinguished from those with moderate to high risk, more suitable, individualized management strategies can be implemented, a significant number of unnecessary surgical resection of gastric GISTs 2–5 cm in size may be avoided.

Previously, some researchers have attempted to describe malignant EUS features but have yielded conflicting results (Table 3). Some have suggested that a large tumor size (>3 cm) and irregular margins are the characteristics most consistent with increased tumor aggressiveness [14–17]. Features such as echogenic foci [14], cystic spaces [14, 15, 18], heterogeneity [17], ulceration [16], and a nonoval shape [16] were found to be less consistently associated with malignant risk. These findings have not been validated in prospective studies; however, no consensus has been reached regarding which features are most correlated with the risk of malignancy. Moreover, some of these studies were published either prior to the recognition of GISTs or before a consensus regarding the risk of malignancy was achieved, or they did not categorize any of the studied lesions as GISTs [14, 15]. Others evaluated either a wide range of tumor sizes or more than just gastric GISTs [17]. In addition, some of the studies did not provide specific histologic criteria that were used to determine the malignancy potential [18]. In the present study, we evaluated the EUS features that are commonly used by endosonographers to describe images of GISTs. Only tumors that were 2–5 cm in size located in the stomach and without local invasion and distant metastasis were included in our study. All the tumors were resected surgically and demonstrated to be GISTs upon a histopathological examination, after which they were assigned a malignancy potential according to the AFIP criteria. Patients on neoadjuvant therapy with tyrosine kinase inhibitors were not included in this study as the treatment may decrease the tumor size and make the accuracy of the mitotic index less reliable [19, 20]. Our study did not reveal any conventional EUS features that are useful for predicting the mitotic index or malignancy potential of gastric GISTs that are 2–5 cm in size. Ultimately,

Table 3. Studies evaluating association of EUS features for predicting the malignancy potential or mitotic index of GI stromal cell tumors

Reference	*N*	Location	Size	Associated features	Not associated features	Assessment
Chak et al. [14]	35	Any	Any	Cystic spaces* Echogenic foci* Irregular borders* Size (4 cm)*	Heterogeneity Mucosal ulceration	Differentiation of benign and malignant stromal cell tumors The study was published prior to the definition of GIST as a distinct concept
Palazzo et al. [15]	56	Any	Any	Cystic spaces* Echogenicity Irregular borders* Growth pattern Mucosal ulceration Size (3 cm)	Heterogeneity	Prediction of benign and malignant GI stromal cell tumors The study was published creation of the risk stratification of GISTs
Jeon et al. [16]	24	Stomach	Any	Irregular borders Mucosal ulceration Size (3 cm)[&] Shape	Cystic spaces Echogenic foci Echogenicity Growth pattern Heterogeneity Hypoechoic halo Surface lobulation	The NIH criteria Low versus intermediate versus high risk Size was an independent factor when patients divided into low versus high risk
Shah et al. [17]	26	Any	Any	Heterogeneity* Irregular borders* Local invasion* Size (5 cm)*	Cystic spaces Echogenic foci	The NIH criteria Very low versus low versus intermediate versus high risk
Ji et al. [18]	76 GIMTs (including 42 GISTs)	Any	Any	Heterogeneity Irregular borders Tumor size Cystic spaces		Not reported
Chen et al. [21]	110	Stomach	Any	Cystic spaces Mucosal ulceration Size (5 cm)*	Calcification	The NIH criteria Very low/low versus intermediate versus high risk
Chen et al. [21]	110	Stomach	Any	Size	Calcification Cystic spaces Mucosal ulceration	Mitotic index (low vs. high)
Chen et al. [22]	50	Stomach	>2 cm	Cystic spaces* Serosal invasion Size (5 cm)*	Echogenic foci Heterogeneity Irregular borders Mucosal ulceration	The modified NIH criteria Very low/low versus moderate/high risk
Chen et al. [22]	50	Stomach	>2 cm	None	Cystic spaces Echogenic foci heterogeneity Irregular borders Mucosal ulceration Size	Mitotic index (low vs. high)
Kim et al. [23]	55	Stomach	2–5 cm	None	Calcification Cystic changes Heterogeneity Hyperechoic foci Hypoechoic foci Mucosal ulceration Surface lobulation Size	The AFIP criteria Very low versus moderate risk
Yang et al. [24]	275	Stomach	<5 cm	Irregular shape* Mucosal ulceration* Size (2 cm)*	Heterogeneity Hyperechoic foci Cystic spaces	The modified NIH criteria Very low/low versus moderate versus high risk

AFIP, Armed Forces Institute of Pathology; GIMT, gastrointestinal mesenchymal tumor; NIH, National Institute of Health; GIST, gastrointestinal stromal tumor; EUS, endoscopic ultrasonography; GI, gastrointestinal. * Independent significant factor in the multivariate analysis. [&] Size was an independent factor when patients divided into low versus high risk.

the tumor size was the only significant factor associated with the mitotic index.

Research on the correlation between EUS features and the mitotic index is lacking. Chen et al. [21] previously reported that tumor size was the only EUS finding that was a significant predictor of a high mitotic index, which is consistent with our results, but they noted nothing of significance in terms of EUS morphological features. They also found that a high risk of malignancy was associated with a 5-cm lesion, although not with cystic changes or surface ulceration. Notably, this study included large-sized GISTs (up to 150 mm), while our data only included cases with tumor sizes between 2 and 5 cm. In another study, none of the EUS features were determined to be predictors of a high mitotic count, while a tumor size >5 cm, the presence of cystic spaces and serosal invasion were independent predictors of a high malignant potential of GISTs; however, irregular borders, heterogeneity, the presence of ulceration, hyperechogenic foci, and serosal invasion were not [22]. Kim et al. [23] retrospectively enrolled patients with 2- to 5-cm gastric GISTs and analyzed the association between EUS features and the risk of malignancy. None of the features were significantly different among the patients in the very low- and moderate-risk groups, implying that EUS findings might present limitations for preoperatively predicting the malignancy of medium-sized GISTs. In contrast, the tumor size was a significant factor for predicting the mitotic index in our study. Recently, a multivariate prediction model for gastric GISTs prior to resection was proposed by Yang et al. [24]. Mucosal ulcerations, tumor sizes larger than 2 cm, and irregular tumor shapes were found to be independent risk factors for a high malignancy potential. In this study, however, small tumors were also included. The evaluation of the intraluminal or extraluminal growth pattern is still arbitrary and probably involves many pitfalls; however, it is still present in some of such studies [15, 16, 25]. In our study, if more than half of the lesions are intraluminal, we labeled them as intraluminal and, vice versa, extraluminal.

The different outcomes among the various studies might be explained partially by interobserver variability in the identification of EUS features. The criteria for identifying high-risk EUS features rely largely on the expertise of endosonographers and, therefore, remain subjective. One study demonstrated that despite the specific definition of EUS features, interobserver agreements on the accurate interpretations of the features ranged from poor to good [14]. The authors reported poor agreement when interpreting echogenicity and irregular luminal borders but good agreement on heterogeneity and irregular extraluminal borders. Another possible reason for the different outcomes among the studies is that the occurrence of some EUS features is not just associated with the biological behavior of tumors [25]. Choi et al. [26] reported that the presence of surface ulceration has no direct correlation with aggressive tumor behavior and results from the ischemic mucosa being pressed on by the growing tumor. However, another group claimed that large tumors tend to grow toward the gastric lumen and lead to mucosal ulceration associated with malignancy [16]. Chen et al. [25] claimed that cystic spaces correspond to cystic degeneration and liquefaction necrosis, and the disproportionality between the rapid tumor growth and relatively slow neovascularization can induce necrosis or cystic degeneration. As a result of malignant changes, GISTs usually have a heterogeneous echo texture with hyperechoic spots or anechoic areas, especially in larger tumors. Yang et al. [24] reported that irregular tumor shape independently associated with a high-risk malignancy potential of gastric GISTs which may result from the biologic diversity in the growth rate of the internal structure. Previously identified high-risk features were obtained mainly from large-size GISTs and account for the reason their findings differ from our cohort.

In our study, the tumor size showed a positive correlation with the mitotic index. The agreement between size, as assessed by the EUS, and surgical pathology was also positive. Specifically, a tumor size of 41 mm showed a 58.3% sensitivity and 83.3% specificity for predicting a high mitotic index. Nevertheless, the tumor size did not perfectly differentiate between low and high mitotic indexes as 5 patients with a tumor size <41 mm had a high mitotic index and 6 patients with a tumor size ≥4.1 cm had a low mitotic index.

According to the AFIP classification system, gastric GISTs >2 but ≤5 cm in size and with ≤5 mitoses/50 HPFs are considered a very low risk for the recurrence, and gastric GISTs with >5 mitoses/50 HPFs are considered a moderate risk. In our cohort, 75.5% of the patients had a very low risk of disease progression. As mentioned above, in a large-scale study by Miettinen et al. [1], only 1.9% of the patients with a very low risk of recurrence showed disease progression during the follow-up. Therefore, a significant proportion of the patients in our cohort underwent surgical resections, despite a very low risk of malignant transformation or metastasis.

This study had several limitations. First, it was a single-center retrospective study; therefore, any potential bias related to data collection could not be completely exclud-

ed. Second, the sample size was small. Third, a retrospective interpretation of images is not the same as actually performing a patient examination. Although few static images may fall short of making a correct diagnosis, the expert reviewed many images, even recorded videos and the reports, which usually included EUS features described in the study of the patients. Additionally, the quality of the recordings could be variable. Finally, there was some variability introduced because of the use of pathologic interpretations from different institutions, although all the pathology reports were reviewed by a single pathologist.

In conclusion, our study shows that conventional EUS morphological features are not reliable for predicting the mitotic index or malignancy potential of 2- to 5-cm gastric GISTs as only the size of the tumor was correlated with the mitotic index. However, the malignant potential of these tumors could not be excluded. Further diagnostic modalities are needed to predict the mitotic index so that unnecessary surgical resection of GISTs with a low risk of malignancy can be prevented.

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Statement of Ethics

The study was approved by the Institutional Ethics Committee (IRB No: 2/25). Written informed consent statements have not been obtained for this study as it is not necessary for a retrospective study according to the Institutional Review Board of Bezmialem Vakif University Hospital.

Conflict of Interest Statement

Drs. Seven, Arici, and Senturk have no conflicts to report.

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No funding sources have been used for this study.

Author Contributions

Gulseren Seven: the concept and design, collecting data, analysis and interpretation of data, drafting and revising the articles, and writing the paper. Dilek Sema Arici: evaluating the pathology reports and revising the paper. Hakan Senturk (corresponding author): the concept and design, interpretation of data, revising the paper, and performing EUS.

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