ORIGINAL ARTICLE

Use of Endoscopic Ultrasound Elastography to Differentiate between Gastrointestinal Stromal Tumor and Leiomyoma Localized in the Upper Gastrointestinal Tract

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Received on: 09 January 2024; *Accepted on*: 22 February 2024; *Published on*: 12 June 2024

Abstract

Background: Gastrointestinal stromal tumors (GISTs) have malignant potential. Distinction of GISTs from leiomyoma is important to the decision of follow-up or treatment for upper gastrointestinal tract subepithelial lesions (SELs). There are few studies on the evaluation of gastrointestinal SELs with endoscopic ultrasound (EUS) elastography.

Aims: To evaluate the efficiency of strain ratio (SR) measurement and Giovannini's classification (Gc) by EUS elastography in differentiating GISTs from leiomyomas.

Materials and methods: Twenty-three lesions with histopathological diagnoses of 13 GISTs and 10 leiomyomas were evaluated. The lesions' SR values were obtained from EUS reports retrospectively. Giovannini's classification was performed according to the elastography images recorded in the system. The effectiveness of SR and Gc in the distinction between GIST and leiomyomas was evaluated.

Results: Twelve of the GISTs and 3 of the leiomyomas were with scores 4 and 5 according to Gc ($p = 0.006$). Gastrointestinal stromal tumors had a higher SR than leiomyomas ($p = 0.001$). For the diagnosis of GISTs, sensitivity/specificity/diagnostic accuracy were 92.3%/80%/87% for SR alone, 92.3%/70%/82.6% for Gc alone, and 84.6%/80%/82.6% for the use of both SR and Gc.

Conclusions: This is the first study in which semi-quantitative (SR) and qualitative (Gc) methods were evaluated together for the distinction of GISTs and leiomyomas. The sensitivity of SR alone for diagnosing GIST is higher than that of Gc alone or the combination of both methods. Although SR alone does not diagnose GIST, it can be used as an auxiliary method in biopsy and follow-up decisions.

Keywords: Endoscopic ultrasound elastoghraphy, Gastrointestinal stromal tumor, Giovannini's classification, Leiomyoma, Strain ratio.

Euroasian Journal of Hepato-Gastroenterology (2024): 10.5005/jp-journals-10018-1419

Introduction

Subepithelial lesions (SELs) of the gastrointestinal system (GIS) are mostly detected incidentally during gastrointestinal endoscopy with a rate of 0.76%.[1] Gastrointestinal stromal tumors (GISTs) and leiomyomas are the most common in upper GIS SELs and they originate from mesenchyme.[2] The GISTs derived from interstitial cells of Cajal are localized in the gastric wall with 60–70 and 20–25% of them are malign.[3,4] However, leiomyomas are mostly benign and localized in the esophageal wall.[5] Therefore, a distinction between GISTs and leiomyoma is necessary for treatment or follow-up decisions. While removal of SELs from muscularis mucosa and submucosa is possible with endoscopic submucosal dissection, SELs originating from the muscularis propria require more complicated procedures (etc. submucosal tunnel endoscopic resection, peroral endoscopic tunnel resection, laparoscopic endoscopic cooperation surgery or conventional surgery).[6,7] Biopsy is the gold standard for diagnosis, especially for lesions in the muscularis propria. Unroofing biopsy or EUS fine needle aspiration (FNA) may be carried out, but hemorragia, perforation, and insufficient cytologic material or false negative results can be seen in these procedures.[8]

On the contrary, EUS elastography has been used in recent years as an auxiliary method in the differentiation of malignant and benign in solid lesions of the pancreas and lymph nodes. Studies have shown that EUS elastography is not an alternative method to biopsy, but can be used to support the decision of biopsy or follow-up. It has low specificity (67–76%) but high sensitivity (92–98%) for pancreatic solid lesions. As lymph nodes, the sensitivity is 88% and the specificity is 85%.[9,10] In EUS elastography, tissue stiffness is assessed based on real-time echogenic changes in the targeted area due to adjacent vascular pulsation. This evaluation is performed by superimposing the image colored according to the tissue hardness into B mode.[11] Thus, qualitative and semi-quantitative methods developed according to the distribution of coloration are used.[12] Giovannini's classification (Gc) is one of the qualitative methods. In this method, lesions are divided into five scores according to the coloration pattern.[13] Strain ratio (SR) is a semi-quantitative method and is calculated by the ratio of

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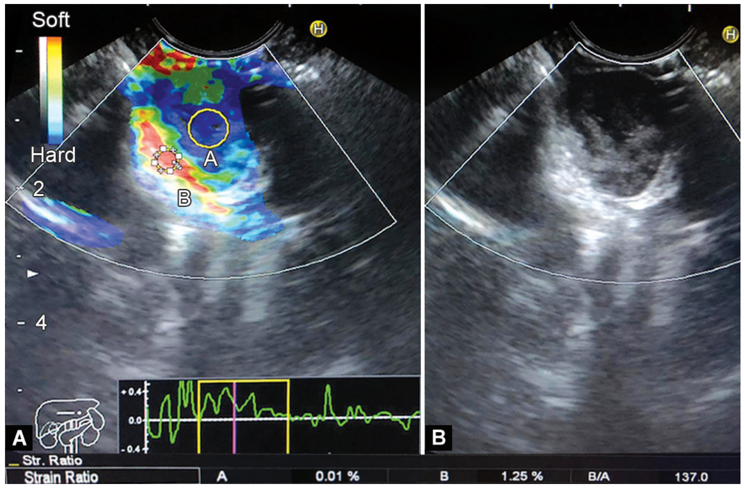
How to cite this article: Erdem RE, Bektaş M, Ellik ZM, *et al*. Use of Endoscopic Ultrasound Elastography to Differentiate between Gastrointestinal Stromal Tumor and Leiomyoma Localized in the Upper Gastrointestinal Tract. Euroasian J Hepato-Gastroenterol 2024;14(1):20–23.

Source of support: Nil

Conflict of interest: None



Figs 1A and B: Gastrointestinal stromal tumor EUS elastography, Gc score 5, predominantly blue color and SR, 137.0

the stiffness of the lesion to be measured to the stiffness of the adjacent soft area. The high SR value means more tissue stiffness. In particular, the hardness of malignant lesions tends to be higher than normal tissue. Based on this principle, elastography is used as an auxiliary method in distinguishing benign from malignant lesions.[9,12]

There are few studies in the literature on the effectiveness of EUS elastography in the evaluation of SELs especially differentiation between GIST and leiomyoma.[8,14–17] In the first study with Gc in the SEL of the GI tract showed that the GISTs had higher scores.[14] Additionally, in other studies GISTs had higher SR.[15,17] However, while Gc is a qualitative method, SR is a semi-quantitative method, and to our knowledge, there is no study evaluating SR and Gc together. In our study, we aimed to evaluate the effectiveness of Gc and SR measurement in the differentiation of GIST and leiomyoma in upper GIS SELs originating from the muscularis propria.

Materials and Methods

Between January 2016 and March 2020, the patients who had SEL and underwent EUS examination were evaluated retrospectively. The inclusion criteria were as follows: (A) patients 18 years and older, (B) lesions with SR values written on the report and coloration patterns recorded in the video system, (C) lesions which were in muscularis propria, (D) lesions which were GIST and leiomyoma with histopathological diagnoses after EUS FNA or postexcision. A total of 23 lesions were included in the study.

This study was performed in line with the principles of the Declaration of Helsinki. Approval was granted by the Ethics Committee of Ankara University (registry No. 2021000089 and approval No. 2021/89). Informed consent was not obtained from the patients because it was a retrospective study.

Endoscopic Ultrasound Examination

After at least 8 hours of fasting, EUS was performed under sedation. The dimension, localization, echogenic features, and layers were evaluated with the radial echoendoscope (Fujinon 7000, EG-530UR scope, Fujifilm, Tokyo, Japan). Subsequently, elastographic measurements were made with the linear echoendoscope (Ultrasound: Hitachi HI VISION Preirus, Tokyo, Japan – Echoendoscope: Pentax EPK-100P linear scope, Tokyo, Japan). Endoscopic ultrasound and EUS elastography were applied by an expert person (MB).

Giovannini's Classification

The images of coloration patterns that had been recorded in the system with elastography mode during B mode examination were evaluated retrospectively. According to the coloration pattern, the lesions scored with Gc. Patients' names and diagnoses were unknown to the person who performed the scoring at the time of scoring. A score of 1 was defined as homogeneous green soft tissue, and a score of 2 was defined as heterogeneous green, yellow, and red colorations. A score of 3 was given to mixed hard and soft tissues with mixed colors. A score of 4 represented hard (blue) lesions with a soft green central area. Finally, a score of 5 was defined as predominantly hard (blue) lesions[13] (Fig. 1).

Measurement of Strain Ratio

While performing the measurement of SR, two areas (areas A and B) were selected. Area A represented the region of interest and area B represented the normal and soft area which was adjacent to the lesion. The ratio of A to B was defined as SR (Fig. 1).

Statistical Analysis

Statistical analysis was performed with statistical package for the social sciences (SPSS) software, version 22.0. Mean and standard deviation (SD) or median and minimum-maximum values were used for continuous variables. Differences between groups of patients for categorical data were evaluated with χ^2 test and Fisher's exact test. Student's *t*-test and Mann–Whitney test were used to evaluate the differences between continuing variables. A *p*-value below 0.05 was considered statistically significant. The receiver operating characteristic (ROC) analysis was used to determine the cut-off value of SR.

Results

A total of 43 lesions were evaluated with EUS elastography. Twenty lesions were excluded (13 lesions were without a histopathological diagnosis, and 7 lesions' histopathological diagnoses were schwannoma, ectopic pancreas, neuroendocrine tumor, and lipoma). Twenty-three lesions with histopathological diagnoses of GIST and leiomyoma were evaluated. Of these lesions, 13 were GISTs and 10 were leiomyomas.

All patients' (n = 23) mean age was 53 ± 15. Eleven (47.8%) of the patients were females. The majority of SELs (56.5%) were

Table 1: Characteristics of the patients and lesions

	All lesions (n = 23) (100%)	*GIST (n = 13) (56.5%)*	*Leiomyoma (n = 10) (43.5%)*	*p-value*
Gender n (%)				0.14
Male	12 (52.2)	5 (38.5)	7 (70)	
Female	11 (47.8)	8 (61.5)	3 (30)	
Age, mean ± SD	53 ± 15.4	60 ± 15	43.8 ± 10.3	0.008
Localization, n (%)				
Esophagus	9 (39.2)	–	9 (90)	0.001
Stomach	13 (56.5)	12 (92.3)	1 (10)	
Duodenum	1 (4.4)	1 (7.7)	–	
Diameter#, median (minimum–maximum)	25 (19–100)	26.5 (20–55)	23.1 (19–100)	0.65
Echogenicity, n (%)				
Homogeneous	12 (52.2)	3 (23.1)	9 (90)	0.003
Heterogeneous	11 (47.8)	10 (76.9)	1 (10)	
Cystic, *n* (%)	4 (30.8)	4 (23.1)	0	
Echogenic focus, *n* (%)	4 (30.8)	3 (23.1)	1 (10)	

#Milimeter

Table 2: Giovannini's classification of the lesions

Score	*GIST (n = 13) (%)*	*Leiomyoma (n = 10) (%)*
Score 1	–	–
Score 2	–	4 (40)
Score 3	1 (7.7)	3 (30)
Score 4	3 (23.1)	2 (20)
Score 5	9 (69.2)	1 (10)

Table 3: Comparison between GISTs and leiomyomas with Gc and SR

Gc	*GIST (n = 13) (%)*	*Leiomyoma (n = 10) (%)*	*p-value*
1–2–3	1 (7.7)	7 (70)	0.006
4–5	12 (92.3)	3 (30)	
SR, median (minimum–maximum)	95.6 (10.6–312)	9.9 (2.5–30.9)	0.001

Table 4: Diagnostic value of SR and Gc for GISTs

	SR ≥ 12	*Giovanini's classification 4–5*	*Giovanini's classification 4–5 and SR ≥ 12*
Sensitivity (%)	92.3	92.3	84.6
Specificity (%)	80	70	80
Diagnostic accuracy (%)	87	82.6	82.6

located in the stomach. The median diameter of the lesions was 25 mm (minimum–maximum: 19–100), and 11 lesions' echo patterns (47.8%) were heterogeneous. All of the SELs were in the muscularis propria. The mean age of the patients with a diagnosis of GIST was higher than those with a diagnosis of leiomyoma (60 ± 15 for patients with GIST and 43.8 ± 10.3 for patients with leiomyoma, $p = 0.008$). Twelve of the GISTs were in the stomach and one in the duodenum. All but one of the leiomyomas were in the esophagus. The majority of GISTs' echo patterns were heterogeneous (76.9%), while the majority of leiomyomas were homogeneous (90%) ($p = 0.003$). The median diameter of GISTs and leiomyomas were 26.5 mm (minimum–maximum: 20–55) and 23.1 mm (minimum–maximum: 19–100), respectively ($p = 0.65$). Four GISTs had an echogenic focus (Table 1).

According to Gc, 1 of the GISTs was with a score of 3, 3 were with a score of 4, and 9 were with a score of 5. On the contrary, 4 of the leiomyomas were with a score of 2, 3 were with a score 3, 2 were with a score of 4, and 1 was a score of 5 (Table 2). Twelve (92.3%) of GISTs and 3 (30%) of leiomyomas were with scores 4 and 5 ($p = 0.006$) (Table 3). The sensitivity, specificity, and diagnostic accuracy of scores 4 and 5 for the diagnosis of GIST were 92.3, 70, and 82.6%, respectively (Table 4).

Median SR values of GISTs and leiomyomas were 95.6 (minimum–maximum: 10.6–312) and 9.9 (minimum–maximum: 2.5–30.9), respectively ($p = 0.001$) (Table 3). When the cut-off value of SR was defined as 12 and above for the diagnosis of GIST, sensitivity was 92.3%, and specificity and diagnostic accuracy were 80 and 87%, respectively. Furthermore, when the SR ≥ 12 and Gc were evaluated together for the diagnosis of GIST, sensitivity was 84.6%, specificity and diagnostic accuracy were 80 and 82.6%, respectively. Two lesions that had a value of SR ≥ 12 and a score of 4–5 according to Gc were leiomyomas and none of the lesions with SR < 12 and with a score of 1–2–3 was GIST (Table 4).

Discussion

Endoscopic ultrasound elastography is an auxiliary method used for the malignant-benign distinction of pancreatic lesions and lymph nodes. Although EUS elastography is not an alternative to biopsy in the studies performed, it is an effective method for making a biopsy or follow-up decision on the lesions.[12] In GIS SELs, there are few studies in the literature on EUS elastography, and there is no defined scoring for these lesions yet.[8,14–17] In the study by Tsuji et al.[14] SELs were evaluated with Gc. In this study, it was observed that GISTs had higher scores than leiomyomas and aberrant pancreas. All GISTs had a score of 4–5 while all leiomyomas had a score of 2 and 3.[14] In our study, except for one of 13 GISTs, the score were 4 and 5. Unlike the study by Tsuji et al.,[14] in this study, 3 (30%) of the leiomyomas were with scores 4 and 5. The sensitivity of scores 4 and 5 in evaluating GISTs (92.3%) was quite high. However, its specificity was lower, at 70%. According to our study, Gc seems to be more reliable in excluding the diagnosis of GIST for lesions with scores 3 and below 3, whereas biopsy is still needed to exclude leiomyoma in lesions with scores of 4 and 5. The disadvantage of Gc is that it is operator dependent. Therefore, this method is subjective and qualitative.

When SELs were compared with SR, GISTs had higher value than leiomyomas, and this difference was statistically significant ($p = 0.001$). When the SR value was 12 and above, the sensitivity for the diagnosis of GIST was 92.3%, and the specificity was higher than the Gc (80%). In the study of Kim et al.,[15] when the SR cut-off value was evaluated as 22.7, the sensitivity was found to be 100% and the specificity as 94.1% in the distinction of GIST and leiomyoma.[15] Antonini et al.[17] reported that the sensitivity and specificity were 81.8 and 85.7%, respectively, with an 11.18 cut-off value of SR.[17] While Kim et al.[15] used the EUS balloon filled with water as a reference area "'B'", Antonini et al. used the peritumoral healthy gastrointestinal wall. It is difficult to stabilize the pressure applied to the lesion during elastography measurement. Therefore, the coloration pattern may change depending on the pressure applied by the probe or the proximity of the lesion to pulsatile vascular structures and the heart.[18] These variable patterns are expected to change at the same level in the tissue and its environment. Therefore, it can be expected that the change of the ratio between the lesion and the reference area around the lesion will be less. The SR value may be more likely to vary when a water-filled balloon is used as the reference area. However, the thin GIS wall causes the reference area to be small. This situation may cause a disadvantage in the measurement of SR of SELs originating from the GIS wall. Therefore, comparative studies with a large number of lesions are needed to determine the correct reference area. In our study, the reference area was selected as the softest healthy area around the lesion. We also determined the SR cut-off value to be close to the value found in the study of Antonini et al.[17] According to our study, sensitivity was 92.3% and specificity was 80% when SR value is 12 and above for the diagnosis of GIST.

Otherwise, when the Gc and SR values were evaluated together for the diagnosis of GIST, lower sensitivity was observed in our study (84.6% with both methods together, 92.3% with SR, and 92.3 with Gc). The specificity was the same with the SR measurement alone (80%), but higher than the evaluation with the Gc alone (70% with Gc).

Our study had some limitations. First, this study was retrospective. Second, our number of patients was small. Third, Gc was done on the images in the recording archive. To avoid bias in scoring, we kept patient names and diagnoses confidential during scoring, and fourth, we know that the majority of lesions found in the muscularis propria of the esophagus are leiomyomas. In addition, most of the lesions located in the muscularis propria in the stomach are GIST. In our study, only one of the leiomyomas was localized in the stomach, while the others were localized in the esophagus and there was no GIST in the esophagus' wall. This was the most important weak point in our study. Nevertheless, the results we found can be a guide in planning the treatment and follow-up of SELs, especially localized in the cardia. These results need to be supported by prospective studies, especially involving large numbers of SELs' which are gastric localized.

In conclusion, this is the first study in which semi-quantitative (SR) and qualitative (Gc) methods were evaluated together for the distinction of GISTs and leiomyoma. If both SR and Gc are used, the sensitivity of EUS elastography for the diagnosis of GIST is lower and specificity does not change. The specificity and diagnostic accuracy of the SR measurement alone in diagnosing GIST is higher than the Gc alone. Therefore, although SR alone does not diagnose GIST, it can be used as an auxiliary method for the biopsy and follow-up decision. However, prospective studies with a large number of patients are needed to support these findings.

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