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Quantitative evaluation of upper gastrointestinal subepithelial lesions using endoscopic ultrasound-guided shear wave elastography

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ABSTRACT

Shear wave elastography provides quantitative data on tissue stiffness, but was not available for endoscopic ultrasound until recently. The present study investigated the utility of a newly developed endoscopic ultrasound-guided shear wave measurement for diagnosing upper gastrointestinal subepithelial lesions. Shear wave velocity (Vs) was measured as an indicator of tissue stiffness, and the total amount of effective shear waves (VsN) was used as a reliability index for Vs values obtained by endoscopic ultrasound-guided shear wave measurements. Among the Vs values obtained, the five with the highest VsN were selected, and their median was defined as the median Vs (Vs-med). The median VsN of the five Vs values was defined as the median VsN (VsN-med). Endoscopic ultrasound-guided shear wave measurements were performed on 23 patients, with no complications occurring in any procedure. Histopathological diagnoses included 12 gastrointestinal stromal tumors, seven leiomyomas, and four schwannomas. Vs-med values for gastrointestinal stromal tumors, leiomyomas, and schwannomas were 2.46, 1.73, and 2.85 m/s, respectively, indicating that gastrointestinal stromal tumors and schwannomas were significantly stiffer than leiomyomas. VsN-med values for gastrointestinal stromal tumors, leiomyomas, and schwannomas were 40.5, 39, and 35.5%, respectively, with no significant differences. Endoscopic ultrasound-guided shear wave measurements are feasible for upper gastrointestinal subepithelial lesions and allow for the objective, non-invasive quantification of lesion stiffness. These results suggest the potential of endoscopic ultrasound-guided shear wave measurements as a valuable tool for the differential diagnosis of upper gastrointestinal subepithelial lesions.

Keywords: endoscopic ultrasound, gastrointestinal stromal tumor, shear wave elastography, strain elastography, subepithelial lesion

Abbreviations:
EUS: endoscopic ultrasound
UGI-SEL: upper gastrointestinal subepithelial lesion
GIST: gastrointestinal stromal tumor

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EUS-FNA: endoscopic ultrasound-guided fine-needle aspiration
EUS-SWM: endoscopic ultrasound-guided shear wave measurement
ROI: region of interest
Vs: shear wave velocity
Vs-med: the median shear wave velocity
VsN: total amount of effective shear waves
VsN-med: the median total amount of effective shear waves

INTRODUCTION

Endoscopic ultrasound (EUS) plays a crucial role in the evaluation of upper gastrointestinal subepithelial lesions (UGI-SEL).[1,2] One of the advantages of EUS is its ability to observe lesions, which are difficult to visualize with transabdominal ultrasound due to interference from gastrointestinal gas, with high resolution from within the gastrointestinal tract. UGI-SEL encompasses a wide range of lesions, from benign lesions including lipomas, ectopic pancreas, and leiomyomas, to those with malignant potential, such as gastrointestinal stromal tumors (GIST).[3] Since treatment strategies significantly vary depending on the histological diagnosis of UGI-SEL, an accurate histological diagnosis is essential. EUS-guided fine-needle aspiration (EUS-FNA) is a useful technique for obtaining tissue samples for the histological diagnosis of UGI-SEL.[4,5] However, the diagnostic yield of EUS-FNA is lower for UGI-SEL than for lymph nodes or pancreatic tumors,[6,7] with a meta-analysis reporting a diagnostic yield of 59.9%.[8] Although EUS-FNA is regarded as a safe method for a tissue diagnosis,[9] there is a very low risk of serious complications, such as significant bleeding or infection.[10,11] Therefore, EUS-FNA may not be recommended for patients receiving antithrombotic therapy or those with severe comorbidities, highlighting the need for complementary diagnostic methods.

It is well known, both empirically and pathologically, that many lesions are harder than normal tissue due to a number of factors, such as fibrosis, edema, and cellular density. Additionally, the "stiffness" of lesions varies according to their type, suggesting the potential of stiffness as an indicator for lesion detection and a specific diagnosis. Elastography is a technique that noninvasively images and quantifies the stiffness of tissues and lesions. In recent years, ultrasound elastography has been increasingly utilized in the medical field, particularly for the differential diagnosis of breast lesions.[12] Ultrasound elastography is categorized into strain elastography, which measures the stiffness of a lesion relative to its surroundings through tissue compression, and shear wave elastography, which quantifies stiffness as Young's modulus, an objective measure, by assessing the propagation speed of shear waves. Both types of elastography are performed with transabdominal ultrasound on extra-gastrointestinal organs, such as the breast,[13,14] and have also been applied to solid organs, such as the liver and pancreas, within the gastrointestinal field.[15,16]

On the other hand, elastography for UGI-SEL cannot be conducted using transabdominal ultrasound due to the presence of air within the gastrointestinal tract, which interferes with measurements. Therefore, it is necessary to perform measurements under EUS; however, to date, only relative stiffness measurements via strain elastography have been possible under EUS. Studies on the utility of EUS-strain elastography for diagnosing UGI-SEL are extremely limited,[17-19] and strain elastography is considered to lack objectivity and reproducibility. Therefore, the utility of elastography for the differential diagnosis of UGI-SEL has yet to be established.

Shear wave management (SWM) is a technique of shear wave elastography that has demonstrated its utility in transabdominal ultrasound.[20,21] Feasibility studies and assessments of activity

in autoimmune pancreatitis have been reported for EUS-guided shear wave measurement (EUS-SWM) applied to intra-abdominal organs.[22,23] To the best of our knowledge, tissue stiffness in UGI-SEL has not yet been assessed using EUS-SWM. Therefore, the present study conducted stiffness measurements of UGI-SEL using EUS-SWM and examined its feasibility and utility.

MATERIALS AND METHODS

Patients

The present study was approved by the Ethics Committee of Nagoya University Hospital and is registered in the University Hospital Medical Information Network (UMIN) clinical trial registry (UMIN-CTR, 000028072; https://www.umin.ac.jp/ctr/index.htm). This study was conducted at Nagoya University between January 2018 and September 2019. We performed EUS-SWM on patients diagnosed with UGI-SEL using EUS. Twenty-three consecutive patients with confirmed histological diagnoses of mesenchymal tumors were enrolled. Patients for whom a histological diagnosis was not obtained were excluded from the study. Written informed consent was obtained from all participants in accordance with the Declaration of Helsinki (1975).

Pathology

Histopathological diagnoses were performed using tissue specimens obtained through endoscopic biopsy, EUS-FNA, or surgical resection. When endoscopic biopsy and surgical resection specimens were both available, the definitive diagnosis was based on the resected specimen.

EUS-SWM procedure

EUS and EUS-SWM were performed on the same day, with EUS-SWM being conducted by a single endoscopist (T.M). Representative cases of EUS-SWM are shown in Figs. 1, 2, and 3.

EUS-SWM was performed using a convex-type ultrasound endoscope (GF-UCT260, Olympus, Tokyo, Japan) and an ultrasound observation system (ARIETTA 850, Hitachi, currently Fujifilm, Tokyo, Japan) under sedation induced by the intravenous administration of 2.5–10 mg of midazolam.

Shear wave velocity (Vs) was used as an indicator of tissue stiffness and was displayed in meters per second (m/s). Shear wave propagation is faster in stiffer tissue. As a reliability index for the Vs values obtained from EUS-SWM, the total amount of effective shear waves (VsN) was used to assess whether shear wave propagation was an appropriate measurement. VsN was displayed as a percentage and appeared simultaneously on the monitor during Vs measurements.

EUS-SWM was conducted with distilled water pooling to avoid compression from the tip of the endoscope. Measurements were taken during breath-holding at the end of either inspiration or expiration to minimize lesion movement caused by respiratory fluctuations. A rectangular region of interest (ROI) measuring 10×5 mm was placed within the target lesion, and Vs within ROI was measured. ROI was adjusted to be positioned 10–20 mm from the EUS probe, ensuring that large vessels or cystic components were excluded.

Vs was measured repeatedly until five Vs values with VsN ≥50% were obtained, with a minimum of five and maximum of 20 measurements. If five Vs values with VsN ≥50% were not obtained, EUS-SWM was terminated after 20 attempts. Based on the Vs values obtained, the median of five Vs values with the highest VsN was defined as the median Vs (Vs-med). Additionally, the median of the corresponding VsN values was defined as the median VsN (VsN-med).

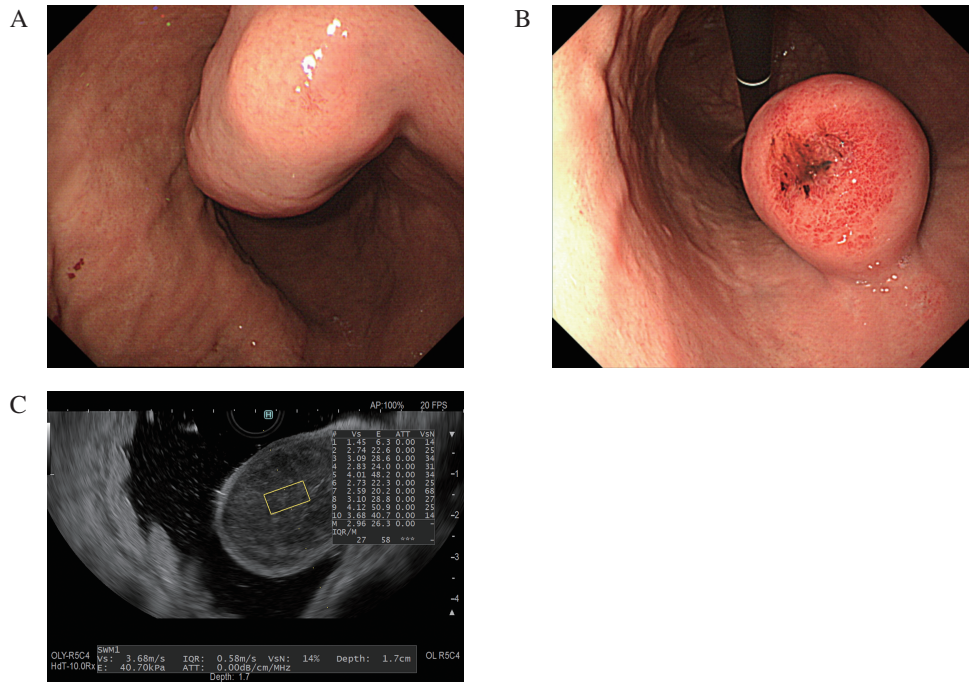

Fig. 1 Endoscopic findings of gastric gastrointestinal stromal tumor (GIST)
Fig. 1A, B: Endoscopic images of gastric GIST
Fig. 1C: Endoscopic ultrasound-guided shear wave measurement (EUS-SWM) of gastric GIST
Vs: shear wave velocity
IQR: interquartile range
Depth: the depth of the region of interest
E: Young's modulus
ATT: attenuation coefficient
VsN: total amount of effective shear waves

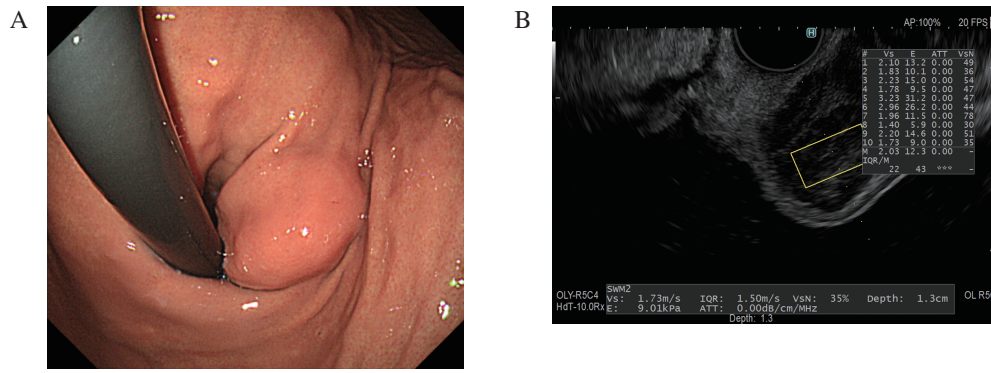

Fig. 2 Endoscopic findings of gastric leiomyoma
Fig. 2A: Endoscopic image of gastric leiomyoma
Fig. 2B: Endoscopic ultrasound-guided shear wave measurement (EUS-SWM) of gastric leiomyoma
Abbreviations are explained in the list to Figure 1.

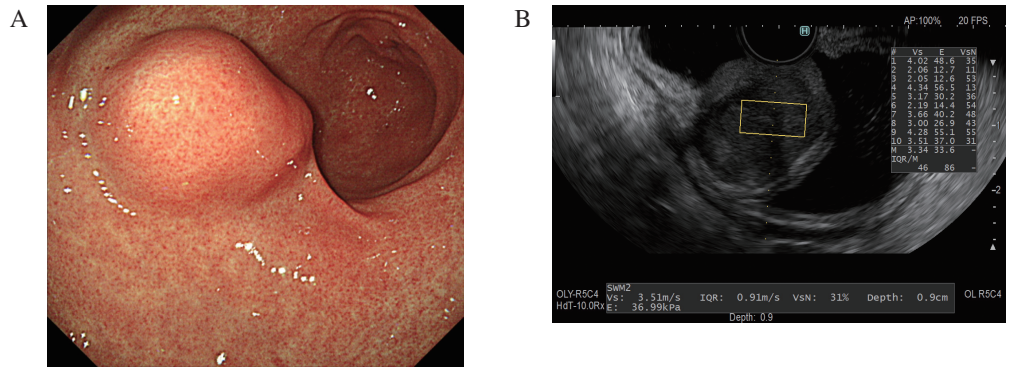

Fig. 3 Endoscopic findings of gastric schwannoma
Fig. 3A: Endoscopic image of gastric schwannoma
Fig. 3B: Endoscopic ultrasound-guided shear wave measurement (EUS-SWM) of gastric schwannoma
Abbreviations are explained in the list to Figure 1.

Primary and secondary outcomes

The primary outcome of the present study was to compare the tissue stiffness of UGI-SEL, as indicated by Vs-med, according to the histological diagnosis. Secondary outcomes included comparisons of VsN-med, the number of measurements, and the success rate of measurements.

Statistical analysis

Descriptive statistics were presented as medians (range). Continuous variables, such as age, tumor size, Vs-med, and VsN-med, were statistically analyzed using the Kruskal–Wallis test, while categorical variables, such as sex, were analyzed using Fisher's exact test. Multiple comparisons between the two groups were conducted using Tukey's honestly significant difference test. Statistical analyses were conducted using JMP pro 17 (SAS Institute, Cary, NC, USA). All tests were two-tailed, with a P-value <0.05 indicating a significant difference.

RESULTS

The background characteristics of the 23 patients who underwent EUS-SWM are shown in Table 1. The cohort consisted of 11 males and 12 females, with a median age of 60 years (range, 33–88 years). Tumor locations were classified into four groups based on esophageal (E) and gastric regions (upper part (U)/middle part (M)/lower part (L)): 3 cases in the E region, 13 in the U region, 5 in the M region, and 2 in the L region. The median tumor size was 23 mm (range, 17–91 mm). Growth patterns included 11 cases of intraluminal growth, 9 of intramural growth, and 3 of extraluminal growth. EUS findings evaluated tumor echogenicity (low/iso/high), the internal echo pattern (homogeneous/heterogeneous), and contour (regular/irregular). Echogenicity was low in 20 cases, iso in 1, and high in 2. The internal echo pattern was homogeneous in 4 cases and heterogeneous in 19. The contour was regular in 13 cases and irregular in 10. The methods used for a tissue diagnosis included mucosal incision-assisted biopsy in 1 case, EUS-FNA in 15, and surgical specimens in 7. Histopathological diagnoses were as follows: 12 cases of GIST, 7 of leiomyoma, and 4 of schwannoma. Table 2 details patient backgrounds for each histopathological diagnosis.

Table 3 shows Vs-med, VsN-med, the number of measurements, and measurement success

rates for each histopathological diagnosis. In comparisons of GIST and leiomyoma, Vs-med was significantly higher in the GIST group (2.46 m/s; range, 1.71–3.29) than in the leiomyoma group (1.73 m/s; range, 1.48–2.11), indicating that GIST were significantly harder (P = 0.014). Similarly, in comparisons between the schwannoma group (2.85 m/s; range, 1.86–3.33) and leiomyoma group, the schwannoma group was significantly harder (P = 0.010; Fig. 4). However, no significant difference was observed in stiffness between the GIST and schwannoma groups (P = 0.60), making it difficult to differentiate between these two groups.

Table 1 Patient characteristics

			n = 23
Male:Female			11:12
Age, median (range)			60 (33–88)
Location	Esophagus		3
	Stomach	Upper part	13
		Middle part	5
		Lower part	2
Tumor size (mm), median (range)			23 (17–91)
Growth pattern	Intraluminal growth		11
	Intramural growth		9
	Extraluminal growth		3
Endoscopic ultrasound findings	Tumor echogenicity	Low	20
		Iso	1
		High	2
	Internal echo pattern	Homogeneous	4
		Heterogeneous	19
	Contour	Regular	13
		Irregular	10
Tissue diagnosis method	Mucosal incision-assisted biopsy		1
	EUS-FNA		15
	Surgery		7
Histopathological diagnosis	GIST		12
	Leiomyoma		7
	Schwannoma		4

GIST: gastrointestinal stromal tumor
EUS-FNA: endoscopic ultrasound-guided fine needle aspiration

Table 2 Patient characteristics by histopathological diagnosis

			GIST (n=12)	Leiomyoma (n=7)	Schwannoma (n=4)	*P*-value
Male:Female			2:10	7:0	2:2	<0.001
Age, median (range)			68 (48–88)	51 (33–60)	53.5 (41–62)	0.006
Location	Esophagus		0	3	0	0.091
	Stomach	Upper part	7	4	2	
		Middle part	4	0	1	
		Lower part	1	0	1	
Tumor size (mm), median (range)			24.5 (18–91)	22 (17–30)	22.5 (18–35)	0.50
Growth pattern	Intraluminal growth		6	5	0	0.044
	Intramural growth		3	2	4	
	Extraluminal growth		3	0	0	
Endoscopic ultrasound findings	Tumor echogenicity	Low	11	7	2	0.10
		Iso	0	0	1	
		High	1	0	1	
	Internal echo pattern	Homogeneous	1	3	0	0.13
		Heterogeneous	11	4	4	
	Contour	Regular	7	3	3	0.64
		Irregular	5	4	1	
Tissue diagnosis method	Mucosal incision-assisted biopsy		0	1	0	0.016
	EUS-FNA		5	6	4	
	Surgery		7	0	0	

GIST: gastrointestinal stromal tumor
EUS-FNA: endoscopic ultrasound-guided fine needle aspiration

Table 3 Results of endoscopic ultrasound-guided shear wave measurements by histopathological diagnosis

	GIST	Leiomyoma	Schwannoma	*P*-value
Vs-med, m/s	2.46 (1.71–3.29)	1.73 (1.48–2.11)	2.85 (1.86–3.33)	0.008
VsN-med, %	40.5 (17–63)	39 (20–54)	35.5 (18–62)	0.88
Number of measurements, median (range)	20 (17–20)	20 (17–20)	20 (8–20)	0.63
Measurement success rate, median (range)	77.5 (45–100)	80 (50–100)	85 (65–100)	0.53

GIST: gastrointestinal stromal tumor
Vs-med: the median shear wave velocity
VsN-med: the median total amount of effective shear waves

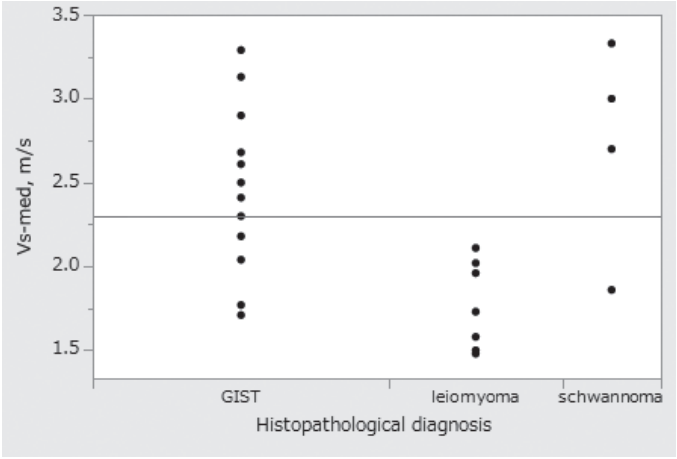

Fig. 4 The median shear wave velocity (Vs-med) of gastric gastrointestinal stromal tumor (GIST), leiomyoma, and schwannoma groups

Regarding VsN-med, the GIST group had a median of 40.5% (range, 17–63), the leiomyoma group had 39% (range, 20–54), and the schwannoma group had 35.5% (range, 18–62), with no significant differences (P = 0.88). The number of measurements was 20 (range, 17–20) for the GIST group, 20 (range, 17–20) for the leiomyoma group, and 20 (range, 8–20) for the schwannoma group, with no significant differences (P = 0.63). Measurement success rates were 77.5% (range, 45–100) for the GIST group, 80% (range, 50–100) for the leiomyoma group, and 85% (range, 65–100) for the schwannoma group, with no significant differences (P = 0.53).

There were no complications observed in any of the EUS-SWM procedures.

DISCUSSION

To the best of our knowledge, this is the first study to apply EUS-SWM to UGI-SEL. Shear wave elastography has traditionally been used only in conventional transabdominal ultrasound examinations. Due to the difficulties associated with visualizing UGI-SEL via transabdominal ultrasound, shear wave elastography has not been applicable to UGI-SEL in clinical practice. In the present study, the tumor stiffness of UGI-SEL in 23 consecutive patients was successfully measured under EUS according to a predetermined protocol. The results obtained indicate that GIST and schwannoma were significantly stiffer than leiomyoma. Additionally, EUS-SWM was performed on all 23 enrolled patients without any complications. The ability to quantify the stiffness of UGI-SEL and assess it objectively is considered an advantage of EUS-SWM, which is in contrast to conventional EUS that requires subjective judgments.

Although few studies have examined the effectiveness of EUS elastography for UGI-SEL, previous studies only utilized strain elastography to measure relative stiffness.[17-19] A key limitation of strain elastography is its inability to provide absolute stiffness values, leading to concerns about reproducibility and objectivity. The EUS-SWM technique employed in the present study offers the advantage of rapidly and repeatedly measuring the objective stiffness of lesions by calculating the propagation velocity (Vs) of the shear wave as an absolute indicator of tissue stiffness. In contrast to strain elastography, which cannot be used to compare stiffness between patients due to its subjective nature, shear wave elastography allows for quantified and comparable

measurements of stiffness across different patients.

Since stiffness measurements using shear wave elastography were previously shown to increase if a target was compressed during the procedure,[24] measurements in the present study were conducted in a water-filled environment to avoid compressing the tumor with the endoscopic scope. Although the findings of SWE are not affected by age or sex, the distance between the ultrasound probe and lesion is a significant factor.[25] In the present study, we ensured that the distance between the ultrasound endoscope probe and the lesion was maintained within 1–2 cm. The ultrasound imaging device ARIETTA850 used for EUS-SWM is equipped with the VsN function, a unique reliability indicator that assesses the credibility of the Vs values obtained. Yada et al reported that a VsN value >50% was a good indicator of accurate SWM in the liver.[20,21] While we also considered VsN values >50% to be an indicator of reliability, the VsN-med for each histopathological diagnosis ranged between 35.5–40.5%, which was <50%. This difference may be attributed to variations in the measurement environments between transabdominal ultrasound and EUS. Additionally, VsN values may differ depending on whether the target is homogeneous, such as in chronic liver disease, or heterogeneous, as with GIST. The further accumulation of cases and verification will be required to establish the optimal VsN threshold for UGI-SEL measurements.

In terms of stiffness measurements, GIST and schwannoma were significantly stiffer than leiomyoma, which is consistent with previous findings on the usefulness of strain elastography for the differential diagnosis of UGI-SEL.[17] The differential diagnosis of UGI-SEL is challenging based solely on endoscopic findings, computed tomography (CT) imaging, and EUS findings.[26-28] By providing information on tissue stiffness, EUS-SWM may serve as a complementary tool in the diagnosis of UGI-SEL. Moreover, the ability to measure stiffness with the press of a button is a significant advantage in terms of simplicity.

EUS-FNA is an essential procedure for the diagnosis of UGI-SEL because it provides a histological diagnosis. Our institution has reported relatively favorable EUS-FNA results using forward-viewing and oblique-viewing convex scopes.[29] However, EUS-FNA is not without its limitations, such as the difficulty of puncturing some sites and the inability to obtain adequate samples,[30] which may impede treatment decisions. EUS-SWM may help in decision-making regarding whether to perform EUS-FNA, particularly for patients at a high risk of complications due to an advanced age, anticoagulant use, or severe underlying conditions. EUS elastography may be useful in distinguishing between benign and malignant tumors, potentially reducing the need for unnecessary EUS-FNA.[31]

The present study has a number of limitations that need to be addressed. The sample size was small. Furthermore, factors that may affect measurements, such as respiratory fluctuations, patient movement, and operator hand tremors, were not completely eliminated. A previous study reported that movement of the target lesion may affect shear wave stiffness measurements.[32] To minimize the impact of respiratory fluctuations, we performed measurements during breath-holding at the end of inhalation or exhalation. To further increase measurement accuracy, methods to compensate for respiratory fluctuations in shear wave measurements need to be examined. VsN values may have decreased under some conditions, such as body movement or hand tremors, and, thus, these measurements were excluded from Vs-med. Conducting multiple measurements, as in the current protocol, is considered to reduce the impact of artifacts due to target lesion movement. Another limitation is that the validity of the measurement protocol for assessing tissue stiffness has not yet been thoroughly examined. In the present study, in consideration of the burden on patients and the examination time, we set the upper limit of measurements to 20 and obtained Vs values based on the described method. However, the appropriate number of measurements and VsN cut-off value remain unresolved issues. Further investigations are

necessary by accumulating more cases. Moreover, the range of ROI in the present study was limited to 10×5 mm, which may not necessarily reflect the overall stiffness of a lesion. There are limitations regarding the size of ROI as well as its placement, such as the requirement to set ROI 1–2 cm away from the probe. Therefore, it becomes impossible to measure the central area of larger tumors. Technological advances, such as the expansion of ROI, are eagerly anticipated. In addition, we did not compare tissue stiffness obtained from EUS-SWM with pathological findings. Since tissue stiffness is affected by a number of factors, such as tumor cell density, inflammation, and edema, future studies need to compare stiffness information from EUS-SWM with histopathological findings.

CONCLUSION

EUS-SWM was feasible for measuring stiffness in UGI-SEL, and the stiffness of lesions was non-invasively and objectively quantified. There were significant differences in stiffness between GIST/schwannoma and leiomyoma ($P = 0.014$, $P = 0.010$), suggesting the potential of EUS-SWM for the differential diagnosis of UGI-SEL. EUS-SWM may become a useful diagnostic tool that increases the diagnostic accuracy of UGI-SEL; however, the small sample size in the present study warrants further data accumulation, including multicenter validation.

DISCLOSURE STATEMENTS

The ARIETTA850 ultrasound system was provided by Hitachi (currently Fujifilm, Tokyo, Japan) for data collection purposes. Hitachi (currently Fujifilm) did not participate in the design, execution, or analysis of this study. The authors declare no potential conflicts of interest. Grants are none reported.

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