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Diagnostic Yields of Endoscopic Ultrasound-Guided Fine-Needle Tissue Acquisition according to the Gastric Location

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Abstract

Aim

The histologic diagnosis of sub-epithelial tumors (SETs) in stomach has been achieved via endoscopic or surgical resection. We evaluated the efficacy of endoscopic ultrasound-guided fine-needle tissue acquisition (EUS-FNTA) for the diagnosis of gastric SETs according to the gastric location.

Method

Thirty-three patients diagnosed with gastric SETs via EUS-FNTA from January 2016 to May 2018 were analyzed retrospectively. Demographic characteristics, diagnostic yields and complications were evaluated.

Results

Nineteen patients (57.6%) were female, with a median age of 57.7 years. EUS revealed a mean longitudinal diameter of 25.6 mm. The most common location of SETs was gastric body (n = 18, 54.5%), followed by cardia and fundus (n = 10, 30.3%), and antrum (n = 5, 15.2%). Twenty-gauge biopsy needle was used most frequently (90.9%). The diagnostic yield was obtained in 23 patients (69.7%). The most common diagnosis was gastrointestinal stromal tumor (69.5%), followed by leiomyoma (13.0%), and ectopic pancreas (8.7%). The diagnostic yield of SETs in gastric antrum (0/5, 0%) was significantly lower than in the gastric body and cardia (23/28, 82.1%, $p = 0.001$). A case of immediate bleeding after EUS-FNTA occurred in one patient (3.0%) who recovered uneventfully. According to studies reported in English literature, the overall diagnostic yield of SETs in gastric antrum was significantly lower than in the gastric body, fundus, and cardia (29.7% vs. 71.4%, $p < 0.001$, n = 191)

Conclusions

Although EUS-FNTA is an advanced diagnostic tool for gastric SETs, it is essential to develop more effective methods for the diagnosis of antral SETs.

Background

Gastric subepithelial tumors (SETs) encompass an extensive range of benign, premalignant, and malignant lesions. SETs are typically concealed by the mucosa. The word ‘submucosal tumor’ is a misleading term, as these lesions are not always confined to the submucosa, and instead may originate in both intramural and extramural locations [1]. Although these lesions are considered ‘rare’, gastric SETs are quite frequently observed incidental to gastroscopy [2, 3]. Many SETs are benign [4, 5]. However, gastric SETs may be premalignant or malignant lesions, such as gastrointestinal stromal tumors (GISTs). Although endoscopic ultrasound (EUS) criteria have been used to differentiate GISTs from leiomyomas [6], tissue diagnosis is considered the gold standard [7]. GISTs are mesenchymal neoplasms with a

characteristic immunohistological expression of c-kit (CD117) that distinguishes them from other benign spindle cell neoplasms, such as leiomyomas or Schwannomas [8, 9].

Tissues from SETs within the second or third layer in EUS can be acquired via jumbo biopsies and endoscopic mucosal resection (EMR) techniques. However, tissue acquisition is difficult from SETs within the fourth layer via EUS. EUS-guided fine-needle tissue acquisition (EUS-FNTA) is an advanced technique for the differentiation of GISTs and leiomyomas within the fourth layer [10].

Until now, the diagnostic accuracy of EUS-FNTA according to the gastric location of SETs has not been well established.

Methods

2.1. Ethical considerations

The present study was conducted in accordance with the ethical guidelines of the Declaration of Helsinki. This study was approved by the Institutional Review Board of Chonnam National University Hospital (IRB No: CNUH-2019-005, approval date: 2019-01-09).

2.2. Patients and study protocol

This study is a retrospective study involving 33 patients with gastric SETs who underwent EUS-FNTA at Chonnam National University Hospital from January 2016 to May 2018. Demographic characteristics, location and size of SETs, EUS findings, methods of EUS-FNTA, diagnostic yield, and complications were evaluated.

2.3. Definition

We classified the gastric location into three areas: upper third, middle third, and lower third. Fundus and cardia were defined as the upper third area of stomach. Corpus was defined as middle third area of the stomach. Antrum and pylorus were defined as the lower third of the stomach.

EUS-guided FNTA comprises both EUS-guided fine-needle aspiration and EUS-guided fine-needle biopsy.

2.4. Endoscopic procedure

The EUS Probe (UM-2R®; Olympus, Tokyo, Japan) and probe driving unit (MAJ-935®; Olympus) were used to map the lesion. The image frequency of the probe was 12 MHz. EUS-guided FNTA was performed with a linear array echoendoscope (GF-UCT260®; Olympus) and probe driving unit (MAJ-1720; Olympus). Under ultrasound guidance, SETs were punctured with 19, 20, 22 or 25 gauge needles (EchoTip ProCore®, Cook Medical Inc, Bloomington, U.S.A; EchoTip Ultra®, Cook Medical; EZ Shot3 Plus®, Olympus). After visualizing the tip of the catheter, the needle was advanced from the catheter sheath through the wall of the gastrointestinal (GI) tract and into the target lesions under ultrasound guidance. The stylet was

removed, and the initial passes were performed by moving the needle back and forth within the target lesion for 15–30 seconds. No suction was applied during biopsy unless the biopsy failed to yield any material or the lesion was cystic.

2.5 Histopathology

The biopsy specimens were expressed onto the glass slides by flushing air into the needle assembly. The needle was reintroduced until an adequate number of biopsy specimens were obtained, as determined by an endosonographer based on gross inspection. The biopsy specimens were transferred into a formalin bottle. Cytological smears with aspirated specimens were also prepared. The smeared slides were fixed with alcohol. The biopsy and aspiration slides of all the cases were evaluated and reviewed by an experienced GI pathologist. Immunohistochemical staining was performed for the differential diagnosis of gastric SETs whenever necessary. An immunohistochemical study was performed to determine the expression of CD 34, CD 117, S100, and smooth muscle actin expressed in the spindle cell lesion placed on the H&E slides. A diagnostic procedure, including immunohistochemical staining, was characterized by the availability of adequate number of biopsy specimens or cytological aspirates.

2.6. Statistical analysis

Statistical analysis was performed using IBM-SPSS version 23.0 (SPSS Inc., IBM, Chicago, IL, USA). Continuous data are expressed as the mean ± standard deviation, or medians (ranges) and categorical data as absolute and relative frequencies. Continuous variables were analyzed using a Student's t-test. Categorical data were examined using Fisher's exact test or x^2 test with Yates's correction.

Results

3.1. Baseline characteristics of the enrolled patients

Nineteen patients (57.6%) were female, with a median age of 57.7 ± 13.2 years. EUS revealed mean longitudinal diameters of 25.6 mm. The most common endoscopic finding was an intact mucosa (81.8%), followed by ulceration (9.1%), dimpling (6.1%) and erosion (3.0%). The fourth layer (54.5%) was the most common layer of SETs, followed by the third layer (21.2%) and the outer wall (6.1%). The most common location of SETs in the stomach was the middle third (n = 18, 54.5%) followed by the upper third (n = 10, 30.3%) and the lower third (n = 5, 15.2%). Longitudinal diameter of SETs was 25.6 ± 12.8 mm (range, 11–52 mm). The transverse axis diameter of SETs was 19.3 ± 12.8 mm (range, 10–45 mm). A 20 gauge needle (EchoTip ProCore®) was used most frequently (90.9%), and 19, 22 and 25 gauge needles were used in each case.

A mild degree of immediate bleeding after EUS-FNTA occurred in one patient (3.0%). We performed endoscopic hemoclipping in this case to achieve hemostasis.

The diagnostic yield was obtained in 23 patients (69.7%). The most common diagnosis was GIST (69.5%) followed by leiomyoma (13.0%) and ectopic pancreas (8.7%). The diagnostic yield of SETs in lower third (0/5, 0%) was significantly lower than in the upper third and middle third (23/28, 82.1%, p = 0.001) (Table 1).

Table 1
Comparison of 33 Patients with SETs according to Gastric Location of the Lesion.

	Total (N = 33)	Upper + middle third (N = 28, %)	Lower third (N = 5, %)
Age, years (mean ± SD)†	57.7 ± 13.2	57.1 ± 13.1	60.8 ± 14.9
Female, n (%)	19 (57.6)	16 (57.1)	3 (60)
Male, n (%)	14 (42.4)	12 (42.9)	2 (40)
Endoscopic finding			
Intact mucosa	27 (81.8)	24 (85.7)	3 (60)
Ulceration	3 (9.1)	2 (7.1)	1 (20)
Dimpling	2 (6.1)	2 (7.1)	
Erosive mucosa	1 (3.0)		1 (20)
Layer			
3th layer	7 (21.2)	6 (21.4)	1 (20)
4th layer	18 (54.5)	16 (57.1)	2 (40)
Outer wall	2 (6.1)	2 (7.1)	
Not clearly identified	6 (18.2)	4 (14.3)	2 (40)
Location			
Cardia and fundus	10 (30.3)	10 (35.7)	
Corpus	18 (54.5)	18 (64.3)	
Antrum	5 (15.2)		5 (100)
Size (mm x mm)			
Longitudinal diameter	25.6 ± 12.8	25.8 ± 13.3	24.0 ± 10.7
Transverse axis	19.3 ± 12.8	19.6 ± 13.7	18.1 ± 7.3
Complications			
bleeding	1 (3.3)	1 (3.6)	0
Needle size			
20 gauge	30 (90.9)	26 (92.9)	4 (80)
19 gauge	1 (3.0)	1 (3.6)	

SET: sub-epithelial tumor

	Total (N = 33)	Upper + middle third (N = 28, %)	Lower third (N = 5, %)
22 gauge	1 (3.0)	1 (3.6)	
25 gauge	1 (3.0)		1 (20)
Frequency of needle passage	2.78 ± 0.88	2.79 ± 0.88	3.6 ± 0.55
SET: sub-epithelial tumor			

3.2 Comparative analysis of EUS, EUS-FNTA, and surgery or endoscopic resection

Using EUS, GIST was most frequently observed (n = 23, 69.7%), followed by neuroendocrine tumor (NET) (n = 2, 6.1%), leiomyoma (n = 2, 6.1%), and ectopic pancreas (n = 2, 6.1%). Fine-needle biopsy resulted in a histopathologic diagnostic yield in 20 patients (60.6%). GIST (n = 14), leiomyoma (n = 3), ectopic pancreas (n = 2), and chronic gastritis (n = 1) were diagnosed. Fine-needle aspiration resulted in a histopathologic diagnostic yield in 7 patients (21.2%). Spindle cell lesions (n = 4), epithelioid lesions (n = 1), a benign epithelial cell (n = 1), and an ectopic pancreas (n = 1) were diagnosed.

There was no statistical significance in diagnostic yield between SETs measuring more than 2 cm (16/22, 72.7%) and SETs less than 2 cm (6/11, 54.5%, $p = 0.296$). In addition, there was no statistical significance in diagnostic yield between SETs larger than 3 cm (6/10, 60%) and those less than 3 cm (16/23, 69.6%, $p = 0.592$).

Diagnostic concordance between EUS-FNTA compared with that of endoscopic or surgical resection was 100% (13/13). Concordance of EUS only compared with that of endoscopic or surgical resection was 82.4% (14/17). The concordance of EUS-FNTA compared with that of EUS only was 48.5% (16/33) (Table 2).

Table 2
Comparison of 33 Cases diagnosed by EUS, EUS-FNTA, and Surgery or ESD.

Patient number	Site of SET	Size (mm x mm)	EUS	EUS-FNTA	Needle Gauge	Model of FNTA needle	Operation or ESD
1	Cardia	52 × 45	GIST	Leiomyoma	20	ProCore	Leiomyoma
2	Antrum	40 × 30	GIST	Undiagnostic	20	ProCore	Ectopic pancreas
3	Cardia	20 × 20	AGC, Bormann IV	Undiagnostic	19	Ultra	Chronic gastritis
4	Corpus	12 × 5	NET	Undiagnostic	20	ProCore	NET
5	Cardia	39 × 20	Leiomyoma	Undiagnostic	20	ProCore	Leiomyoma
6	Corpus	20 × 15	Leiomyoma	Undiagnostic	20	ProCore	Leiomyoma
7	Corpus	16 × 11	GIST	GIST	20	ProCore	GIST
8	Corpus	13 × 8	GIST	GIST	20	ProCore	GIST
9	Corpus	21 × 19	GIST	GIST	20	ProCore	GIST
10	Corpus	30 × 28	GIST	GIST	20	ProCore	GIST
11	Fundus	25 × 15	GIST	GIST	20	ProCore	GIST
12	Corpus	20 × 18	GIST	GIST	20	ProCore	GIST
13	Corpus	34 × 24	GIST	GIST	20	ProCore	GIST
14	Corpus	32 × 28	GIST	GIST	20	ProCore	GIST
15	Corpus	25 × 15	GIST	GIST	20	ProCore	GIST

AGC: advanced gastric cancer, ESD: endoscopic submucosal dissection, EUS-FNTA: endoscopic ultrasound-guided fine-needle tissue acquisition, EZ Shot: EZ Shot3 Plus®, GIST: gastrointestinal stromal tumor, N/A: not available, NET: neuroendocrine tumor, Procore: EchoTip ProCore®, Ultra: EchoTip Ultra®

Patient number	Site of SET	Size (mm x mm)	EUS	EUS-FNTA	Needle Gauge	Model of FNTA needle	Operation or ESD
16	Corpus	25 × 22	GIST	GIST	20	ProCore	GIST
17	Cardia	13 × 11	GIST	GIST	20	ProCore	GIST
18	Corpus	30 × 15	Pancreatic tail cancer	GIST	20	ProCore	N/A
19	Corpus	70 × 70	GIST	GIST	20	ProCore	N/A
20	Cardia	23 × 9	GIST	Undiagnostic	20	ProCore	N/A
21	Corpus	15 × 10	Early gastric cancer	Undiagnostic	20	ProCore	N/A
22	Cardia	23 × 12	GIST	Ectopic pancreas	20	ProCore	N/A
23	Antrum	15 × 15	Ectopic pancreas	Ectopic pancreas	20	ProCore	N/A
24	Corpus	29 × 11	NET	Leiomyoma	22	EZ Shot	N/A
25	Corpus	25 × 20	GIST	Leiomyoma	20	ProCore	N/A
26	Antrum	17 × 13	GIST	GIST	25	ProCore	N/A
27	Cardia	16 × 14	Ectopic pancreas	Chronic gastritis	20	ProCore	N/A
28	Antrum	18 × 12	GIST	Undiagnostic	20	ProCore	N/A
29	Antrum	30 × 20	Gastritis cystica profunda	Undiagnostic	20	ProCore	N/A
30	Cardia	48 × 44	GIST	GIST	20	ProCore	N/A

AGC: advanced gastric cancer, ESD: endoscopic submucosal dissection, EUS-FNTA: endoscopic ultrasound-guided fine-needle tissue acquisition, EZ Shot: EZ Shot3 Plus®, GIST: gastrointestinal stromal tumor, N/A: not available, NET: neuroendocrine tumor, Procore: EchoTip ProCore®, Ultra: EchoTip Ultra®

Patient number	Site of SET	Size (mm x mm)	EUS	EUS-FNTA	Needle Gauge	Model of FNTA needle	Operation or ESD
31	Corpus	21 × 14	GIST	Chronic gastritis	20	ProCore	N/A
32	Corpus	16 × 15	GIST	Undiagnostic	20	ProCore	N/A
33	Cardia	11 × 10	GIST	GIST	20	ProCore	N/A

AGC: advanced gastric cancer, ESD: endoscopic submucosal dissection, EUS-FNTA: endoscopic ultrasound-guided fine-needle tissue acquisition, EZ Shot: EZ Shot3 Plus®, GIST: gastrointestinal stromal tumor, N/A: not available, NET: neuroendocrine tumor, Procore: EchoTip ProCore®, Ultra: EchoTip Ultra®

Discussion

SETs can be identified via endoscopy or EUS. The size and the pillow sign can be evaluated with endoscopy. EUS can be used to distinguish intramural from extramural lesions as well as the origin of the layer and echo patterns such as hyperechoic, hypoechoic, or anechoic lesion. However, the diagnostic accuracy of EUS is relatively low without histologic confirmation [7, 11]. The concordance of EUS with the histology is only about 43–66.7% [7, 11]. In our study, the agreement between EUS-FNTA and EUS (48.5%, 16/33) was similar to that of a previous study.

SETs can be histologically diagnosed via both endoscopic and surgical resection [12, 13]. Recently, new techniques such as endoscopic full-thickness resection and endoscopic submucosal tunnel resection were developed to remove SETs in deeper layers where it was difficult to enucleate SETs using conventional methods [14, 15]. However, it is not always easy to perform histological diagnosis via endoscopic or surgical resection for all benign looking lesions because of their invasiveness and considerable complication rates. Therefore, it is reasonable to perform EUS-FNTA for histologic confirmation of SETs [16, 17].

Several studies confirmed the usefulness of EUS-FNTA.[18–21] EUS-guided fine-needle biopsy for suspected GI stromal tumors was technically similar and the safety was equivalent to that of fine-needle aspiration, with better tissue acquisition [18]. Needles of various sizes ranging from 19 to 25 gauge were used to perform EUS-FNTA [10, 19, 22, 23]. It was assumed that the19-gauge large-bore needles might be increase the diagnostic yield of SETs compared with small-bore needles. However, the 19-gauge needle showed no superiority compared with 22-gauge needles [10]. Various needle passage frequencies (1 to 7) were used in other studies [10, 22]. To date, however, no clear consensus is available regarding the optimal frequency of needles. In the present study, the mean frequency of needle passage was 2.78. Our method using EUS-FNTA was similar to that of other studies.

In the present study, the histopathological diagnosis of gastric SETs based on FNTA in 33 cases was analyzed. GIST was the most common cause of SETs. The diagnostic yield was 69.7% (23/33). The reliability of diagnostic yield with EUS-FNTA was 100% (13/13). EUS-FNTA was more accurate compared with EUS only (82.4%, 14/17). The concordance between EUS and EUS-FNTA was relatively low (48.5%, 16/33).

In our study, the needle passage was more frequent in the lower third than in the upper to mid third, which was 3.6 times versus 2.79 times. However, the diagnostic yield of SETs obtained via EUS-FNTA in the lower third of the gastric region was very low (0/5). On the other hand, a considerable diagnostic yield of SETs was obtained with EUS-FNTA in the upper to middle third of the stomach (23/28, 82.1%). According to published studies in English language, three studies reported the diagnostic yields of EUS-FNTA according to the gastric location [10, 24, 25]. Eckardt et al. [10] showed lower diagnostic yield in the lower third area (36.4%) compared with the upper to middle third of the stomach (75%, $p = 0.008$). Lee et al. [24] (25% vs. 59%, $p = 0.183$) and Suzuki et al. [25] (33.3% vs. 80.5%, $p = 0.013$) also showed a lower diagnostic yield in the lower third compared with the upper to middle third of the stomach. The diagnostic yield of overall cases, including our study, were significantly lower in the lower third of the stomach compared with the upper to middle third (29.7% vs. 71.4%, $p < 0.001$, n = 191) (Table 3).

Table 3
Review of four original studies published in English showing diagnostic rates of EUS-FNTA by gastric location

Case (n)	Biopsy needle (gauge)	Size of SET (median) (mm)	Diagnostic rate depending on location of SET (%)			Upper + middle vs Lower	References
			Upper third	Middle third	Lower third	P value	
46	19G	24	10/12 (83.3)	8/12 (66.7)	8/22 (36.4)	0.008	Eckardt [10]
65	TCB	37	15/26 (57.7)	21/35 (60)	1/4 (25)	0.183	Lee [24]
47	22G or Echo Tip	N/A	22/26 (84.6)	11/15 (73.3)	2/6 (33.3)	0.013	Suzuki [25]
33	20G (90%)	26	8/10 (80)	15/18 (83.3)	0/5 (0)	< 0.001	Our case
191			55/74 (74.3)	55/80 (68.8)	11/37 (29.7)	< 0.001	

EUS-FNTA: endoscopic ultrasound-guided fine-needle tissue acquisition; G: gauze; TCB: true cut biopsy, N/A: not available, SET: sub-epithelial tumor

The two most common causes of non-diagnostic EUS-FNTA were insufficient tissue acquisition and puncture failure in the gastric wall. The antral wall of the stomach is known to be relatively thicker than that of the corpus or cardia. Lee et al. [24] reported that the puncture failure rate was relatively higher in the lower third (50%) compared with upper to middle third (11.4%) of the stomach. These results suggested that thickening of the gastric wall influences the diagnostic yields of EUS-FNTA. Adequate needle gauge and frequency of needling vary with the gastric location of SETs. Suzuki et al. [25] suggested that it was more difficult to maintain a scope stably in the lower third area of the stomach. In addition, it is known that ectopic pancreas is more frequently detected in the antrum compared with corpus or cardia [26–29]. Ectopic pancreas is a heterogeneous lesion associated with muscular wall thickening, so it might be difficult to obtain adequate tissue from ectopic pancreas using EUS-FNTA [30].

Recently, an electrocautery-enhanced delivery system was applied to facilitate self-expandable metal stent insertion under combined endoscopic and EUS guidance at once [31–33]. EUS-FNTA needle with an electrocautery function may enhance the penetration ability for thick gastric antral wall and reduce the mechanical force to the wall. The electrocautery function can overcome difficulty of the antral FNTA procedure to obtain a better sample rate.

Our study has several limitations. First, it was a single-center study with a retrospective design based on observational data. Therefore, the possibility of selection bias exists. Second, in the absence of on-site cytopathologists during the EUS-FNTA procedure, the specimen adequacy was only assessed macroscopically by endosonographers.

Conclusion

Although EUS-FNTA is a good method facilitating the diagnosis of gastric SETs, it is essential to develop more effective methods for the diagnosis of antral SETs.

Abbreviations

EMR endoscopic mucosal resection

EUS endoscopic ultrasound

EUS-FNTA EUS-guided fine-needle tissue acquisition

GIST gastrointestinal stromal tumor

NET neuroendocrine tumor

SET subepithelial tumor

Declarations

Ethics approval and consent to participate

Ethics Committee of the Chonnam National University Hospital approved this current study (CNUH-2019-005).

Consent for publication

Not Applicable

Availability of data and material

The datasets used and/or analyzed during the current study available from the corresponding author on request.

Competing interests

The authors have no conflicts of interests

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Nothing to declare

Authors' contributions

All authors have read and approved this manuscript.

DHK developed the concept of study, analyzed of electronic medical records, and wrote manuscript. CHP made substantial contributions to the conception and design of the study, interpreted data, wrote the paper and revised it critically for intellectual contents. EC, HSK and SKC performed the literature review and collected clinical data. All authors (DHK, CHP, SYP, EC, HSK and SKC) have read and approved the final manuscript.

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