Analysis of Natural History of Upper Gastrointestinal Subepithelial Tumors and Factors Related to Tumor Growth Demonstrated by Endoscopic Ultrasonography

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Background/Aims: Small subepithelial tumors (SETs) are often found incidentally during esophagoduodenoscopy, and EUS is a useful tool for assessing SETs. This study aimed to evaluate the natural history of SETs and to clarify the predictive factors of growth using EUS.

Materials and Methods: We retrospectively investigated SETs less than 30 mm and identified the EUS features. A significant increase in SET size was defined as a lengthening of more than 25% of the longest diameter in the last follow-up EUS features compared with the initial study.

Results: A total of 99 patients with 105 upper gastrointestinal SETs were enrolled. The mean follow-up period for SETs was 22.8 months. Among the 105 SETs, 12 (11.4%) were significantly larger at follow-up. Univariate analysis revealed that the presence of hypoechoic areas was associated with significant SET growth ($P=0.021$). In multivariate analysis, the presence of hypoechoic areas (OR, 8.96; 95% CI, 1.89 $\sim$ 42.54) and anechoic areas (OR, 7.85; 95% CI, 1.09 $\sim$ 56.37) were related with significant growth of SETs. Six of the 12 SETs showing significant growth were removed, and identified as gastrointestinal stromal tumors.

Conclusions: Majority of small SETs showed no significant increase during follow-up. Presence of hypoechoic areas and anechoic areas were associated with SET growth. Therefore, small SETs with hypoechoic area or anechoic area may be considered for regular follow-up in the clinical field. (Korean J Helicobacter Up Gastrointest Res 2016;16:19-25)

Key Words: Subepithelial tumors; Endoscopic ultrasonography; Natural history

INTRODUCTION

With the increasing emphasis on the importance of health check-ups, endoscopic examinations have become more prevalent globally. When patients undergo esophagogastroduodenoscopy (EGD) during health screenings, subepithelial tumors (SETs) often are discovered accidentally during the inspection. Regarding large SETs, most clinicians agree that surgical resection is the best treatment method. However, physicians might feel conflicted over the management of small SETs, because some small SETs are malignant or have malignant potential, such as gastrointestinal stromal tumors (GISTs) or carcinoids.1,2 A few study groups have proposed guidelines about the surveillance of SETs and indications for their surgical treatment.5,5 However, the management of small SETs remains controversial.

EUS is a widely used tool for assessing SETs in the gastrointestinal tract, because it provides various endosono-graphic features of a SET, as well as its exact size and layer of origin.6,9 A number of prospective and retrospective studies have suggested that several EUS features may represent malignancy; in particular, there is a high possibility that hypoechoic SETs originating from the second (muscularis mucosa) or fourth layer (muscularis propria) of the stomach are mesenchymal tumors (typically GISTs).8,13 The EUS features representing the malignancy of a SET are a mass diameter greater than 30 mm, heterogeneous echogenicity, echogenic foci, cystic spaces, irregular margins invading other layers or structures, and adjacent malignant-looking lymph nodes.3,8 Unfortunately, concerning small SETs, the EUS findings which could be used to predict their malignant potential (such as increases in size) are still inadequate.

Therefore, we investigated the natural history of small
sets located in the upper gastrointestinal tract using data from EUS performed in the last ten years, and determined the predictive factors associated with SET growth based on EUS features.

MATERIALS AND METHODS

1. Study population

We retrospectively analyzed data from participants who had visited Kosin University Gospel Hospital (Busan, Korea; a tertiary teaching hospital) from October 2004 to June 2014 and enrolled the patients with upper gastrointestinal SETs of less than 30 mm who at least one follow-up EUS examination was conducted after the initial EUS. Among them, SETs arising from the second or fourth layer at the first EUS examination were included. The follow-up interval was at least 3 months after the initial EUS examination. Therefore, we excluded participants with upper gastrointestinal SETs originating from the third layer. Fig. 1 shows the flow of the current study. This study protocol was approved by the Institutional Review Board of Kosin University Gospel Hospital (IRB No. 2014-08-096).

2. EUS

The EUS parameters included location, tumor diameter, tumor morphology, layer of origin, presence of internal hyperechoic spots, hypoechoic or anechoic areas, and outer marginal irregularity. Hypoechoic area in SETs was defined as an area with lower echogenicity compared with the nearby gastric muscularis propria. And, anechoic area was defined as a small focal area with no echogenicity (Fig. 2). Additional parameters, including a comparison between initial and follow-up SET size, were recorded during the follow-up EUS examination. EUS was performed using a radial (GF-UM2000; Olympus, Tokyo, Japan) and/or ultrasonographic miniprobe (12 to 20 MHz; Olympus). A significant increase in the size of an SET was defined as an increase of the longest diameter by more than 25% in the last EUS feature compared with the initial EUS examination. All of the photographs of the enrolled SETs were reviewed by one skilled endoscopist.

3. Statistical analyses

All statistical analyses were conducted with PASW Statistics software version 18.0 (IBM Co., Armonk, NY, USA). Categorical variables were analyzed using a chi-
Table 1. Baseline Characteristics of the Participants

| Characteristic                        | Enrolled patients (n=99)* | Patients with significant growth (n=12) |
|---------------------------------------|--------------------------|----------------------------------------|
| Age (yr)                              | 58.7±10.5                | 58.8±7.7                                |
| Median age (yr)                       | 58 (28~81)               | 59 (46~69)                              |
| Gender                                |                          |                                        |
| Male                                  | 49 (49.5)                | 6 (50.0)                                |
| Female                                | 50 (50.5)                | 6 (50.0)                                |
| Number of follow-up EUS examinations  |                          |                                        |
| 1                                     | 80 (80.8)                | 0 (0.0)                                 |
| 2                                     | 16 (16.2)                | 12 (100.0)                              |
| 3                                     | 3 (3.0)                  | 0 (0.0)                                 |
| Follow-up period (mo)                 | 22.8±18.9                | 37.7±23.9                               |
| Median of follow-up period (mo)       | 18 (3~94)                | 40 (6~72)                               |
| Number of SETs                        |                          |                                        |
| 1                                     | 95 (96.0)                | 11 (91.7)                               |
| 2                                     | 2 (2.0)                  | 1 (8.3)                                 |
| 3                                     | 2 (2.0)                  | 0 (0.0)                                 |
| Location of SETs                      |                          |                                        |
| Esophagus                             | 21 (20.0)b               | 2 (16.7)                                |
| Stomach                               | 80 (76.2)b               | 10 (83.5)                               |
| Duodenum                              | 4 (3.8)b                 | 0 (0.0)                                 |
| Layer of SETs                         |                          |                                        |
| Second layer                          | 13 (12.4)b               | 1 (8.3)                                 |
| Fourth layer                          | 92 (87.6)b               | 11 (91.7)                               |
| Initial length of diameter (mm)       | 11.6±5.3b                | 10.9±4.9                                |
| Median of initial length of diameter (mm) | 9.5 (3.2~29.0)b           | 10.6 (3.2~18.6)                         |

Values are presented as mean±SD, median (range), or n (%).
SETs, subepithelial tumors.
*Total number of enrolled patients; †Total number of SETs was 105.

Results

1. Participant characteristics

A total of 105 upper gastrointestinal SETs originating
from the second and fourth layers in 99 patients were examined by EUS at least twice between October 2004 and June 2014. The median age of the patients was 58 years (range, 28∼81 years), and 49 patients (49.5%) were male. The mean and median follow-up periods in which the SETs were examined were 22.8 and 18 months (range, 3∼94 months), respectively. Eighty patients (80.8%) underwent 1 follow-up examination, and 95 patients (96.0%) had only one SET in the upper gastrointestinal tract, whereas 2 or more SETs were discovered in 4 patients (4.0%). According to location, the number of SETs was 21 (20.0%), 80 (76.2%), and 4 (3.8%) in the esophagus, stomach, and duodenum, respectively. The proportion of SETs by location was 12.4% in the second layer and 87.6% in the fourth layer. The mean initial diameter of the SETs was 11.6 mm, and the median initial diameter was 9.5 mm (range, 3.2∼29.0 mm). The clinical data and SET features are shown in Table 1.

2. Rate of increase and factors related to growth of SETs

Among 105 SETs, 12 (11.4%) were verified as having increased significantly in size at a follow-up EUS (Table 2). The SETs which increased significantly in size were located

| Table 2. Relating Factors for Growth of SETs |
|---------------------------------------------|
| No significant growth | Significant growth | \( P \) value | \( \text{Adjusted OR (95\% CI)}^a \) |
| \( n=93 \) | \( n=12 \) | Univariate | Multivariate |
| Gender | | | |
| Male | 45 (88.2) | 6 (11.8) | >0.99 | 0.603 | 0.70 (0.19∼2.65) |
| Female | 48 (88.9) | 6 (11.1) | | | |
| Age (yr) | | | 0.690 | 0.239 | 3.87 (0.41∼36.98) |
| <50 | 18 (94.7) | 1 (5.3) | | | |
| ≥50 | 75 (87.2) | 11 (12.8) | | | |
| Location | | | >0.99 | - | - |
| Esophagus | 19 (90.5) | 2 (9.5) | | | |
| Stomach | 70 (87.5) | 10 (12.5) | | | |
| Duodenum | 4 (100.0) | 0 (0.0) | | | |
| Layer | | | >0.99 | - | - |
| Second | 12 (92.3) | 1 (7.7) | | | |
| Fourth | 81 (88.0) | 11 (12.0) | | | |
| Initial EUS size (mm) | | | 0.767 | - | - |
| <10 | 44 (89.8) | 5 (10.2) | | | |
| 10∼29 | 49 (87.5) | 7 (12.5) | | | |
| Heterogeneity | | | >0.99 | - | - |
| Homogenous | 78 (88.6) | 10 (11.4) | | | |
| Heterogenous | 15 (88.2) | 2 (11.8) | | | |
| Hyerechoic spot | | | >0.99 | - | - |
| Present | 12 (92.3) | 1 (7.7) | | | |
| Absent | 81 (88.0) | 11 (12.0) | | | |
| Hypoechoic area | | | 0.021* | 0.006* | 8.96 (1.89∼42.54)* |
| Present | 7 (63.6) | 4 (36.4) | | | |
| Absent | 86 (91.5) | 8 (8.5) | | | |
| Anechoic area | | | 0.182 | 0.041* | 7.85 (1.09∼56.37)* |
| Present | 5 (83.3) | 1 (16.7) | | | |
| Absent | 88 (89.8) | 11 (10.2) | | | |
| Marginal irregularity | | | 0.354 | - | - |
| Regular | 80 (87.0) | 12 (13.0) | | | |
| Irregular | 15 (100.0) | 0 (0.0) | | | |

Values are presented as n (%) or OR (95% CI).
SETs, subepithelial tumors.

*Logistic model including terms of gender, age, origin layer, and internal foci.

\( *P<0.05 \).
in the esophagus (2/21, 9.5%) and stomach (10/80, 12.5%). There was no significant growth of the duodenal SETs (0/4, 0%). And, among the 10 SETs of stomach which were significantly increased, 8 SETs (80.0%) were located in the body and 2 SETs (20.0%) were located in the antrum.

Factors related to tumor growth are summarized in Table 2. In univariate analysis, hypoechoic area had a statistically significant association with the SET growth ($P=0.021$). In multivariate analysis revealed that the presence of hypoechoic area (OR, 8.96; 95% CI, 1.89~42.54) and anechoic area (OR, 7.85; 95% CI, 1.09~56.37) were related with significant growth of SETs. There was no other statistically significant factor identified by multivariate analysis.

3. Pathologic diagnosis of the SETs with size increases

In the 12 SETs which significantly increased in size, pathologic diagnoses were confirmed in a total of 6 SETs: 5 after operation and 1 after endoscopic submucosal dissection (Table 3). Interestingly, all of them were diagnosed as GISTs originating from the fourth layer of the stomach. Among the 6 GISTs, 5 (83.3%) were identified as being at low risk for malignancy by the National Institutes of Health (NIH) criteria. Additionally, one GIST with anechoic area was verified as being at high risk for malignancy by the NIH criteria.

**DISCUSSION**

An SET is defined as a protruding elevated lesion covered with normal mucosa that arises from any layer of the gastrointestinal tract. SETs are occasionally discovered during EGD examinations, and the prevalence of SETs in the upper gastrointestinal tract during EGD screening has been shown to be approximately 0.76% in Korea. In particular, patients with relatively small SETs often are identified by EGD. EUS is a technique which integrates endoscopy and high-frequency ultrasound with a small ultrasonic transducer located at the end of the scope. EUS can be used to determine whether a bulging lesion in the gastrointestinal tract is an SET or another type of lesion (such as an extrinsic compression, focal fold thickening, etc.). After a lesion is identified as an SET, EUS also can be used to evaluate its layer of origin, size, and echogenicity. Therefore, EUS is a useful tool to identify SETs and determine their natural history.

Understanding the natural history of SETs is important

**Table 3. Detailed Features of the 12 Patients Showed a Significant Growth of SETs**

| Age (yr)/sex | Hypoechoic area | Anechoic area | Site/layer | Mean initial diameter (mm) | Mean follow-up diameter (mm) | Follow-up period (mo) | Treatment modality | Diagnosis |
|--------------|----------------|--------------|------------|---------------------------|-----------------------------|----------------------|--------------------|-----------|
| 63/F         | Present        | Absent       | Stomach/4th| 10.2                      | 15.3                        | 63                   | Operation          | GIST (low risk)   |
| 51/F         | Absent         | Present      | Stomach/4th| 18.3                      | 40.0                        | 52                   | Operation          | GIST (low risk)   |
| 69/M         | Absent         | Present      | Stomach/4th| 21.0                      | 57.0                        | 32                   | Operation          | GIST (high risk)  |
| 57/F         | Present        | Absent       | Stomach/4th| 9.4                       | 16.0                        | 67                   | Operation          | GIST (low risk)   |
| 68/F         | Absent         | Absent       | Stomach/4th| 6.5                       | 36.1                        | 50                   | Operation          | GIST (low risk)   |
| 46/M         | Absent         | Absent       | Stomach/4th| 6.0                       | 10.6                        | 72                   | ESD                |              |
| 64/M         | Absent         | Absent       | Esophagus/4th| 12.2                      | 15.7                        | 22                   | Follow-up          |              |
| 62/M         | Present        | Absent       | Stomach/4th| 6.6                       | 8.4                         | 6                    | Follow-up loss     |              |
| 50/F         | Absent         | Absent       | Stomach/4th| 11.1                      | 15.1                        | 20                   | Follow-up          |              |
| 66/M         | Present        | Absent       | Stomach/4th| 15.8                      | 27.8                        | 48                   | Follow-up loss     |              |
| 52/F         | Absent         | Absent       | Esophagus/2nd| 12.7                      | 15.9                        | 7                    | Follow-up          |              |
| 57/M         | Absent         | Absent       | Stomach/4th| 3.2                       | 4.4                         | 13                   | Follow-up loss     |              |

F, female; M, male; SETs, subepithelial tumors; ESD, endoscopic submucosal dissection; GIST, gastrointestinal stromal tumor.
for SET management. Unfortunately, there have been only a few studies analyzing the natural history of SETs using EUS examination. In the current study, 11.4% of SETs less than 30 mm increased significantly in size during a mean period of 22.8 months. The proportion of significant growth was 9.5% and 12.5% in the esophagus and stomach, respectively. These results are similar to those of other studies. Bruno et al. evaluated 49 patients with small SETs (<30 mm) located in the fourth layer of the gastrointestinal tract during a mean follow-up period of 31.0 months. Among them, five patients had size increases of at least 25% in the initial diameter, so the total percentage of small SETs that increased in size was 10.2%. When the SETs were analyzed according to location, the proportion of SETs that increased in size in the stomach was 11.6%. Gill et al. investigated upper gastrointestinal SETs less than 30 mm by EUS. A total of 51 patients with small SETs arising from second and fourth layer were followed for 29.7 months (mean), and SET growth were identified in 7/51 patients (13.7%) in follow-up EUS. However, our results are slightly different from those of Melzer and Fiddler, who studied 25 patients with SETs less than 40 mm for a mean period of 19 months. They reported that significant growth occurred for 17.4% of SETs, which was higher than the rate in our study. Kim et al. investigated the natural history of SETs less than 30 mm during a median period of 24 months, and analyzed the growth of SETs between 10 to 30 mm and less than 10 mm. Of 589 SETs in the stomach, they reported that 8.2% increased significantly in size, and that gastric SETs of 10 to 30 mm increased significantly more rapidly than gastric SETs less than 10 mm in size. We suppose that the number and the size of the enrolled SETs could have affected the results of the studies. However, most of the small SETs were unchanged during a period of about 18 to 30 months, broadly.

Clinically, the matter of concern for physicians assessing SETs is to differentiate between benign and malignant lesions. If all the tissue of an SET can be obtained during an EGD or EUS examination using EUS-guided fine needle aspiration (EUS-FNA) or EUS-guided core needle biopsy, that is the ideal way to discriminate between benign and malignant lesions. However, it might be challenging to obtain adequate tissue from small SETs or SETs positioned in difficult locations, and a recent study reported that the diagnostic yield of EUS-FNA for gastric SETs less than 20 mm was 73%. Unfortunately, many centers are not equipped with EUS-FNA biopsy or EUS-guided core needle biopsy. Thus, it is worth investigating the predictive factors for growth of SETs using less invasive methods, such as EUS. In the current study, the presence of hypoechoic areas or anechoic areas within SETs was significantly related with the growth of small SETs in the upper gastrointestinal tract. These results are in agreement with those of previous studies about factors relating to the growth of SETs. Onishi et al. reported that internal hypoechoic areas shown with EUS was suggested that might be a predictive factor for the expansion potential of gastric GISTs (OR, 5.38; 95% CI, 1.19~24.39). In addition, Hata et al. demonstrated that the detection of anechoic lesions by EUS (OR, 5.90; 95% CI, 1.37~18.80; P=0.039) was a predictor of the increase in size of gastric SETs. It is uncertain whether anechoic areas are directly connected to the cystic spaces which are related with malignant GISTs; however, the possibility might be considered. Regarding hyperechoic spot, it is widely accepted that echogenic foci on EUS are associated with malignant GISTs, and Chak et al. already showed the relation between echogenic foci and malignancy in stromal cell tumors (OR, 19.25; 95% CI, 2.88~128.52). Unfortunately, there was no significant association between hyperechoic spot and tumor growth in our study, and further studies will be necessary.

There are several limitations to the current study. Our study was a retrospective analysis from a single center, so the follow-up interval and equipment were not standardized. Further, although they were all experts, four endoscopists performed the EUS inspections. Therefore, one of them examined all EUS features of the enrolled SETs repeatedly to control for inter-observer variation. Also, among the 105 SETs, the proportion of SETs located in the duodenum was small. This might have been due to the low prevalence of primary neoplasms in the small intestine, which is known to be approximately 4% (range, 1.6~6%) of all tumors of the gastrointestinal tract. Therefore, more large-scale studies are needed in the future. Lastly, only a half of the 12 patients with increases in SET size
had the SETs removed to confirm the pathologic diagnosis surgically or endoscopically. Unfortunately, the remaining patients were either lost to follow-up or refused surgery due to the location of the SETs, such as the esophagus.

In conclusion, most of the small SETs less than 30 mm were stable during a mean period of 23 months during the 10 years of our study. Interestingly, the presence of hypoechoic area and anechoic area were related with significant growth of SETs. Therefore, the small SETs especially with hypoechoic area or hypoechoic area in EUS could be allowed for follow-up regularly in the clinical field.

REFERENCES

1. Miettinen M, Sarlomo–Rikala M, Lasota J. Gastrointestinal stromal tumors: recent advances in understanding of their biology. Hum Pathol 1999;30:1213–1220.
2. American Gastroenterological Association Institute. American Gastroenterological Association Institute medical position statement on the management of gastric subepithelial masses. Gastroenterology 2006;130:2215–2216.
3. Hwang JH, Rulyak SD, Kimmey MB; American Gastroenterological Association Institute technical review on the management of gastric subepithelial masses. Gastroenterology 2006;130:2217–2228.
4. Demetri GD, Benjamin RS, Blanke CD, et al; NCCN Task Force. NCCN Task Force report: management of patients with gastrointestinal stromal tumor (GIST)—update of the NCCN clinical practice guidelines. J Natl Compr Canc Netw 2007;5 Suppl 2:S1–S29; quiz S30.
5. Nishida T, Kawai N, Yamaguchi S, Nishida Y. Submucosal tumors: comprehensive guide for the diagnosis and therapy of gastrointestinal submucosal tumors. Dig Endosc 2013;25:479–489.
6. Argüello L. Endoscopic ultrasonography in submucosal lesions and extrinsic compressions of the gastrointestinal tract. Minerva Med 2007;98:389–395.
7. Boyce GA, Sivak MV Jr, Rösch T, et al. Evaluation of submucosal upper gastrointestinal tract lesions by endoscopic ultrasound. Gastrointest Endosc 1991;37:449–454.
8. Palazzo L, Landi B, Cellier C, Cuillerier E, Roseau G, Barbier JP. Endosonographic features predictive of benign and malignant gastrointestinal stromal cell tumors. Gut 2000;46:88–92.
9. Rösch T, Kapfer B, Will U, et al: German EUS Club. Endoscopic ultrasonography. Accuracy of endoscopic ultrasonography in upper gastrointestinal submucosal lesions: a prospective multicenter study. Scand J Gastroenterol 2002;37:856–862.
10. Brand B, Oesterhelweg L, Binmoeller KF, et al. Impact of endoscopic ultrasound for evaluation of submucosal lesions in gastrointestinal tract. Dig Liver Dis 2002;34:290–297.
11. Chak A, Canto ML, Rösch T, et al. Endosonographic differentiation of benign and malignant stromal cell tumors. Gastrointest Endosc 1997;45:468–473.
12. Martínez-Ares D, Souto-Ruiz J, Yáñez López J, Vázquez Iglesias JL. Usefulness of endoscopic ultrasonography in the preoperative diagnosis of submucosal digestive tumours. Rev Esp Enferm Dig 2005;97:419–426.
13. Jeon SW, Park YD, Chung YJ, et al. Gastrointestinal stromal tumors of the stomach: endosonographic differentiation in relation to histological risk. J Gastroenterol Hepatol 2007;22:2069–2075.
14. Onishi M, Tominaga K, Sugimori S, et al. Internal hypoechoic feature by EUS as a possible predictive marker for the enlargement potential of gastric GI stromal tumors. Gastrointest Endosc 2012;75:731–738.
15. Kim MY, Jung HY, Choi KD, et al. Natural history of asymptomatic small gastric subepithelial tumors. J Clin Gastroenterol 2011;45:330–336.
16. Bruno M, Carucci P, Repici A, et al. The natural history of gastrointestinal subepithelial tumors arising from muscularis propria: an endoscopic ultrasound survey. J Clin Gastroenterol 2009;43:821–825.
17. Lim YJ, Son HJ, Lee JS, et al. Clinical course of subepithelial lesions detected on upper gastrointestinal endoscopy. World J Gastroenterol 2010;16:439–444.
18. Rösch T. Endoscopic ultrasonography: equipment and technique. Gastrointest Endosc Clin N Am 2005;15:13–31, vii.
19. Gill KR, Camelli L, Conigliaro R, et al. The natural history of upper gastrointestinal subepithelial tumors: a multicenter endoscopic ultrasound survey. J Clin Gastroenterol 2009;43:725–726.
20. Melzer E, Fidder H. The natural course of upper gastrointestinal submucosal tumors: an endoscopic ultrasound survey. Isr Med Assoc J 2000;2:430–432.
21. Sepe FS, Moparty B, Pitman MB, Saltzman JR, Brugge WR. EUS-guided FNA for the diagnosis of GI stromal cell tumors: sensitivity and cytologic yield. Gastrointest Endosc 2009;70:254–261.
22. Akahoshi K, Oya M, Koga T, et al. Clinical usefulness of endoscopic ultrasound-guided fine needle aspiration for gastric subepithelial lesions smaller than 2 cm. J Gastrointestin Liver Dis 2014;23:405–412.
23. Hata S, Ani M, Suzuki T, et al. Clinical significance of endoscopic ultrasound for gastric submucosal tumors. Clin Res Hepatol Gastroenterol 2013;37:207–212.
24. Baert AL. Encyclopedia of diagnostic imaging. Guildford: Springer Verlag, 2007.