

## Retrospective Cohort Study

**Endosonographic surveillance of 1-3 cm gastric submucosal tumors originating from muscularis propria**

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**Abstract****AIM**

To observe the natural course of 1-3 cm gastric submucosal tumors originating from the muscularis propria (SMTMPs).

**METHODS**

By reviewing the computerized medical records over a period of 14 years (2000-2013), patients with 1-3 cm gastric SMTMPs who underwent at least two endoscopic ultrasound (EUS) examinations were enrolled. Tumor progression was defined as a  $\geq 1.2$  times enlargement in tumor diameter observed during EUS surveillance. All patients were divided into stationary and progressive subgroups and further analyzed. We also reviewed the patients in the progressive subgroup again in 2016.

**RESULTS**

A total of 88 patients were studied, including 25 in the progressive subgroup. The mean time of EUS surveillance was 24.6 mo in the stationary subgroup and 30.7 mo in the progressive subgroup. Risk factors for tumor progression included larger tumor size and irregular border. Initial tumor size  $> 14.0$  mm may be considered a cut-off size for predicting tumor progression. Seventeen patients underwent surgery, of whom 13 had gastrointestinal stromal tumors (GISTs) and 4 had leiomyomas. Tumor progression was found only in patients with GISTs. All of the tumors exhibited benign behaviors without metastasis until 2016.

**CONCLUSION**

Most 1-3 cm gastric SMTMPs (71.6%) are indolent. Tumor progression was found only in GISTs, and it is a good predictor for differentiating GISTs from leiomyomas. Predictors of tumor progression include

larger tumor size (> 14.0 mm) and irregular border.

**Key words:** Gastrointestinal stromal tumor; Submucosal tumors originating from the muscularis propria; Stomach; Endosonographic surveillance

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**Core tip:** Most gastric submucosal tumors originating from muscularis proprias (SMTMPs) are gastrointestinal stromal tumors (GISTs) or leiomyomas. GISTs have a malignant potential but leiomyomas are benign. We enrolled patients with 1-3 cm gastric SMTMPs and under endoscopic ultrasound surveillance over a period of 14 years between 2000 and 2013 to observe the natural behaviors of such tumors. We also reviewed the patients with progressive tumors again in 2016.

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## INTRODUCTION

Due to advances in endoscopy and its widespread use, detection of submucosal tumors (SMTs) of the gastrointestinal (GI) tract is not uncommon. In the evaluation of SMTs of the GI tract, endoscopic ultrasound (EUS) is a useful tool for identifying the tumor's layer of origin, measuring its size, providing the details of tumor echotexture, and differentiating it from external compression<sup>[1]</sup>. Among SMTs in the stomach, gastrointestinal stromal tumors (GISTs) are the most common<sup>[2]</sup>. When EUS reveals a hypoechoic submucosal tumor originating from the muscularis propria (SMTMP) in the stomach, GIST is considered first followed by leiomyoma<sup>[3-9]</sup>. Because all GISTs have a malignant potential and leiomyomas have a benign nature, tissue acquisition is often recommended for such tumors. At present, EUS-guided fine needle aspiration (EUS-FNA) is a feasible method. However, the diagnostic rate may be limited when the tumor is smaller or the tumor location is difficult to approach<sup>[10-12]</sup>.

Based on the National Institute of Health Consensus, tumor size and mitotic activity are the two most important factors for predicting malignant potential of a GIST<sup>[13]</sup>. Obviously, tissue obtained by EUS-FNA can demonstrate GISTs only but cannot provide further information regarding mitotic activity. EUS features suggestive of a malignant GIST include larger tumor size, heterogeneous hypoechoic texture, irregular tumor border, and internal cystic or calcified changes<sup>[8,14,15]</sup>. At present, a GIST > 3 cm is considered to have higher malignant potential and is recommended for surgical

resection<sup>[16]</sup>. As for GISTs < 1 cm, they are frequently considered to harbor a low risk of malignancy and tissue acquisition in these cases is controversial<sup>[17]</sup>. Notably, GISTs in the stomach are often indolent and rapid progression is uncommon. It should be considered whether all the myogenic submucosal tumors in the stomach are necessary for pathologic demonstration to differentiate GISTs from leiomyomas, especially in 1-3 cm tumors. Until now, associated discussions regarding the natural course and management of 1-3 cm gastric SMTMPs are limited. Here, we reviewed computerized medical records over a period of 14 years from our institution to study the natural behaviors of such tumors.

## MATERIALS AND METHODS

### Patient selection

All the patients who underwent at least two EUS examinations to follow gastric SMTMP during a period of 14 years between January 2000 and December 2013 were retrospectively reviewed using the computerized medical record system of Kaohsiung Chang Gung Memorial Hospital, a tertiary medical center in Kaohsiung City in Taiwan.

### EUS modality and examination

In all patients, EUS was performed using a miniprobe with a 12 MHz radial scan (Olympus UM-2R, Tokyo, Japan). When EUS showed a myogenic tumor with hypoechoic echotexture originating from the muscularis propria in the stomach, it was regarded as a gastric GIST first or leiomyoma. We used the maximal tumor diameter as tumor size. The intervals of EUS follow-up were not defined, mainly depending upon the clinician's discretion.

### Inclusion and exclusion criteria

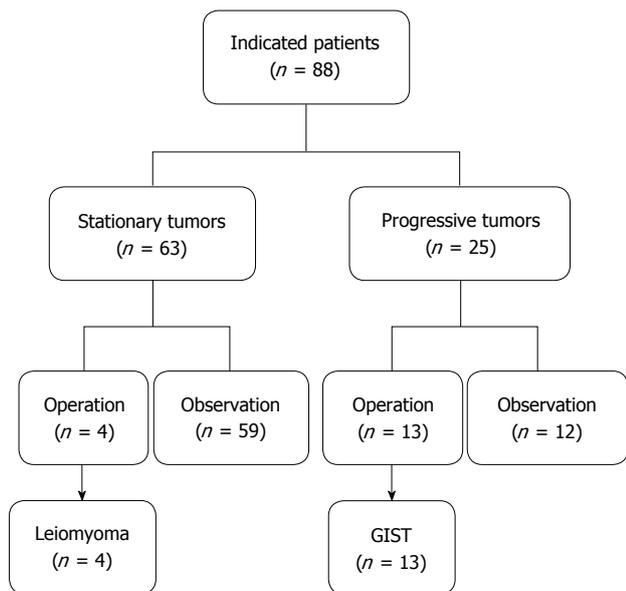
If the tumor size exceeded 3 cm, we recommended FNA or surgical resection. When a tumor was < 1 cm, we considered it to be benign. Therefore, we excluded the patients with an initial tumor size larger than 3 cm or persistently smaller than 1 cm. We also excluded the patients who underwent EUS only once without subsequent follow-up. We also enrolled the patients whose small tumors subsequently grew to 1 cm or more during surveillance. Therefore, only the patients with 1-3 cm myogenic tumors under EUS surveillance were enrolled in this study.

### Pathological classification to predict malignant potential of GISTs

If a patient underwent surgery to remove a GIST, the pathology of GIST was classified into "very low risk", "low risk", "intermediate risk", or "high risk" using tumor size and mitotic count based on the National Institute of Health consensus<sup>[13]</sup>.

### Data collection and analysis

We defined a ratio of follow-up tumor size to initial



**Figure 1** Flow chart of management of 88 indicated patients with submucosal tumors originating from the muscularis propria in the stomach. EUS: Endoscopic ultrasound; GIST: Gastrointestinal stromal tumor.

tumor size  $\geq 1.2$  as tumor progression based on the Response Evaluation Criteria in Solid Tumor (RECIST)<sup>[18]</sup>. Patients were then divided into a progressive subgroup and a stationary subgroup. Baseline characteristics of each subgroup, initial tumor size, echotexture, border and location of myogenic tumors, the number of surveillance procedures, and the interval and duration of EUS were recorded and further analyzed.

**Second review for patients with progressive tumors**

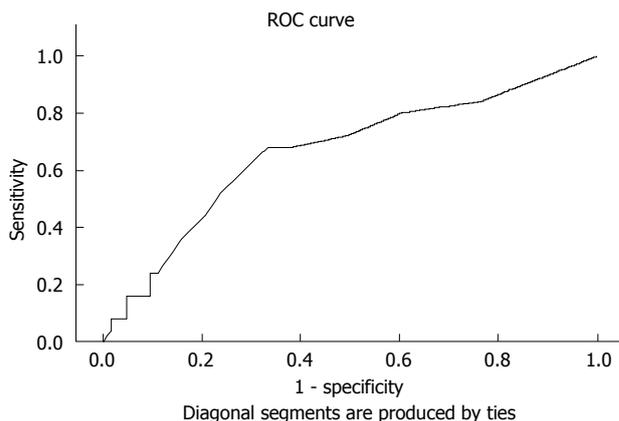
We followed the patients in the progressive subgroup again in 2016 by medical record review and phone call contact.

**Statistical analysis**

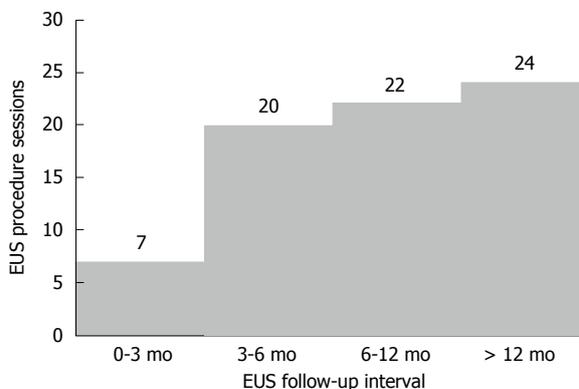
Continuous variables were analyzed using the Mann Whitney *U* test and categorical variables analyzed using the Pearson  $\chi^2$  test. The sensitivity and specificity of various tumor sizes were analyzed using a receiver operating characteristic (ROC) curve, and the optimal cutoff value was determined. All statistical analyses were performed using SPSS statistical software (SPSS for Windows, version 13; SPSS Inc., IL). A *P*-value < 0.05 was considered statistically significant.

**RESULTS**

During the 14 years between 2000 and 2013, 6755 EUS procedures were performed by four endosonographers. Of these, 1725 EUS results were associated with gastric SMTMPs. Based on the inclusion and exclusion criteria, 88 patients (44 males and 44 females) were identified and enrolled in the study. The initial patient age was  $57.1 \pm 11.0$  years (mean  $\pm$  SD) and the initial tumor size was  $14.7 \pm 4.9$  mm.

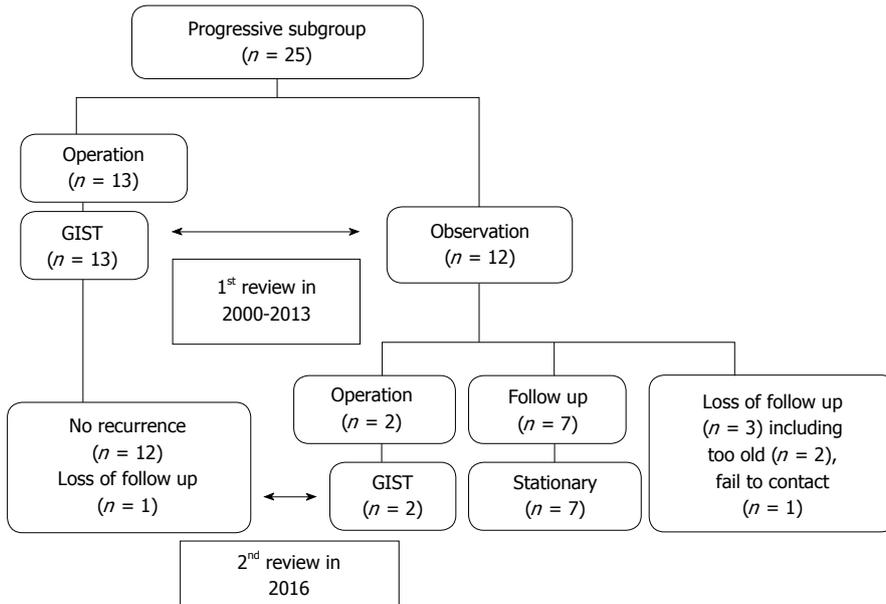


**Figure 2** Receiver operating characteristic curve analysis of tumor size for predicting potential tumor progression. Initial tumor size of 1.4 cm was determined as the optimal cut-off size, with a sensitivity of 68.0%, a specificity of 66.7%, and an accuracy of 67.0%.



**Figure 3** Intervals of endoscopic ultrasound follow-up in 25 patients with 1-3 cm gastric submucosal tumors originating from the muscularis propria in tumor progression. EUS: Endoscopic ultrasound.

Both the duration and interval of EUS surveillance ranged from 1.1 mo to 144.9 mo. The number of EUS surveillance procedures ranged from 2 to 9. Of the 88 patients, 25 (28.4%) were in the progressive subgroup and 63 (71.6%) in the stationary subgroup (Figure 1). The basic characteristics and EUS findings in each subgroup are shown in Table 1. By comparing the progressive and stationary subgroups, initially larger tumor size and irregular tumor border were identified to be predictors of tumor progression. Regarding initial tumor size, we performed an ROC curve analysis to determine the optimal cut-off size for predicting potential tumor progression. We found 1.4 cm to be the optimal cut-off tumor size associated with tumor progression, with a sensitivity of 68.0%, a specificity of 66.7%, and an accuracy of 67.0 % (Figure 2). The interval of EUS surveillance in the progressive subgroup is shown in Figure 3. The interval of most EUS examinations was  $\geq 3$  mo (66/73 = 90.4%). A total of 17 patients underwent surgery. Of these, 13 patients from the progressive subgroup were confirmed to have GISTs and 4 patients from



**Figure 4** Flow chart of patients in the progressive subgroup. These patients were reviewed twice; the first was based on medical records in 2013 and the second was performed by phone calls as well as based on medical records in 2016.

**Table 1** Basic characteristics and endoscopic ultrasound findings in 88 patients with suspected gastrointestinal stromal tumors in the stomach

Basic characteristic or EUS finding	Stationary group n = 63	Progressive group n = 25	P value
Age (mean ± SD, yr)	57.4 ± 10.6	56.4 ± 12.4	0.690
Sex (M/F)	35/28	9/16	0.100
Location			0.650
Cardia	16	5	
Fundus	16	8	
Body	24	11	
Antrum	7	1	
EUS tumor size and echotexture			
Initial tumor size (mean ± SD, mm)	13.9 ± 4.5	16.6 ± 5.5	0.020
Homogeneous/heterogeneous	44/19	12/13	0.060
hypoechoicity			
Smooth/irregular tumor border	56/7	15/10	0.002
With/without internal cystic change or calcification	8/55	4/21	0.680
EUS surveillance			
Surveillance duration (mean ± SD, mo)	24.6 ± 20.3	30.7 ± 21.7	0.220

EUS: Endoscopic ultrasound.

the stationary subgroup were confirmed to have leiomyomas. Basic characteristics and EUS findings for patients with confirmed GISTs and leiomyomas are shown in Tables 2-4. CD117 was positive in all 13 patients with confirmed GISTs (100%), whereas CD34 was positive in 11 (84.6%). Pathology results for confirmed cases suggested 4 GISTs with a very low malignant potential, 6 with a low potential, 2 with an intermediate potential, and 1 with a high potential. No

patient was found to have malignant transformation or distant metastasis during surveillance. Notably, tumor progression (tumor enlargement  $\geq 1.2$  times) was only shown in the cases with GISTs. Among another 12 patients in the progressive subgroup, we followed them until 2016. Two patients eventually underwent surgery due to gradually enlarged tumors and were confirmed to have GISTs with a low malignant potential. Two patients refused EUS surveillance due to old age ( $> 80$  years). Seven patients who took regular follow-ups remained condition stable without tumor metastasis. One patient was lost to follow-up. The flow chart of these 12 patients in the progressive subgroup is shown in Figure 4.

## DISCUSSION

GISTs are the most common mesenchymal tumors in the GI tract. Pathologically, most GISTs are composed of spindle cells and epithelioid cells which are derived from interstitial cells of Cajal<sup>[19-21]</sup>. Most GISTs (approximately 65%) occur in the stomach, followed by 30%-35% in the small intestine and 5%-10% in the colon. About 95% of GISTs are characterized by the positive expression of c-kit receptor tyrosine kinase (CD117), whereas approximately 60%-70% of the tumors are positive for CD34<sup>[22-24]</sup>. Most gastric GISTs are asymptomatic and are detected incidentally as submucosal tumors during endoscopy. Therefore, the real incidence of GISTs in the stomach remains unclear. EUS is the most common modality for the evaluation of submucosal tumors. A suspected GIST is a hypoechoic and myogenic tumor originating mostly from the muscularis propria and occasionally from the muscularis mucosae. Similar to GISTs in terms of

**Table 2 Basic characteristics and endoscopic ultrasound findings in 13 patients with confirmed gastrointestinal stromal tumors in the stomach**

Case	Age (yr)/sex	Location	Heterogeneous hypoechoic echotexture	Irregular border	Internal cystic change or calcification	Initial size (I, mm)	Final size (F, mm)	Tumor progression (F/I ≥ 1.2)	Surveillance procedures	Surveillance duration (mo)	Malignant potential
1	41/F	Body	+	-	-	15	23	+	4	82.1	Very low
2	67/F	Fundus	+	-	+	15	23	+	5	66.5	Very low
3	50/F	Cardia	-	+	-	16	20	+	4	22.8	Very low
4	70/M	Body	-	-	-	15	20	+	8	37.9	Very low
5	57/F	Cardia	+	+	-	28	50	+	3	19.3	Low
6	46/M	Fundus	+	+	-	30	35	+	2	3.4	Low
7	55/F	Antrum	-	-	-	18	23	+	2	63.0	Low
8	69/F	Body	-	-	-	21	28	+	2	3.7	Low
9	49/M	Body	+	+	-	24	30	+	3	47.9	Low
10	61/F	Fundus	+	+	-	24	33	+	6	41.9	Low
11	54/M	Body	+	+	-	21	28	+	5	32.1	Intermediate
12	59/F	Body	+	+	-	18	23	+	2	5.5	Intermediate
13	60/F	Fundus	+	+	-	30	51	+	2	31.3	High

**Table 3 Basic characteristics and endoscopic ultrasound findings in 4 patients with confirmed leiomyomas in the stomach**

Case	Age (yr)/sex	Location	Heterogeneous hypoechoic echotexture	Irregular border	Internal cystic change or calcification	Initial size (I, mm)	Final size (F, mm)	Tumor progression (F/I ≥ 1.2)	Surveillance procedures	Surveillance duration (mo)
1	69/F	Body	-	-	-	10	10	-	2	3.5
2	52/M	Fundus	-	-	-	10	9	-	2	3.7
3	64/F	Antrum	+	-	-	13	13	-	3	21.3
4	50/M	Cardia	+	+	+	18	20	-	2	3.0

**Table 4 Comparison of basic characteristics and endoscopic ultrasound findings between patients with gastrointestinal stromal tumors and leiomyomas by the Mann -Whitney U test**

Basic characteristic or EUS finding	GIST n = 13	Leiomyoma n = 4	P value
Age (median, range, yr)	57 (41-70)	58 (50-69)	0.785
Sex (M/F)	4/9	2/2	0.482
Location			0.868
Cardia	2	1	
Fundus	4	1	
Body	6	1	
Antrum	1	1	
EUS tumor size and echotexture			
Initial tumor size (median, mm)	21	11.5	0.015
Final tumor size (median, mm)	28	11.5	0.003
Homogeneous/heterogeneous hypoechoicity	4/9	2/2	0.482
Smooth/irregular tumor border	5/8	0/4	0.682
With/without internal cystic change or calcification	1/12	0/4	0.567
EUS surveillance			
Surveillance duration (median, range, mo)	31.3 (3.1-81.0)	3.6 (3.0-21.4)	0.023
Surveillance procedure (median, range, times)	3 (2-8)	2 (2-3)	0.163
Tumor progression	13	0	< 0.001

GISTs: Gastrointestinal stromal tumors; EUS: Endoscopic ultrasound.

EUS findings, leiomyomas are also tumors of muscular origin. Unlike GISTs, leiomyomas are negative for CD117 and CD34, but positive for smooth muscle actin (SMA) and desmin on immunohistochemical staining. Moreover, leiomyomas are completely benign.

Recent studies have demonstrated that all GISTs have a malignant potential. Therefore, suspected GISTs should be confirmed histologically and managed accordingly. However, GISTs often behave differently

at different locations. A GIST in the stomach is often more indolent than a GIST with a similar size and mitotic count located in another GI tract site<sup>[25]</sup>. Therefore, EUS surveillance alone is feasible for a small suspected GIST in the stomach that does not require immediate tissue proof or resection<sup>[2,26]</sup>.

Most GISTs < 1 cm harbor a very low malignant potential, while GISTs ≥ 3 cm with irregular tumor borders, heterogeneous hypoechoogenicity, and internal

cystic or calcified changes suggest a higher malignant potential. All leiomyomas are benign. Therefore, we were interested in the natural course of 1-3 cm SMTMPs in the stomach. To evaluate tumor growth, we calculated the ratio of follow-up tumor size to initial tumor size on EUS and defined the ratio of  $\geq 1.20$  as tumor progression based on RECIST. Among 88 patients with 1-3 cm gastric myogenic tumors, we found that most tumors were indolent and tumor progression was detected in 25 (28.4%) patients. No patients suffered from major complications such as tumor bleeding, obstruction, perforation or malignant transformation during surveillance. A total of 19 (17 + 2) patients underwent surgery. Of these, 15 patients had GISTs and 4 patients had leiomyomas. Notably, tumor progression (tumor enlargement  $\geq 1.2$  times) was found only in GISTs but not in leiomyomas. Therefore, tumor progression may be a good predictor for differentiating GISTs from leiomyomas. Moreover, we found that larger tumors with irregular margins showed a tendency toward progressive change and should be monitored more closely. From the ROC curve analysis, we found 1.4 cm to be the optimal cut-off tumor size associated with tumor progression. The same 1.4 cm cut-off size was reported by Fang *et al.*<sup>[27]</sup> in their study, which is similar to that reported by Lachter *et al.*<sup>[28]</sup> who found tumor size larger than 1.7cm to be indicative of tumor progression. Tumors with heterogeneous hypoechotexture showed no statistical significance for predicting tumor progression ( $P = 0.06$ ) in our study, but the finding is limited by our small number of cases and requires clarification in a larger study. Regarding the appropriate interval of EUS surveillance, it is difficult to conclude how often a suspected gastric GIST should be followed since malignant GISTs were not detected during surveillance in our study. Although an evidence-based optimal EUS surveillance policy remains lacking for small GISTs, yearly EUS follow-up for small sized GISTs (< 3 cm) should be considered from a study of Prachayakul *et al.*<sup>[26]</sup> in 2012. At present, a guideline from European society of medical oncology recommended that an interval of 3 mo in the first follow-up and then annual EUS surveillance may be optimal for small suspected GISTs if no tumor growth occurs during surveillance<sup>[29]</sup>. In this review of 1725 EUS surveillances for gastric submucosal tumors from the 14 years of medical records, we found that most 1-3 cm SMTMPs in the stomach were indolent with only 28.4% of patients experiencing tumor progression (tumor enlargement  $\geq 1.2$  times). EUS surveillance is optimal for small gastric myogenic submucosal tumors without immediately obtaining tissue. Tumor progression is a good predictor for differentiating GISTs from leiomyomas. Risk factors for tumor progression include larger tumor and irregular borders. Initial tumor size > 14.0 mm may be considered a cut-off size for predicting tumor progression.

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## COMMENTS

### Background

Most gastric submucosal tumors originating from muscularis propria (SMTMPs) are gastrointestinal stromal tumors (GISTs) and leiomyomas. Leiomyoma is benign but GIST has a malignant potential. Surgery is recommended if GISTs larger than 3 cm. Endoscopic ultrasound (EUS) fine needle aspiration is helpful to differentiate between GISTs and leiomyomas, but sometimes it is difficult to obtain tissue and cannot provide mitotic activity of GISTs.

### Research frontiers

Because studies regarding the natural behaviors of 1-3 cm gastric SMTMPs are limited, the authors made a retrospective study by reviewing the past 14 years of computerized medical records in a tertiary medical center between 2000 and 2013.

### Innovations and breakthroughs

Most gastric SMTMPs are indolent from our study. Risk factors for tumor progression include larger tumor size and irregular border.

### Applications

Initial tumor size > 14.0 mm may be considered a cut-off size for predicting tumor progression. Therefore, a gastric SMTMP with irregular border or  $\geq 14.0$  mm in size should be observed closely and treated accordingly.

### Terminology

GISTs are the common submucosal tumors arising from the muscularis propria in the stomach and have a malignant potential though the behavior of most tumors is indolent. EUS is a useful tool to detect submucosal tumors of the gastrointestinal tract.

### Peer-review

This study provides important information (long term surveillance, EUS surveillance interval, a cut-off value of tumor size of > 14.0 mm) in the management of gastric small SMTMPs.

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