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***Retrospective Cohort Study***

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

Hu ML *et al.* EUS surveillance in 1-3 cm gastric submucosal tumor originating

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**Abstract**

***AIM***

To observe the natural courses of 1-3 cm gastric submucosal tumor originating from muscularis propria (SMTMP).

***METHODS***

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

***RESULTS***

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

***CONCLUSION***

Most 1-3cm gastric SMTMP were indolent (71.6%). Tumor progression was found only in GISTs and was a good predictor for differentiating GISTs from leiomyomas. Predictors for tumor progression included a larger tumor size (> 14.0 mm) and irregular border.

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

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**Core tip:** Most gastric submucosal tumor originating from muscularis proprias (SMTMPs) are gastrointestinal stromal tumors (GISTs) or leiomyoma. GIST has malignant potential but leiomyoma is benign. We enrolled those patients during the 14 years between 2000 and 2013 with 1-3cm of gastric SMTMP and under endoscopic ultrasound surveillance 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[1]. Among SMTs in the stomach, gastrointestinal stromal tumors (GISTs) are the most common[2].When EUS reveals a hypoechoic submucosal tumor originating from muscularis propria (SMTMP) in the stomach, GIST is considered first followed by leiomyoma[3-9]. Because all GISTs have malignant potential and leiomyomas are 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[10-12].

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[13].Obviously, tissue obtained by EUS FNA can demonstrate GIST only but cannot provide further information regarding mitotic activity. EUS features suggestive of a malignant GIST include a larger tumor size, heterogeneous hypoechotexure, an irregular tumor border, and internal cystic or calcified changes[8,14,15]. At present, a GIST > 3 cm is considered to have higher malignant potential and is recommended for surgical resection[16]. As for GISTs < 1 cm, they are frequently considered to harbor a low risk of malignancy and tissue acquisition in these cases is controversial[17]. 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, associateddiscussions regarding the natural course and management of 1-3 cm gastric SMTMP are limited. Here, we reviewed the past 14 years of computerized medical records from our institution to study the natural behaviors for such tumors.

**MATERIALS AND METHODS**

***Patient selection***

All the patients who underwent at least two EUS examinations to follow up gastric SMTMP during the 14 years between Jan 2000 and Dec 2013 wereretrospectively 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 the miniprobe with a12MHzradial scan (Olympus UM-2R, Tokyo, Japan). When EUS showed a myogenic tumor with hypoechoic echotexture originating from 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 depended 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 in benign behavior. Therefore, we excluded the patients with tumor sizes initially larger than 3 cm or persistently smaller than 1cm. 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 1cm or more during surveillance. Therefore, only the patients with 1-3 cm of myogenic tumors under EUS surveillance were enrolled in this study.

***Pathological classification to predict malignant potential of GIST***

If the patient underwent surgery to remove GIST, the pathology of GIST is classified into “very low risk”, “low risk”, “intermediate risk”, and “high risk” groups using tumor size and mitotic count based on the National Institute of Health Consensus[13].

***Data collection and analysis***

We defined a ratio of follow- up tumor size to initial tumor size ≥ 1.2 as tumor progression based on the Response Evaluation Criteria in Solid Tumor (RECIST)[18]. Patients were then divided into the progressive subgroup and the stationary subgroup. Baseline characteristics of each subgroup, initial tumor sizes, echotextures, borders and locations of myogenic tumors, the number of surveillance procedures, and the interval and duration of EUS were recorded and further analyzed. In progressive subgroup, we still follow up these patients until 2016.

***Second review for patients with progressive tumors***

In progressive subgroup, we followed up these patients 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 were analyzed using the Pearson χ2 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 the statistical analyses were performed using SPSS statistical software (SPSS for Windows, version 13; SPSS Inc., IL). A *P* value of < 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 SMTMP. 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 ± 11.0 years (mean ± SD) and the initial tumor size was 14.7 ± 4.9 mm. 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 times. Of the 88 patients, 25(28.4%) were in the progressive subgroup and 63 (71.6%) were in the stationary subgroup. A flowchart is shown in Figure 1. The basic characteristics and EUS findings in each subgroup are shown in Table 1. In comparison with progressive and stationary subgroups, an initially larger tumor size and an irregular tumor border were 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 is ≥ 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 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, 3 and 4. CD117 was positive in all 13patientswith confirmed GISTs (100%), whereas CD34 was positive in 11 (84.6%). Pathology results for confirmed cases showed 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 ≥ 1.2 times) was only shown in the cases with GISTs. Among another 12 patients in progressive subgroup, we followed up them until 2016. Two patients eventually underwent surgery due to gradually enlarged tumors and were confirmed GISTs in low malignant potential. Two patients refused EUS surveillance due to old age (> 80 years). 7 patients who took regular follow up remained condition stable and without tumor metastasis. One patient we couldn’t contact by phone call was loss of follow up. The flowchart of these 12 patients in progressive subgroup was listed 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[19-21]. Most GISTs (about 65%) occur in the stomach, followed by 30%-35% in the small intestine and 5%-10% in the colon. About 95% GISTs are characterized by the positive expression of c-kit receptors tyrosine kinase (CD117), whereas approximately 60%-70% of the tumors are positive for CD34[22-24]. Most gastric GISTs are asymptomatic and are detected incidentally as submucosal tumors during endoscopy. Therefore, the real incidence of GIST 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 muscularis propria and occasionally from muscularis mucosae. Similar to GISTs in terms of EUS findings, leiomyomas are also tumors of muscular origin. Unlike GISTs, leiomyomas are negative for CD117 and CD34, but they are positive for smooth muscle actin (SMA) and desmin on immunohistochemical staining. Moreover, leiomyomas are completely benign.

Recent studies have demonstrated that all GISTs have 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[25].Therefore, EUS surveillance alone is feasible for a small suspected GIST in the stomach that does not require immediate tissue proof or resection[2,26].

Most GISTs < 1 cm harbor a very low malignant potential while GISTs ≥ 3 cm with irregular tumor borders, heterogeneous hypoechogenicity, and internal cystic or calcified changes suggest a higher malignant potential. All leiomyomas are benign. Therefore, we were interested in the natural course of 1-3cm SMTMP 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 ≥ 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 patients (28.4%). 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 ≥ 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 show 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. in their study[27], and is similar to that reported by Lachter et al. who found a tumor size larger than 1.7cm to be indicative of tumor progression[28].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-up since malignant GIST were not detected during surveillance in our study. Although an evidences-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*[26] in 2012.At present, a guideline from European society of medical oncology (ESMO) 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 during surveillance[29]. In this review of 1725 EUS surveillances for gastric submucosal tumors from the 14 years of medical records, we found that most 1-3cm SMTMP in the stomach were indolent with only 28.4% of patients experiencing tumor progression (tumor enlargement ≥ 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 a larger tumor and irregular borders. An initial tumor size > 14.0mm may be considered a cut-off size for predicting tumor progression.

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**COMMENTS**

***Background***

Most gastric submucosal tumor originating from muscularis propria (SMTMP) are gastrointestinal stromal tumors (GISTs) and leiomyomas. Leiomyoma is benign but GIST has malignant potential. Surgery is recommended if GISTs larger than 3cm and observation if < 1 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 GIST.

***Research frontiers***

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

***Innovations and breakthroughs***

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

***Applications***

An 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 ≥ 14.0 mm in size should be observed closely and treated accordingly.

***Terminology***

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

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**Peer-review report classification**

Grade A (Excellent): A

Grade B (Very good): B

Grade C (Good): 0

Grade D (Fair): 0

Grade E (Poor): 0

Indicated patients

(*n*=88)

Stationary tumors

(*n*=63)

Progressive tumors

(*n*=25)

Observation (*n* =12)

Operation (*n* =13)

Observation

(*n* =59)

Operation

(*n*=4)

Leiomyoma

(*n* =4)

GIST

(*n* =13)

**Figure 1 Flowchart of 88 indicated patients with submucosal tumors originating from muscularis propria in the stomach.** EUS: Endoscopic ultrasound.



**Figure 2 Regarding initial tumor size, a receiver operating characteristic curve analysis determined 1.4 cm as the optimal cut-off size for predicting potential tumor progression 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 cmgastric submucosal tumor originating from muscularis propria in tumor progression.** EUS: Endoscopic ultrasound.



**Figure 4 All the patients in progressive subgroup were reviewed again twice.** The first review was based on medical records in 2013 and the second review was by phone calls as well as medical records in 2016.

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

|  |  |  |  |
| --- | --- | --- | --- |
| **Basic characteristics and EUS findings** | **Stationary group** ***n* = 63** | **Progressive group*****n* = 25** | ***P* value**  |
| Age (mean ± SD, yr) | 57.4 ± 10.6 | 56.4 ± 12.4 | 0.69 |
| Sex (M/F)  | 35/28 | 9/16 | 0.10 |
| Location |  |  | 0.65 |
|  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 | 0.02 |
|  Homogeneous/ heterogeneous hypoechoic  | 44/19 | 12/13 | 0.06 |
|  Smooth/ irregular tumor border  | 56/7 | 15/10 | 0.002 |
| With/without internal cystic change or calcification | 8/55 | 4/21 | 0.68 |
| EUS surveillance  |  |  |  |
|  Surveillance duration (mean ± SD, mo) | 24.6 ± 20.3 | 30.7 ± 21.7 | 0.22 |

EUS: Endoscopic ultrasound.

**Table 2 Basic characteristics and endoscopic ultrasound findings in13 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** | **Surveillanceduration (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 analyzed by the Mann -Whitney *U* test**

|  |  |  |  |
| --- | --- | --- | --- |
| **Basic characteristics and EUS findings** | **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 echotextures** |  |  |  |
| Initial tumor size (median, mm) | 21 | 11.5 | 0.015 |
|  Final tumor size (median, mm ) | 28 | 11.5 | 0.003 |
|  Homogeneous/ heterogeneous hypoechoic  | 4/9 | 2/2 | 0.482 |
|  Smooth/ irregular tumor border  | 5/8 | 2/2 | 0.682 |
| With/without internal cystic change or calcification | 1/12 | 0/4 | 0.567 |
| **EUS surveillance**  |  |  |  |
|  Surveillance duration (median, range, months) | 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.