



Research Article

# Clinicopathological Characteristics of the Subepithelial Tumors in Different Locations with in Gastrointestinal Tracts - A Multiple Center Retrospective Study

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## Abstract

**Aim:** The detection rate of gastrointestinal subepithelial tumors (SETs) has been arising. This study aimed to investigate the clinicopathological features of SETs in different gastrointestinal locations. **Methods:** From January 2015 to December 2021, the retrospective medical records of 1965 patients with 1998 SETs diagnosed by endoscopy and histopathology were collected from multiple endoscopic centers in Shanghai. The clinicopathological features and distribution characteristics of SETs were analyzed. **Results:** The current study consisted of 1965 patients ( $57.2 \pm 12.0$  years), and 1998 SETs were identified. The mean diameter of SETs was  $11.2 \pm 8.0$ mm. Gastrointestinal stromal tumor (GIST;  $n=750$ , 37.5%) was the most common type of SETs, followed by leiomyoma ( $n=641$ , 32.1%), lipoma ( $n=199$ , 9.9%), neuroendocrine tumor ( $n=158$ , 7.9%), ectopic pancreas ( $n=152$ , 7.6%), cyst ( $n=30$ , 1.5%), schwannoma ( $n=13$ , 0.7%), inflammatory fibroid polyp ( $n=12$ , 0.6%), glomus tumor ( $n=9$ , 0.5%), Bruner's gland adenoma ( $n=8$ , 0.4%), granular cell tumor ( $n=6$ , 0.3%) and other rare type ( $n=20$ , 1.0%). Of all the SETs, 1257 SETs (62.9%) were identified in the stomach, GIST was the most frequent SETs in the stomach; 412 SETs (20.6%) in the esophagus, the majority ( $n=377$ ) were leiomyomas; 55 SETs (2.8%) in the duodenum, the most common was ectopic pancreas ( $n=15$ ); 274 SETs (13.7%) in the colorectum, the most common was neuroendocrine tumors, which accounted for 147 cases. **Conclusions:** The distribution and histopathologic characteristics of SETs in different segments of gastrointestinal tract were significantly different. Hence, the diagnosis and management of SETs can be improved by identifying their distribution characteristics.

**Keywords:** Subepithelial Tumors; Gastrointestinal Tracts; Endoscopic Ultrasonography; Clinicopathological Features; Diagnosis.

Introduction

The subepithelial tumors (SETs) of gastrointestinal tracts are tumors originating from muscularis mucosa, submucosa, muscularis propria. In recent years, with the extensive use of digestive endoscopy and advancements in diagnosis, the detection rate of gastrointestinal SETs has been arising. Most of the SETs are asymptomatic and considered to be benign and slow-growing, which can be detected during routine endoscopy examinations [1,2]. However, the managements on SETs are still controversial due to their rare occurrence, unknown histopathology and malignant potential.

In clinical practice, although computed tomography (CT) and endoscopic ultrasonography (EUS) are helpful to judge the original layer and size of SETs, it is still difficult to accurately determine the pathological origin of SETs [3,4]. The final diagnosis of SETs mainly depends on tissue acquirement. Due to the malignant potential, clinical symptoms or patients’ discomfort during long-term endoscopic follow-up, endoscopic or surgery resection could be recommended to remove SETs as best practices [5]. Therefore, it is necessary to understand the distribution and clinicopathological characteristics of SETs for an accurate implementation of management strategies.

This study aimed to investigate the distribution and clinicopathological characteristics of SETs in different segments of gastrointestinal tracts for guiding the selection of the most appropriate and effective treatment strategy.

Methods

This multi-centers, retrospective analysis was performed at Shanghai JiaoTong University Affiliated Sixth People’s Hospital. The study protocol was approved by the institutional ethics committee of our hospital, and was performed with the Declaration of Helsinki. The medical records of patients with gastrointestinal submucosal tumors were collected from five endoscopic centers of tertiary hospitals in Shanghai between January 2015 and December 2021. Finally, 1965 patients with 1998 SETs were included in this study. All included patients underwent EUS, and the final diagnosis was confirmed by histopathology. The patients’ general characteristics and endoscopic presentations including age, gender, tumor size, tumor location, original layer of lesions and final pathological diagnosis were collected and analyzed.

Statistical analysis

Statistical tests were conducted with SPSS v25.0 (IBM USA). The quantitative data were presented as mean ± standard deviation

(SD)and median(range). The categorical data was compared using Chi-square test or Fisher’s exact test. One-way analysis of variance was used to compare multiple groups for continuous variables. and A p-value of <0.05 was deemed statistically significance.

Results

The characteristics of overall population and different pathological types of SETs

The current study consisted of 872 males (44.4%) and 1093 females (55.6%), with a mean age of 57.2 ± 12.0 years (range, 18–86 years). A total of 1998 SETs were identified, among which 1932 patients (98.3%) had single lesion and 33 patients (1.7%) had two lesions. The proportions of patients with <50, 50-70 and >70 years were 21.7% (426/1965), 67.2% (1321/1965) and 11.1% (218/1965), respectively. The mean diameter of SETs was 11.2 ± 8.0 mm (range, 3.0-88.0 mm). Of all the lesions, 1257 SETs (62.9%) were identified in the stomach, 412 SETs (20.6%) in the esophagus, 55 SETs (2.8%) in the duodenum, 114 SETs (5.70%) in the colon, and 156 SETs (8.0%) in the rectum (Table 1).

Total patients	N=1965
Gender	
Male (n/%)	872 (44.4%)
Female (n/%)	1093(55.6%)
Male to female ratio	1:1.25
Age(yrs)	
Mean ± SD	57.2 ±12.0
Median (range)	59(18-86)
<50yrs	426 (21.7%)
50-70yrs	1321 (67.2%)
>70yrs	218 (11.1%)
Tumor size (mm)	
Mean ± SD	11.2 ± 8.0
Median (range)	10.0 (3.0-88.0)
Tumor Location	
Esophagus	412(20.6%)
Stomach	1257 (62.9%)
Small intestine	55 (2.8%)
Colon	114 (5.7%)
Rectum	160 (8.0%)
patients’ numbers	
Single lesion (n/%)	1932 (98.3%)
Multiple lesions (n/%)	33 (1.7%)

**Table 1:** The general characteristics of patients with SETs.

Among different histopathological type of SETs, gastrointestinal stromal tumor (GIST; n=750, 37.5%) was the most common type, followed by leiomyoma (n=641, 32.1%), lipoma (n=199, 9.9%), neuroendocrine tumor (NETs, n=158, 7.9%), ectopic pancreas (n=152, 7.6%), cysts (n=30, 1.5%), Schwannoma (n=13, 0.7%), inflammatory fibroid polyp (n=12, 0.6%), glomus tumor(n=9, 0.5%), Brunner’s gland adenoma (n=8, 0.4%), granular cell tumor (n=6, 0.3%), and other types including lymphangioma, hamartoma, neurofibroma, adenomyoma (n=20, 1.0%).

The average age of patients with different SETs and mean diameter of SETs are shown in (Table 2). Notably, the mean diameter of NETs was shorter, while the average age of patients with ectopic pancreas was much younger (47.2±13.6 years). SETs with diameter <20 and ≥20mm accounted for 1885 and 243 cases, respectively. From the results of EUS, both GIST and leiomyoma originated from either muscularis mucosa or muscularis propria, while 97.7% of GISTs originated from muscular is propria.

SMT pathology	GIST	Leiomyoma	Lipoma	neuroendocrine tumor	Ectopic pancreas	Cyst	schwannoma	inflammatory fibroid polyp	Glomus tumor	Brunner’s gland adenoma	Granular cell tumor	Others	<i>P-value</i>
Cases (n/%)	750(37.5%)	641(32.1%)	199(9.9%)	158(7.9%)	152(7.6%)	30(1.5%)	13(0.7%)	12(0.6%)	9(0.5%)	8(0.4%)	6(0.3%)	20(1.0%)	/
Age, years (mean ± SD)	59.8±10.8	56.3±11.5	62.7±9.4	51.8±12.8	47.2±13.6	57.2±11.0	61.1±12.3	55.2±14.0	60.4±9.0	52.9±10.4	48.8±10.8	57.2±12.0	<0.001
Size,mm (mean ± SD)	10.7±7.8	11.0±8.7	13.9±8.7	7.4±3.3	13.1±6.0	9.2±5.3	21.6±9.7	13.4±6.9	16.9±9.4	11.7±5.3	10.0±1.8	13.4±4.9	<0.001
<20mm (n=1755)	670	568	162	155	121	28	6	9	5	7	6	18	<0.001
≥20mm (n=243)	80	73	37	3	31	2	7	3	4	1	0	2	
Original layer													
muscularis mucosa	17(2.3%)	292(45.5%)	0	17(10.7%)	0	10(33.3%)	1(7.7%)	0	0	0	0	3(15%)	<0.001
submucosa	0	0	199(100%)	141(89.3%)	127(83.5%)	20(66.7%)	1(7.7%)	12(100%)	5(55.6%)	8(100%)	6(100%)	7(35%)	
Muscularis propria	733(97.7%)	350(54.5%)	0	0	25(16.5%)	0	12(84.6%)	0	4(44.4%)	0	0	10(50%)	

Table 2: The characteristics on different pathological types of SETs.

All of the lipoma, inflammatory fibroid polyps, granular cell tumors and Brunner’s gland adenomas originated from the submucosa layer, 83.5% of ectopic pancreas, 89.3% of NETs and 66.7% of cysts from submucosa, and 84.6% of Schwannoma from muscularis propria.

The distribution characteristics of SETs in different locations

Esophagus

Among the 412 SETs in the esophagus. the main type of SETs was leiomyoma (n=377), followed by cyst (n=18), GIST (n=7) and lipoma (n=4). Other types of SETs, such as neurofibroma, granular cell tumor, neuroendocrine tumor and glomus tumor, were rare. Based on the EUS data, among leiomyomas in the esophagus, most of the lesions (n=272) originated from the muscularis mucosa layer, while 105 lesions from muscularis propria layer. The mean diameter of leiomyomas was 10.9±6.0 mm. The features of SETs in the esophagus are shown in (Table 3).

Type of SETs	Cases (n=412)	Size, mm (mean ± SD)	Original layer		
			Muscularis mucosa (M)	Submucosa layer (SM)	Muscularis propria (MP)
Leiomyoma	377	10.9 ± 6.0	272	0	105
Cyst	18	7.5 ± 4.9	8	10	0
GIST	7	12.8 ± 7.1	2	0	5
Lipoma	4	14.7 ± 3.8	0	4	0
Neurofibroma	2	16.0 ± 6.6	0	0	2
Granular cell tumor	1	8.0	1	0	0
Neuroendocrine tumor	1	5.0	0	1	0
Glomus tumor	1	4.0	1	0	0
Hamartoma	1	10.1	0	0	1

Table 3: The distribution characteristics on different pathological type of SETs in esophagus.

Stomach

A total of 1257 SETs were located in the stomach. GISTs accounted for 735 cases, and was the most common histopathological type in the stomach, while leiomyomas, ectopic pancreas and lipomas accounted for 257, 137 and 82 cases, respectively. Both GISTs and leiomyomas originated from the muscularis propria or muscularis mucosa layer. All the lipoma and most of the ectopic pancreas originated from the submucosa layer. The characteristics of these lesions are shown in (Table 4).

Type of SETs	Cases (n=1257)	Size,mm (mean ± SD)	Original layer		
			Muscularis mucosa (M)	Submucosa layer (SM)	Muscularis propria (MP)
GIST	735	10.5 ± 8.0	14	0	721
Leiomyomas	257	11.2 ± 9.0	15	0	242
Ectopic pancreas	137	13.1 ± 6.1	21	115	0
Lipoma	82	12.6 ± 10.1	0	82	0
Schwannoma	12	22.1 ± 9.9	0	3	9
Inflammatory fibroid polyp	11	13.5 ± 6.2	6	5	0
Neuroendocrine tumor	7	10.4 ± 8.0	0	7	
Glomus tumor	8	18.5 ± 8.6	0	4	4
Cyst	2	14.5 ± 2.0	0	2	0
Brunner's gland adenoma	1	10.0	0	1	0
Neurofibroma	4	15.0 ± 6.4	0	0	4
Angiolipoma	1	14.5	0	0	1

**Table 4:** The distribution characteristics on different pathological type of SETs in stomach.

We further compared the features between GISTs and leiomyomas in the stomach, as shown in (Table 5). There was no significant difference in the patients' gender and mean diameter of lesions between the two groups. However, the average age of patients with leiomyomas (56.0±11.2 years) was much younger (P<0.05) than those with GISTs (59.7±10.7 years). In addition, 53.7% of GISTs (n=395) were located in the fundus, while 41.6% of leiomyomas (n=125) were located in the gastric body, and the difference on the location distribution was also significant (P<0.05). Moreover, there was significant difference in the original layer between GIST and leiomyoma (P<0.05). GISTs were more frequently originated from the muscularis propria.

	GIST (n=735)	Leiomyomas (n=256)	P value
Gender			
Male(n)	276	80	>0.05
Female(n)	459	176	
Mean age(yrs)	59.7 ± 10.7	56.0 ± 11.2	<0.05
Mean tumor size(mm)	10.4 ± 7.3	11.2 ± 8.2	>0.05
Location (n/%)			
Cardia	12(1.6%)	33(12.9%)	<0.05
Fundus	395(53.7%)	97(37.9%)	
Gastric body	268(36.4%)	125(41.6%)	
Antrum	58(8.0%)	1(0.4%)	
Gastric angle	2(0.3%)	0	
Origination			
muscularis mucosa	17(2.3%)	15(5.9%)	<0.05
muscularis propria	718(97.7%)	241(94.1)	

**Table 5:** The Comparison on the demographic and lesion characteristics between GISTs and leiomyomas in stomach.

Duodenum

There were 55 SETs located in the duodenum. Ectopic pancreas (n=15) was the most common type, followed by lipomas (n=10), cysts (n=7), Brunner’s gland adenoma (n=7), NETs (n=3), leiomyomas (n=2), hamartomas (n=4), lymphangiomas (n=2), GIST (n=1) and adenomyoma (n=1). The features of SETs in the duodenum are described in (Table 6).

Type of SETs	Cases (n=55)	Size,mm (mean ± SD)	Original layer		
			Muscularis mucosa (M)	Submucosa layer (SM)	Muscularis propria (MP)
Ectopic pancreas	15	12.9 ± 4.5	0	11	4
lipoma	10	13.2 ± 4.7	0	10	0
Cyst	10	11.2 ± 1.9	0	10	0
Brunner’sgland adenoma	7	11.7 ± 5.3	0	7	0
neuroendocrine tumors	3	11.0 ± 3.6	0	3	0
Leiomyomas	2	20.0 ± 1.0	1	0	1
GIST	1	15.0	0	0	1
Hamartoma	4	10.0 ± 2.3	0	4	0
Lymphangioma	2	15.5 ± 0.7	1	1	0
Adenomyoma	1	11.1 ± 3.2	1	0	0

**Table 6:** The distribution characteristics on different pathological type of SETs in duodenum.

Colorectum

There were 274 SETs located in the colorectum, NET was the most common type, which accounted for 147 cases, the mean diameter of NETs was 7.5 ± 4.7 mm. Of all the NETs, 131 lesions originated from the submucosa layer, and 16 lesions from muscularis mucosa layer. Lipomas was accounted for 103 cases, the average diameter was 15.0±7.7 mm. In addition, there were 7 GISTs, 5 leiomyomas, 5 granular cell tumors and 7 other types. All the lipomas and granular cell tumors located in the colorectum originated from the submucosa. The characteristics of SETs in the colorectum are shown in (Table7).

Type of SETs	Cases (n=274)	Size,mm (mean ± SD)	Original layer		
			Muscularis mucosa (M)	Submucosa layer (SM)	Muscularis propria (MP)
Neuroendocrine tumors	147	7.5 ± 4.7	16	131	0
Lipoma	103	15.0 ± 7.7	0	103	0

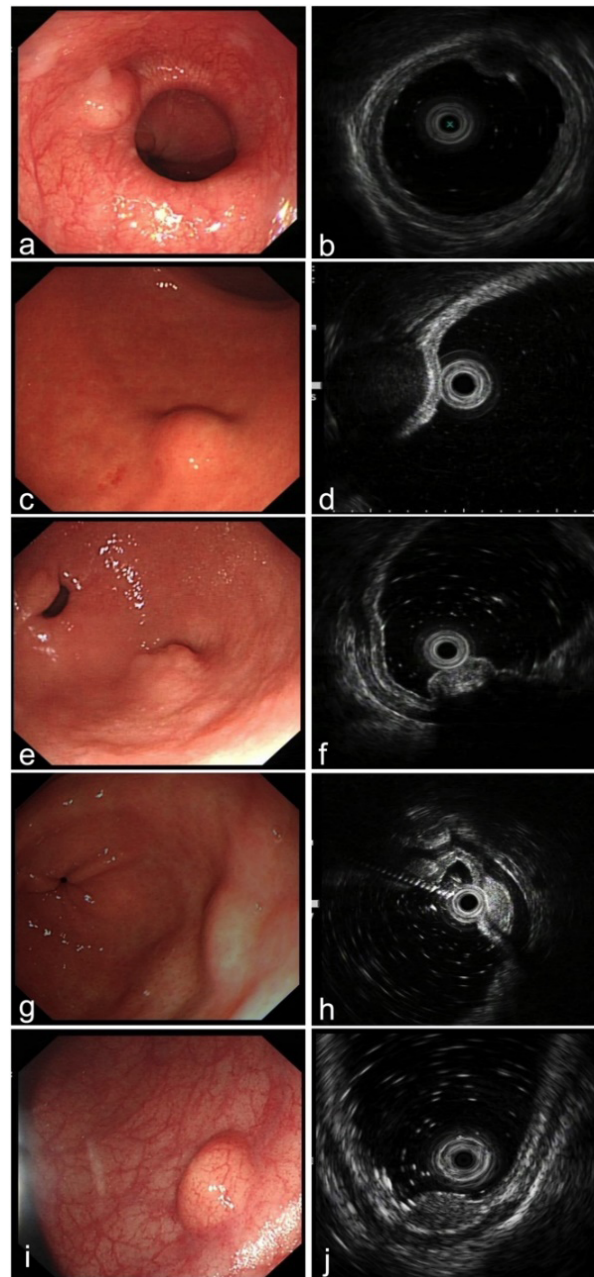
GIST	7	22.9 ± 21.4	0	1	6
Leiomyomas	5	12.0 ± 10.4	3	0	2
Granular cell tumors	5	10.4 ± 1.7	0	5	0
Schwannoma	1	15.1	1	0	0
Inflammatory fibroid polyp	1	12.0	0	1	0
Lymphangioma	2	12.6 ± 3.9	1	1	0
Neurofibroma	3	15.3 ± 3.4	0	1	2

**Table 7:** The distribution characteristics on different pathological type of SETs in colorectum.

**The appearance of gastrointestinal SETs on conventional endoscopy and EUS**

The endoscopic appearances of the five most common SETs are shown in (Figure 1) The endoscopic appearances of leiomyoma and GIST were similar, they present as oval, hemispherical or irregular firm bulges with smooth surface. On EUS, both leiomyomas and GISTs appeared as homogenous, hypoechoic masses with clear margins, and usually originated from the muscularis mucosa or muscularis propria layer. Endoscopically, the distinctive features of ectopic pancreas are broad-based, firm and irregular mass with umbilicated depression. On EUS, it appeared as hypoechoic or mix echogenic lesion, which usually originated from the submucosa layer or partially involved in the multiple layers with disruption of the layers. Lipomas present as soft and compressible protuberate with yellowish and smooth surface. EUS showed hyperechoic mass with a clear margin, which usually originated from the submucosa layer. NETs appeared as polyps-like plaques with yellowish surface, EUS indicated hypoechoic nodule with clear boundary and usually originated from the muscularis mucosa or submucosa layer or partially involved in the deeper layer of tracts.





**Figure 1(a-b):** Esophageal leiomyoma; it appears hemispherical protuberance with smooth surface. On EUS, it presents homogenous, hypoechoic mass with clear margin, which is originated from muscularis mucosa; **(c-d)** GIST in the body of the stomach, GIST appears protuberant lesion with smooth surface. On EUS, it appears homogenous and hypoechoic mass that is originated from muscularis propria. **(e-f)** Ectopic pancreas in the antrum. ectopic pancreas presents irregular and protuberant lesion, EUS showed mix echogenic mass originating from submucosa layer. **(g-h)** Lipoma in the antrum, it presents as protuberant lesion with yellowish surface, EUS showed hyperechoic mass with a clear margin, which is originated from the submucosa layer. **(i-j)** NET appears as polyps-like plaques with dendritic vessels on the surface, EUS showed hypoechoic lesion with clear boundary, which is originated from muscularis mucosa.

## Discussion

It is necessary to early diagnose and assume the histopathological type of gastrointestinal SETs. However, the profile of gastrointestinal SETs remains unclear due to lack of histopathological data [6]. In this work, we retrospectively summarized the distribution and clinicopathological characteristics of SETs in different parts of gastrointestinal tracts.

Previous reports have shown that leiomyomas are the most common benign SETs of the esophagus. They mainly occur in the middle and distal one-third of the esophagus, which may be important for esophageal SETs in the clinical diagnosis [7,8]. Our data revealed that most of SETs in the esophagus (n=377/412, 91.5%) were leiomyomas. Although it is relatively easy to distinguish from leiomyomas and esophageal cancer by conventional endoscopy, it may be difficult to distinguish from other esophageal SETs and extraluminal compression. Thus, EUS and EUS-FNA are often used to assist in the diagnosis. Meanwhile, the possibility of esophageal leiomyomas complicated with esophageal cancer should be considered to avoid missed diagnosis. In addition, esophageal GISTs and granular cell tumors are rare, more attention should be paid during the diagnosis due to their malignant potential and difficulty in distinguishing [9].

SETs in the stomach are heterogenous in nature, and the majority of these tumors were considered as benign or malignant potential and rarely an overt malignancy [10]. Therefore, based on the distribution and prognosis of SETs in the stomach, histopathologic confirmation is useful in guiding the treatment direction [11]. In this study, we found that GISTs were the most common SETs in the stomach (735/1257, 58.5%) and gastrointestinal tracts (750/1998, 37.5%), which mainly originated from the muscularis propria layer. GISTs mainly occurred in the fundus and the body of stomach. Although we found the distribution locations of GISTs and leiomyomas in the stomach were significantly different, it remained difficult to distinguish small GISTs from leiomyomas due to lack of specific manifestations.

Ectopic pancreas is a rare congenital malformation, which can be characterized by the abnormal migration of pancreatic tissues with no anatomic, neural or vascular connection to pancreas [12]. It can form anywhere along the gastrointestinal tract. The present study showed that 90.1% (137/152) of ectopic pancreas were located in the stomach, and most of them (83.5%) were originated from the submucosal layer. In addition, lipomas (82/199, 41.2%) were also the common identified SETs in the stomach. Lipomas are benign and slow-growing tumors, which usually appear as soft and solitary lesions with yellow surface, resembling a cushion sign when pressed with biopsy forceps. EUS showed that it presented as a hyperechoic lesion originating from the submucosal layer [13]. It may not be difficult in diagnosis according to these endoscopic features.

The rare SETs in the stomach, including schwannomas, inflammatory fibroid polyps, NETs, glomus tumors, and cysts and so on, were also identified. Schwannomas are benign lesions originating from the muscularis propria layer, and the appearance on EUS is similar to GISTs or leiomyomas, but the final diagnosis needs to be confirmed by histopathology [14]. Inflammatory fibroid polyps are benign lesions that usually occur in the prepyloric region [15]. Occasionally, it is difficult to distinguish inflammatory fibroid polyps from protruded early gastric cancer. Image enhance endoscopy and EUS are useful to assist in the diagnosis. Inflammatory fibroid polyps appear as broad-based and polyp-like protrusion with slight depression or ulceration on the central surface. On EUS, they present as homogeneous and hypoechoic lesions with indistinct boundary originating from the muscularis mucosa or submucosal layer. Gastric NETs are malignant potential lesions and should be detected by biopsy tissue [16].

In the duodenum, the most common SETs were ectopic pancreas, followed by lipomas, cysts, Brunner's gland adenoma, leiomyomas and GISTs. The endoscopic characteristics of lipomas, leiomyomas and GIST in the duodenum are similar to those in the stomach. Cysts are benign and soft lesions with transparent surface, which can be pressed by biopsy forceps. On EUS, they are anechoic, homogeneous lesions with distinct margins. Brunner's gland adenomas are also rare benign lesions, which can occur in any segment of digestive tracts. However, this tumor is usually asymptomatic and incidentally discovered in 50-60 years-old patients during routine examinations [17].

In this study, we showed that the average age of patients with Brunner's gland adenoma was about 52.9±10.4 years. On endoscopy, the majority of Brunner's gland adenomas appear as polyp-like lesion, while they present as hypoechoic lesions originating from the muscularis mucosa or submucosa layer. Currently, endoscopic resection is recommended as the standard management of Brunner's gland adenomas [17].

Different from the upper gastrointestinal tracts, the most common SETs in the colorectum are NETs, followed by lipomas. There are few GISTs, leiomyomas and other SETs. NETs are malignant potential tumors that occur in any part of the gastrointestinal tract. The majority of NETs in this study were identified in the rectum, and the mean diameter was smaller. NETs appear as yellowish polypoid or flat doughnut-shaped lesions. EUS showed hypoechoic, homogenous lesions with clear margins originating from the muscularis mucosa or submucosa layer. NETs can invade into the deeper layer of digestive tract wall, and even occur in the lymph nodes and remote metastasis. Therefore, EUS is recommended for improving the diagnosis of SETs. Although the surface of NETs is covered with normal-looking mucosa, they are usually diagnosed by standard biopsy. Based on these features, the management of NETs should be active. Endoscopic



or surgical resection may be adopted for diagnosing NETs without the involvement of muscularis propria layer and remote metastasis [18]. The appearance of lipomas and other rare SETs on endoscopy and EUS is similar to the above description.

## Conclusions

Gastrointestinal SETs are relatively common tumors encountered during the routine endoscopic examinations, but their histopathological features may be varied. The conventional endoscopy is difficult to assess their origin and nature. EUS is useful for determining the size, original layer, echogenicity, margins and morphology of SETs, as well as the situations of surrounding lymph nodes and adjacent organs. However, there are still some limitations on the final diagnosis. Thus, it is necessary to identify the features of gastrointestinal SETs on conventional endoscopy and EUS, as well as the distribution characteristics of SETs in different segments of gastrointestinal, which will be helpful to greatly improve the accuracy of SET diagnosis and guide the management direction.

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## Author contributions

ZXD, XYZ and YQQ undertook most of the study and analyzed the data. ZXD, YQQ and FDC drafted the manuscript. ZLX, JC, YWS, JX and SW collected all the information of patients and medical records from five hospitals. HZ and XJW supervised the project and revised the manuscript. All authors approved the final version of the manuscript.

## Conflicts of interest

The authors declare that there is no conflict of interest regarding the publication of this paper.

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