Digestion

Research Article

Digestion
DOI: 10.1159/000527421

Received: January 18, 2022
Accepted: September 15, 2022
Published online: December 5, 2022

Natural History of Small Gastric Subepithelial Lesions Less than 20 mm: A Multicenter Retrospective Observational Study (NUTSHELL20 Study)

Keiichiro Abe[a] Keiichi Tominaga[a] Akira Yamamiya[a] Yasunori Inaba[a] Akira Kanamori[a] Masayuki Kondo[a] Tsunehiro Suzuki[b] Hidetaka Watanabe[c] Masaki Kawano[d] Takashi Sato[e] Naoto Yoshitake[f] Tsuneo Ohwada[g] Maki Konno[h] Kazunobu Hanatsuka[i] Hironori Masuyama[j] Kenichi Goda[a] Yasuo Haruyama[k] Atsushi Irisawa[a] NUTSHELL20 Study group

[a]Department of Gastroenterology, Dokkyo Medical University School of Medicine, Tochigi, Japan; [b]Department of Internal Medicine, Japanese Red Cross Ashikaga Hospital, Tochigi, Japan; [c]Honcho Internal Medicine Clinic, Tochigi, Japan; [d]Kawano Clinic, Tochigi, Japan; [e]Department of Gastroenterology, Japanese Red Cross Nasu Hospital, Tochigi, Japan; [f]Department of Gastroenterology, National Hospital Organization Tochigi Medical Center, Tochigi, Japan; [g]Ohwada Naika, Tochigi, Japan; [h]Department of Gastroenterology, Tochigi Cancer Center, Tochigi, Japan; [i]Hanatsuka Clinic, Tochigi, Japan; [j]Masuyama GI Clinic, Tochigi, Japan; [k]Integrated Research Faculty for Advanced Medical Sciences, Dokkyo Medical University School of Medicine, Tochigi, Japan

Keywords
Gastric subepithelial lesion · Esophagogastroduodenoscopy · Natural history · Tumor growth rate

Abstract

Background and Aim: Small gastric subepithelial lesions (SELs) are sometimes encountered in daily esophagogastroduodenoscopy (EGD) practice, but whether once-annual or twice-annual endoscopy can provide sufficient follow-up remains unclear. Because follow-up based on small-SEL characteristics is important, this study clarified the natural history of gastric SELs less than 20 mm. ***Methods:*** This retrospective multicenter observation study conducted at 24 Japanese hospitals during April 2000 to March 2020 examined small gastric SELs of ≤20 mm diameter. The primary outcome was the rate of size increase of those SELs detected using EGD, with growth times assessed irrespective of SEL pathological diagnoses. ***Results:*** We examined 824 cases with tumors of 1–5 mm diameter in 298 (36.2%) cases, 6–10 mm in 344 (41.7%) cases, 11–15 mm in 112 (13.6%) cases, and 16–20 mm in 70 (8.50%) cases. An increase of small gastric SELs was observed in 70/824 patients (8.5%). The SELs larger than 6 mm increased, even after 10 years. No-change and increasing groups had no significantly different malignant findings at diagnosis. In cases of gastrointestinal stromal tumors (GISTs), internal cystic change in endoscopic ultrasound (EUS) is a risk factor for an increased tumor size. The predictive tumor growth cutoff size at initial diagnosis was 13.5 mm. ***Conclusions:*** Small gastric SELs less than 20 mm have an approximately 8.5% chance of increase. Predictive markers for GIST growth are tumor size ≥13.5 mm and internal cystic change in EUS.

Karger@karger.com
www.karger.com/dig

Correspondence to:
Keiichi Tominaga, tominaga@dokkyomed.ac.jp

Introduction

Gastrointestinal (GI) subepithelial lesions (SELs) in the GI tract are tumors that originate from the muscularis mucosa, submucosa, or muscularis propria. Typically, SELs are observed incidentally in 0.8–2% of patients undergoing upper GI endoscopy [1]. Most SELs are small (≤20 mm), but they have diverse prognoses, varying from benign to potentially malignant. Most such tumors are benign, with fewer than 15% found to be malignant at presentation [2]. Guidelines of the American Society of Gastrointestinal Endoscopy indicate that SEL management depends on a lesion's etiology, location, size, symptoms, and patient-related factors [3]. Endoscopic ultrasound (EUS) is known to play a major role in obtaining information of morphology and the existing layer of the GI wall [4, 5]. Another important feature of EUS is that EUS-guided fine-needle aspiration (FNA)/fine-needle biopsy can be performed if necessary [6]. Collecting tissue samples reliably using EUS-FNA/fine-needle biopsy is difficult unless some special method is used for SELs of 15 mm or smaller [7–10].

Small SELs are sometimes encountered in daily GI endoscopic practice: one rarely observes an increase of gastric SELs less than 20 mm during follow-up. According to Japanese guidelines [11] for gastric SELs, we recommend endoscopic surveillance 1–2 times per year for small SELs less than 20 mm diameter with asymptomatic and no readily apparent malignant finding, even if no biopsy has been performed. However, cases of rapid growth of small SELs less than 20 mm have been reported [12–15]. Even for a small SEL, management must be executed carefully. Proposing an appropriate surveillance method based on the natural history of small SELs including a gastrointestinal mesenchymal tumor (GIMT) is important to establish appropriate management [16]. This retrospective multicenter study was conducted to clarify the natural history of gastric SELs less than 20 mm.

Patients and Methods

Study Design

This retrospective multicenter observation study was conducted at 23 Japanese hospitals located in Tochigi prefecture from April 2000 through March 2020 to examine gastric SELs less than 20 mm. Data were abstracted retrospectively from records of patients who had undergone GI endoscopy.

The primary outcome was the rate of size increase of SELs less than 20 mm that had been detected incidentally by esophagogastroduodenoscopy (EGD) in daily practice. We assessed the time necessary for growth, irrespective of the pathological diagnosis of SELs. The secondary outcome was evaluation of the natural history of gastrointestinal stromal tumors (GISTs) diagnosed from histopathological findings based on comparison of data obtained from the increasing and no-change groups. In addition, cases for which detailed size information was available from medical reports were extracted for comparison of their tumor growth rates and doubling times. We defined the ratio of the follow-up tumor size to initial tumor size of greater than or equal to 1.2 mm as tumor progression based on the Response Evaluation Criteria in Solid Tumors (RECIST) [17]. The following equation was used to calculate the doubling time: tumor growth rate (%) = $(A - B)/B \times 100$, where B denotes the tumor diameter at the time of diagnosis and A represents that after tumor growth. The time course of the tumor growth rate is presented as scattergrams with trend lines. The point at which the tumor growth rate became 100% was defined as the doubling time.

This study, which was approved by the Ethics Committee of the Dokkyo Medical University Hospital with protocol number R-35-6J, was performed in accordance with ethical principles associated to the World Medical Association Declaration of Helsinki update 2013 and was registered at the University Hospital Medical Network Clinical Trials Registry [R000050088]. The Ethics Committee of the Dokkyo Medical University Hospital deemed, because of the study's retrospective nature, that written informed consent was replaceable by the obligation of informing participants and giving participants the right to opt out. Opting out was made available to participants from the website of the Department of Gastroenterology, Dokkyo Medical University.

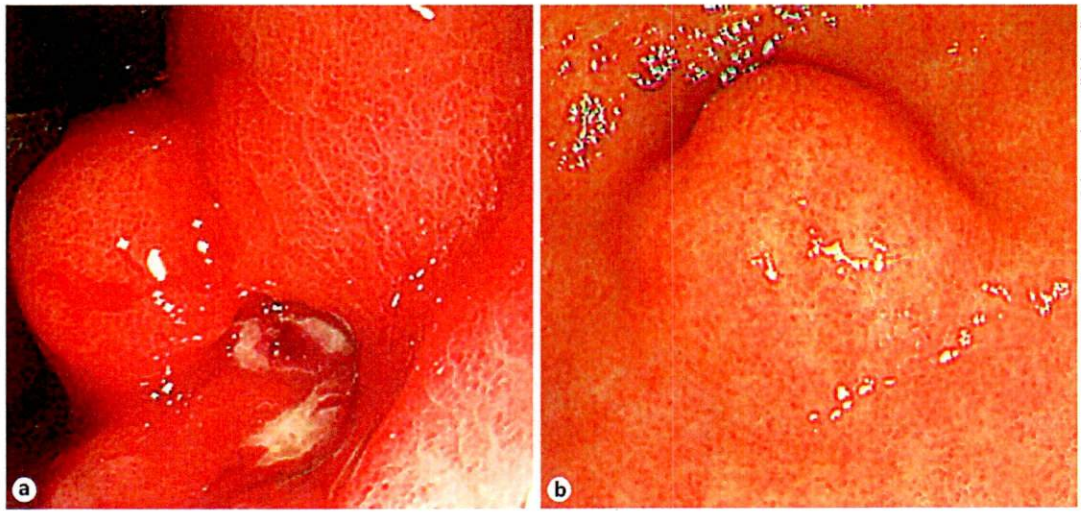
Patient Selection and Data Collection

A questionnaire was administered to 274 institutions in Tochigi prefecture, Japan, to assess the presence or absence of small gastric SELs less than 20 mm that were followed up for more than 1 year from April 2000 through March 2020, irrespective of the interval of endoscopic surveillance. Relevant cases were found at 102 institutions. Among them, 59 institutions for which detailed patient information including endoscopic findings could not be obtained were excluded; eventually, 824 cases at 24 institutions were examined for this study (shown in online suppl. Fig. 1; see www.karger.com/doi/10.1159/000527421 for all online suppl. material).

Endoscopic Evaluation and Surveillance

For this surveillance, the presence of SELs was confirmed by endoscopic observation, irrespective of whether EUS was performed or not. The SEL size was measured by comparison with the endoscopic diameter (approximately 10 mm in peroral endoscope, 6 mm in transnasal endoscope), measure forceps, or EUS image including the EUS mini-probe. Size changes were also evaluated using the initial method of measurement. The SEL sizes were divided into four groups of 1–5 mm, 6–10 mm, 11–15 mm, and 16–20 mm considering the occurrence of measurement error. Cases for which detailed tumor diameters were presented in medical reports were extracted.

The survey items were age, gender, lesion size at initial diagnosis, lesion size (large diameter) at growth, endoscopic findings (site, morphology, presence or absence of malignant findings), and the interval of endoscopic surveillance. The malignant findings were defined as ulceration and irregular margins (shown in Fig. 1) [18]. Moreover, cases for which detailed sizes were available from



Color version available online

Fig. 1. Representative images of EGD of ulceration and irregular margins. **a** Ulceration. **b** Irregular margins.

Table 1. Patient characteristics and tumor appearance

	Total (n = 824)
Gender (males/females)	307/517
Surveillance period (years; median [range])	5 (1–20)
<5 years	383
5–9 years	329
10–14 years	97
15–20 years	15
Surveillance procedure (times; median [range])	4 (2–25)
Age at the initial detection (years; median [range])	66 (29–92)
Initial tumor size, n	
1–5 mm/6–10 mm/11–15 mm/16–20 mm	298/344/112/70
Tumor location (upper/middle/lower)	563/102/159
Malignant findings, n (%) at diagnosis	11 (1.3)
Ulceration, n (%)/irregular margins, n (%)	2 (0.2)/9 (1.1)

medical reports were extracted separately. All clinical data were obtained from the chart, anonymized, and then registered in the database.

Pathological Diagnosis and Pathological Classification of GIST

Definitive histopathological diagnosis was obtained either by EUS-FNA, boring biopsy, or open biopsy. When surgery was performed, the GIST was classified histopathologically as a very low risk, low risk, intermediate risk, or high risk based on the National Institutes of Health consensus using the tumor size and mitotic count [19].

Statistics

The quantitative data are presented as a median (range). Continuous variables were analyzed using Mann-Whitney and Kruskal-Wallis tests. Categorical variables were analyzed using the χ^2 test or Fisher's exact probability test. To compare differences in clinical characteristics between the no-change group and the increasing group, the propensity score matching method was applied with a caliper value of 0.25 that was calculated using gender, age, and surveillance duration. The sensitivity and specificity of various tumor sizes were analyzed using a receiver operating characteristic (ROC) curve. The optimal cutoff value was determined. The analysis was conducted using software (SPSS ver. 27 for Windows; SPSS Japan Inc.), with a two-sided p value <0.05 inferred as significant.

Results

Patient Characteristics

Table 1 presents characteristics of all 824 patients. The median age of the patients was 66 years [range, 29–92 years]. The male-to-female ratio was 307:517. In terms of tumor location, 563 (68.4%) were in the upper part, 102 (12.3%) were in the middle part, and 159 (19.3%) were in the lower part. The median surveillance period was 5 years [range, 1–20 years] years, with a range of 1–20 years: 383 cases (46.6%) were followed up for <5 years, 329 cases (39.9%) for 5–9 years, 97 cases (11.8%) for 10–14 years, and 15 cases (1.82%) for 15–20 years. At the time of initial diagnosis, the tumor size was 1–5 mm in 298 (36.2%) cases, 6–10 mm in 344 (41.7%) cases, 11–15 mm in 112 (13.6%) cases, and 16–20 mm in 70 (8.50%) cases. Malig-

Table 2. Characteristics by surveillance period

	Total (n = 824)	<5 years (n = 383)	5–9 years (n = 329)	10–14 years (n = 97)	15–20 years (n = 15)	p value
Gender (males/females)	307/517	137/246	134/195	30/67	6/9	0.291
Age at the initial detection (years; median [range])	66 (29–92)	67 (29–89)	65 (30–85)	66 (32–92)	68 (45–88)	0.106
Tumor location (upper/middle/lower)	563/102/159	262/47/74	223/41/65	67/14/16	11/0/4	0.988
Surveillance period (years; median [range])	5 (1–20)	3 (1–4.5)	7 (5–9.7)	11 (10–14)	17 (15–20)	<0.001*
Surveillance procedure (times; median [range])	4 (2–25)	3 (1–13)	5 (1–19)	10 (2–16)	14 (3–32)	<0.001*
Initial tumor size, n						
1–5 mm/6–10 mm/11–15 mm/16–20 mm	298/344/112/70	157/149/46/31	111/151/42/24	29/33/20/15	1/10/4/0	0.02*
Malignant findings (n) at the time of diagnosis	11 (2/9)	4 (1/3)	4 (0/4)	2 (0/2)	1 (1/0)	0.153
Ulceration, n (%)	2 (0.2)	1 (0.3)	0 (0)	0 (0)	1 (6.7)	<0.001*
Irregular margins, n (%)	9 (1.0)	3 (0.8)	4 (1.2)	2 (2.1)	0	0.710
Tumor increase, n (%)	70 (8.5)	20 (5.2)	35 (1.6)	15 (15.5)	0 (0)	0.009*
Number of patients with malignant findings at the time of diagnosis, n (%)	3 (27.3)	1 (33.3)	1 (25.0)	1 (5.0)	0 (0)	0.709
Malignant findings (n) at increase	13	3 (1/3)	4 (1/3)	6 (1/6)	0/0	0.02*
Ulceration, n (%)	3 (4.3)	1 (0.3)	1 (0.3)	1 (1.0)	0 (0)	0.709
Irregular margins, n (%)	12 (16.4)	3 (0.8)	3 (0.9)	6 (6.2)	0 (0)	<0.001*

* Statistically significant.

Table 3. Size changes in gastrointestinal SELs (by size at diagnosis)

	Total (n = 824)
1–5 mm at diagnosis, n (%), surveillance period, years; median (range)	298 (36.2), 4 (1–4)
No change in SEL size (n)	282
Change in SEL size, n (<5 mm, 5–9 mm, ≥10 mm increase groups)	16 (5, 9, 2)
<5 years	13 (5, 8, 0)
5–9 years	3 (0, 1, 2)
10–14 years	0 (0, 0, 0)
15–20 years	0 (0, 0, 0)
6–10 mm at diagnosis, n (%), surveillance period, years; median (range)	344 (41.7), 5 (1–20)
No change in SEL size (n)	321
Change in SEL size, n (<5 mm, 5–9 mm, ≥10 mm increase groups)	23 (13, 6, 4)
<5 years	7 (5, 2, 0)
5–9 years	11 (5, 4, 2)
10–14 years	5 (3, 0, 2)
15–20 years	0 (0, 0, 0)
11–15 mm at diagnosis, n (%), surveillance period, years; median (range)	112 (13.6), 6 (1–17)
No change in SEL size (n)	92
Change in SEL size, n (<5 mm, 5–9 mm, ≥10 mm increase groups)	20 (7, 5, 8)
<5 years	5 (1, 2, 2)
5–9 years	11 (3, 3, 5)
10–14 years	4 (3, 0, 1)
15–20 years	0 (0, 0, 0)
16–20 mm at diagnosis, n (%), surveillance period, years; median (range)	70 (8.5), 5 (1–16)
No change in SEL size (n)	59
Change in SEL size, n (<5 mm, 5–9 mm, ≥10 mm increase groups)	11 (2, 7, 2)
<5 years	3 (0, 2, 1)
5–9 years	4 (2, 2, 0)
10–14 years	4 (0, 3, 1)
15–20 years	0 (0, 0, 0)

SEL, subepithelial lesion.

Table 4. Size change (location) of gastrointestinal SELs

	Total (n = 824)	Lower region (n = 159)	Middle region (n = 102)	Upper region (n = 563)
1–5 mm at diagnosis, n (%), surveillance period, years; median (range)	298 (36.2), 4 (1–4)	39 (4.7), 4 (1–11)	45 (5.5), 4 (1–11)	214 (26.0), 4 (1–13)
No change in the SEL size (n)	282	36	42	204
Change in the SEL size, n (<5 mm, 5–9 mm, ≥10 mm increase groups)	16 (5, 9, 2)	3 (3, 0, 0)	3 (1, 1, 1)	10 (4, 5, 1)
<5 years	13 (5, 8, 0)	2 (2, 0, 0)	1 (1, 0, 0)	9 (4, 5, 0)
5–9 years	3 (0, 1, 2)	1 (1, 0, 0)	1 (0, 1, 0)	1 (0, 0, 1)
10–14 years	0 (0, 0, 0)	0	1 (0, 0, 1)	0
15–20 years	0 (0, 0, 0)	0	0	0
6–10 mm at diagnosis, n (%), surveillance period, years; median (range)	344 (41.7), 5 (1–20)	66 (8.0), 5 (1–19)	38 (4.6), 6 (1–12)	240 (29.1), 5 (1–20)
No change in SEL size (n)	321	61	36	224
Change in SEL size, n (<5 mm, 5–9 mm, ≥10 mm increase groups)	23 (13, 6, 4)	5 (2, 1, 2)	2 (2, 0, 0)	16 (3, 10, 3)
<5 years	7 (5, 2, 0)	0	0	8 (3, 4, 1)
5–9 years	11 (5, 4, 2)	5 (2, 1, 2)	2 (2, 0, 0)	4 (0, 4, 0)
10–14 years	5 (3, 0, 2)	0	0	4 (0, 2, 2)
15–20 years	0 (0, 0, 0)	0	0	0
11–15 mm at diagnosis, n (%), surveillance period, median (range), years	112 (13.6), 6 (1–17)	29 (3.5), 5 (1–13)	11 (1.3), 8 (1–12)	72 (8.7), 5.5 (1–20)
No change in the SEL size (n)	92	26	8	58
Change in the SEL size, n (<5 mm, 5–9 mm, ≥10 mm increase groups)	20 (7, 5, 8)	3 (2, 0, 1)	3 (2, 0, 1)	14 (5, 4, 5)
<5 years	5 (1, 2, 2)	0	0	5 (1, 2, 2)
5–9 years	11 (3, 3, 5)	2 (1, 0, 1)	2 (2, 0, 0)	7 (2, 2, 3)
10–14 years	4 (3, 0, 1)	1 (1, 0, 0)	1 (0, 0, 1)	2 (2, 0, 0)
15–20 years	0 (0, 0, 0)	0	0	0
16–20 mm at diagnosis, n (%), surveillance period, years; median (range)	70 (8.5), 5 (1–16)	25 (3.0), 7 (1–13)	8 (1.0), 6.5 (2–10)	37 (4.5), 4 (1–14)
No change in SEL size (n)	59	24	6	29
Change in SEL size, n (<5 mm, 5–9 mm, ≥10 mm increase groups)	11 (2, 7, 2)	1 (1, 0, 0)	2 (0, 1, 1)	8 (2, 5, 1)
<5 years	3 (0, 2, 1)	0	1 (0, 1, 0)	1 (0, 2, 0)
5–9 years	4 (2, 2, 0)	1 (1, 0, 0)	1 (0, 0, 1)	5 (1, 2, 1)
10–14 years	4 (0, 3, 1)	0	0	2 (1, 1, 0)
15–20 years	0 (0, 0, 0)	0	0	0

SEL, subepithelial lesion.

nant findings (ulceration or irregular margins) were observed in 11 cases (1.33%) at diagnosis (2 ulcerations, 9 irregular margins). The EUS findings in 42 cases included homogeneous in 27 cases, heterogeneous in 15 cases, smooth tumor border in 30 cases, irregular tumor border in 12 cases, lobulation of the tumor surface in 5 cases, internal cystic change in 7 cases, and calcification in 6 cases.

Changes in SEL Size for Respective Surveillance Periods

Changes in the SEL size were analyzed according to the surveillance period (Table 2). An increase in the gastric SEL size was observed in 70/824 patients (8.5%). Increasing SEL sizes were observed in 20/383 (5.2%) patients at <5 years of surveillance period, 35/329 (10.6%) cases at 5–9 years, 15/97 (15.5%) cases at 10–14 years, and 0 (0%) cases at 15–20 years. They were most commonly observed at 10–14 years of surveillance period. Malignant findings were observed in 13 (18.6%) of 70 patients who had increasing SELs. Irregular margins at tumor increase were visualized significantly more frequently than ulceration (3 ulcerations and 12 irregular margins, $p < 0.001$). Furthermore, among the cases which showed an increase during the 10–14 years surveillance period, significantly more cases had malignant findings at the time of increase than during other surveillance periods ($p = 0.02$).

Detailed Analyses of Cases Showing an Increase

An increase of SEL was observed in 70/824 patients (8.5%). An initial increase of less than 5 mm was observed in 23 cases (32.9%), 5–9 mm in 28 cases (40.0%), and more than 10 mm in 19 cases (27.1%).

Table 3 presents results obtained from examining the increase during the surveillance period for each SEL size at diagnosis. Although median surveillance period for each size (5 mm or less, 4 years [range, 1–15 years]; 6–10

Table 5. Patient demographics and tumor appearance after propensity score matching[a].

	No-change group ($n = 32$)	Increasing group ($n = 32$)	p value
Gender (males/females)	6/26	6/26	1.000
Surveillance duration (years; median [range])	6.5 (1–12)	6.5 (1–12)	1.000
Age at the initial detection (years; median [range])	65.5 (51–77)	65.5 (51–77)	1.000
Initial tumor size (n)			0.467
1–5 mm	12	9	
6–10 mm	12	11	
11–15 mm	3	8	
16–20 mm	5	4	
Tumor location (n)			0.687
Upper	25	23	
Middle	2	4	
Lower	5	5	
Malignant findings, n (%) at diagnosis	0 (0)	1 (3.1)	0.500
Ulceration, n (%)	0 (0)	0 (0)	ns
Irregular margins, n (%)	0 (0)	1 (3.1)	0.500

[a] Propensity score was calculated by gender, age, and surveillance.

mm, 5 years [range, 1–20 years]; 11–15 mm, 6 years [range, 1–17 years]; 16–20 mm, 5 years [range, 1–16 years]) was similar among groups, 16 cases (16/298, 5.37%) were 5 mm or less, 23 cases (23/344, 6.69%) were 6–10 mm, and 20 cases (20/112, 17.9%) were 11–15 mm; 11 cases (11/70, 15.7%) were 16–20 mm at diagnosis. Furthermore, in cases with a size of 5 mm or less at diagnosis, the size increased in 81.3% (13/16) of cases within 5 years. No case was found to have an increase after 10 years. However, the SELs found to be 6 mm or larger tended to increase even after 10 years. Analysis by location indicated the tendency reported above, especially in the upper part (shown in Table 4).

Comparison between Groups with "Increasing" Lesion Size and "No-Change"

To elucidate risk factors associated with an increase in SELs, the no-change group and increasing group were compared using propensity score matching that matched the gender, age, and surveillance duration (shown in Table 5). Results indicate that 32 exact pairs were matched. After matching, the basic characteristics and surveillance period were all compensated among groups. After propensity score matching, it was not clear that the endoscopic malignant findings could increase SELs in this study.

Analyses of Cases for Which Detailed Sizes Were Available from Medical Reports

Among all patients (824 cases), detailed sizes were available from medical reports in 355 cases (Table 6). In terms of tumor location, 251 (70.7%) were in the upper part, 38 (10.7%) were in the middle part, and 66 (18.6%) were in the lower part. The median of the surveillance period was 5 years [range, 2–17 years], and the median of the tumor size at diagnosis was 10 mm [range, 4–19 mm]. An increase in the gastric SEL size was observed in 23/355 patients (6.5%). Malignant findings were obtained in 8 cases (2.3%) at diagnosis.

The tumor growth rate was greater than 100% in 12 (3.4%) cases (shown in Fig. 2). Table 6 presents results of analyses of the increasing group (23 cases) and the no-change group (332 cases). Endoscopic diagnosis (p = 0.367) revealed no difference in the ratio of presence of malignant findings. The median of the surveillance period until tumor growth was 6 years [range, 2–8 years] for 5 mm increase, and 8 years [range, 4–10 years] for 10 mm increase. The median doubling time was 8 years [range, 4–13 years].

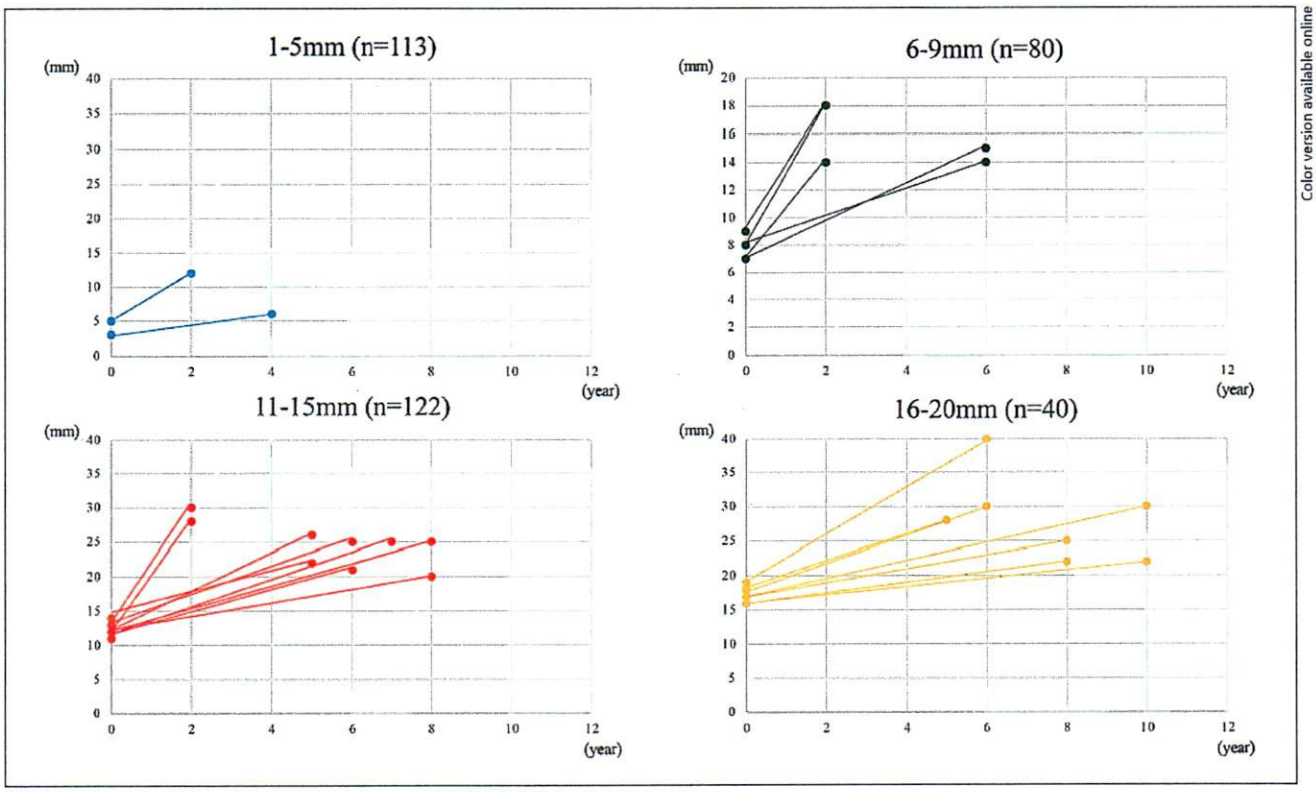
Course of Patients with Malignant Findings in EGD

Increasing tumors were found in 3 of the 9 cases with irregular margins. The histopathological diagnosis respectively included 1 GIST, 1 leiomyoma, and 1 inflammatory fibroid polyp.

Table 6. Analysis of SELs for which detailed size information was available from medical reports

	Total (n = 355)	No-change group (n = 332)	Increasing group (n = 23)	p value
Gender (males/females)	129/225	116/215	13/10	0.08
Surveillance period (years; median [range])	5 (1–12)	5 (2–16)	6.5 (1–12)	0.346
Age at the initial detection (years; median [range])	65 (29–92)	65 (29–92)	64 (42–83)	0.505
Initial tumor size (mm; median [range])	8 (2–20)	8 (2–20)	12 (3–19)	0.001*
Tumor location (n)				0.413
Upper	246	233	17	
Middle	38	35	3	
Lower	66	63	3	
Malignant findings, n (%) at diagnosis	8 (2.3)	7 (2.1)	1 (4.2)	0.432
Ulceration, n (%)	1	1 (0.3)	0 (0)	0.869
Irregular margins, n (%)	7 (2.0)	6 (1.8)	1 (4.2)	0.390
Doubling time		–	8.0 (4–12)	
Time to increase the tumor diameter by 5 mm		–	6.0 (2–8)	
Time to increase the tumor diameter by 10 mm		–	8.0 (4–10)	

* Statistically significant



Color version available online

Fig. 2. Tumor growth rate of SELs.

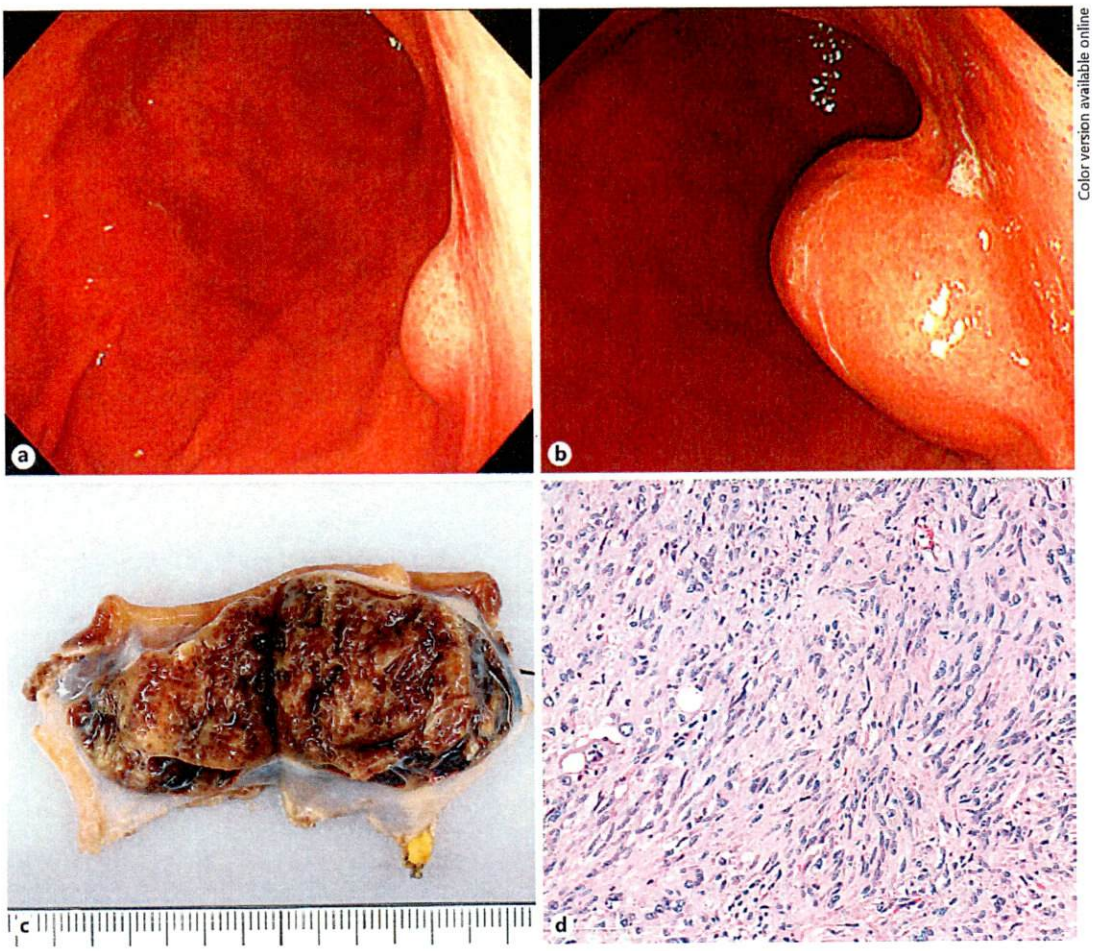


Fig. 3. GIST case with increasing tumor size: **a**, at diagnosis; **b**, 7 years after diagnosis; **c**, resected specimen. A submucosal tumor measuring 40 × 30 × 18 mm in size; **d**, histopathological findings. The tumor comprises spindle-shaped cells (hematoxylin-eosin staining; magnification, ×200).

Characteristics and Changes of Small GIST Cases Diagnosed Using Histopathology

Histopathological diagnoses were obtained in 34 cases (10.8%), including 26 GISTs, 2 leiomyomas, 1 schwannoma, 3 aberrant pancreases, 1 malignant lymphoma, and 1 inflammatory fibroid polyp. A GIST was resected in all cases. A case of laparoscopy and endoscopy cooperative surgery because of tumor increase is shown in Figure 3. Among the 355 cases for which the size details were obtained and investigated for this study, 26 (7.32%) were diagnosed histopathologically as GISTs (shown in Table 7). The median tumor size at diagnosis was 15 mm [range, 8–20 mm]. There was no case of 1–5 mm at the time of initial endoscopic diagnosis that was diagnosed histopathologically as GISTs. Sizes at initial diagnosis were 6–10 mm in 3 cases (11.5%), 11–15 mm in 15 cases (57.7%), and 16–20 mm in 8 cases (30.8%). The median surveillance period was 6 years [range, 3–14 years], with 14 cases (53.8%) increasing during that period. One patient had malignant findings (irregular margins) at diagnosis. Moreover, tumor size was significantly larger in the increasing group ($p = 0.004$) (Table 8). No significant difference was found from malignant findings at diagnosis, but internal cystic changes in ultrasound endoscopy findings were significantly greater in the increasing group ($p = 0.03$). Regarding initial tumor size, we applied ROC curve analysis to determine the optimal cutoff size for predicting potential tumor increase. Results showed 13.5

Table 7. Characteristics of small GIST cases

	Total ($n = 26$)
Gender (males/females)	17/9
Surveillance period (years; median [range])	6 (3–14)
Age at the initial detection (years; median [range])	65 (42–86)
Initial tumor size (mm; median [range])	15(8–20)
Initial tumor size (*n*)	
(1–5 mm/6–10 mm/11–15 mm/16–20 mm)	0/3/15/8
Tumor increase (*n*)	
No change/increasing	12/14
Tumor location (*n*)	
Upper/middle/lower	22/2/2
Malignant findings, *n* (%) at diagnosis	8 (2.3)
Ulceration, *n* (%)	0
Irregular margins, *n* (%)	1 (3.9)
Mitosis (/50 high-power field [HPF]), *n* (%)	
<5/50	21 (87.5)
6–10/50	4 (8.3)
>10/50	1 (4.2)
Risk assessment, *n* (%)	
Very low risk	14 (53.8)
Low risk	9 (34.6)
Intermediate risk	2 (7.69)
High risk	1 (3.85)

GISTs, gastrointestinal stromal tumors.

mm as the optimal cutoff tumor size associated with tumor increase, with sensitivity of 92.9% and specificity of 58.3% (shown in Fig. 4). In terms of mitosis, <5/50 was noted in 21 patients, 6–10/50 in 4 patients, and >10/50 in 1 patient. Risk assessment showed that most cases were very low and low risk (23 cases, 88.5%), 2 cases (7.69%) were intermediate risk, and only 1 case (3.85%) was high risk. The intermediate-risk and high-risk cases had no malignant findings at diagnosis or during the surveillance period.

Discussion

In Japan, small SELs are not uncommonly encountered in daily practice. Contrary to situations in the USA and Europe, several differences among those tumors exist in Japan. The first point of difference is the detection rate of gastric SELs in EGD examination. Whereas the incidence of gastric SELs was reported as 0.36% from a routine Swedish EGD [1], it was approximately 3% in Japan [20]. Most SELs that were detected incidentally in routine EGD were of a few millimeters to less than 20 mm in diameter. Most are found in the upper part of the stomach. Histopathologically obtained results suggest that they were almost all GISTs or leiomyomas [21]. The second point is the size of gastric SELs at detection. Because systematic screening for gastric cancer by EGD and upper GI series is established as a nationwide program in Japan [22], small gastric SELs with no clinical symptom are often detected during medical health examinations [23]. By contrast, Western countries have no similar screening system. As a result, large gastric SELs account for most SELs detected in Western countries [24]. Although SELs less than 20 mm are generally followed up [25, 26], no report of the relevant literature has described the long-term natural history of small SELs. For our study, we examined 824 patients with SELs less than 20 mm, which revealed that 70 patients (8.5%) had increasing SELs. Consequently, the SELs encountered in daily practice might increase, even if small. Therefore, regular surveillance is necessary.

According to the SEL management [11] proposed in Japan, if the diameter is less than 20 mm and if no malignant finding (ulceration, irregular margins, tendency to increase) is obtained, surveillance interval are recommended once or twice a year. However, National Comprehensive Cancer Network Guideline [27] in the USA has insufficient data to construct an appropriate strategy to address SELs less than 20 mm detected either incidentally or from endoscopy. Regular surveillance every 6–12 months is recommended if the patient complains of symptoms, even a small SEL without high-risk findings (so-called malignant findings) on EUS. The European Society for Medical Oncology (ESMO) guidelines [28] recommend annual surveillance with EUS for SELs less than 20 mm without histopathologic diagnosis. Follow-up for a short period of about 3 months at the beginning of detection is recommended. It has also been shown that the surveillance interval can be extended gradually if no increase is found in SELs during the surveillance period. The increase in gastric SELs found in this study was 8.5%, but it was 5.4% in ≤5 mm cases at diagnosis, 6.7% in 6–10 mm cases, 17.9% in 11–15 mm cases, and 15.7% in 16–20 mm cases. The rate of increase was higher if the lesion was larger than 11 mm at initial EGD. Furthermore, most SELs with 10 mm or less showed a tendency to increase within 10 years. Consequently, when a gastric SEL is detected by EGD, endoscopic surveillance is needed even for small SELs. Considering the possibility that the detected SEL is a GIST, we believe that endoscopic surveillance once or twice a year is appropriate for patients without a pathological diagnosis, as recommended in the

Table 8. Analysis of the small GIST case

	No-change group ($n = 12$)	Increasing group ($n = 14$)	p value
Gender (males/females)	9/3	8/6	0.296
Surveillance period (years; median [range])	6(4–14)	7(3–12)	0.335
Age at the initial detection (years; median [range])	65(52–86)	62(42–83)	0.183
Initial tumor size (mm; median [range])	11.5(8–18)	15(9–20)	0.004*
Tumor location (n)			
Upper/middle/lower	11/0/1	11/2/1	0.397
Malignant findings, n (%) at diagnosis			
Ulceration /irregular margins	0/0	0/1	0.583
EUS findings at diagnosis			
Homogeneous/heterogeneous	8/6	7/5	0.437
Smooth/irregular tumor border	12/0	10/4	0.070
With internal cystic change	0	5	0.030*
With internal calcification	2	3	0.578
Lobulation of the tumor surface	1	2	0.560

* Statistically significant.

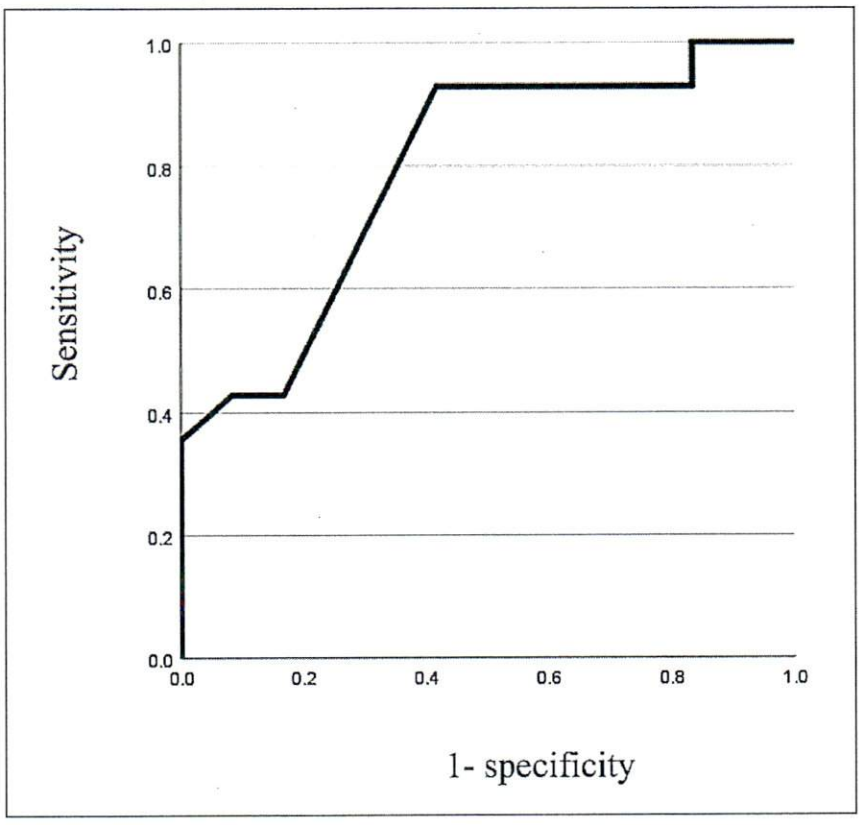


Fig. 4. Characteristic curve analysis of tumor size for predicting potential tumor increase. An initial tumor size of 13.5 mm was ascertained as the optimal cutoff size, with a sensitivity of 92.9% and specificity of 58.3%.

ESMO guidelines. However, if the size of SELs at initial EGD is less than 5 mm without increasing, then surveillance for more than 10 years might be unnecessary.

Analyses of cases for which detailed sizes were available in medical reports demonstrated that growth was observed in 23 cases (6.5%). The tumor growth rate (%) exceeded 100% in half of the cases (12 cases, 52%). The natural history of SELs was not reported comprehensively for most cases, although it was reported for several cases of small GISTs.

Irrespective of their small size, GISTs are tumors with malignant potential [29]. Sekine et al. investigated the natural history of GISTs, which revealed that all GISTs observed at least 1 year of surveillance (median, 55 months) had increased in size during the surveillance period [30]. Furthermore, GISTs less than 20 mm increased significantly more than GISTs less than 20 mm. In another study, tumor growth was observed in approximately 2% of gastric SELs of less than 20 mm in size suspected to be GISTs in the natural history with a median follow-up of 28 months (3–156 months) [26]. For our study, 26 cases of GISTs were analyzed with median follow-up of 6 years (3–14 years): an increase was indicated in 14 cases (58.3%). Although malignant findings in conventional EGD were not related to increasing factors, internal cystic changes on EUS were regarded as related to the size increase. Past reports have described internal cystic changes in EUS as a predictor of an increasing GIST; it was found in 48% of patients with GISTs less than 20 mm [31]. For the study presented herein, we analyzed the ROC curves to ascertain the optimal cutoff size for predicting potential tumor growth: it was 13.5 mm. Although not all cases could be investigated histopathologically, approximately 80% of gastric SELs are regarded as GISTs. Therefore, more intensive surveillance is necessary in cases of suspected GISTs with a tumor diameter of 13.5 mm or more and internal cystic changes in EUS, irrespective of the presence or absence of malignant findings in EGD.

This study has several limitations. First, this is a multicenter retrospective study with no fixed surveillance interval among centers. Nevertheless, the present data generally reflect the natural history of SELs because surveillance was done fundamentally once a year and because no case of rapid increase was included. Second, the subjects include various pathological SELs. However, because many of the gastric SELs are GIMTs [32], which include GISTs, we believe that these study results can serve as a guideline for daily practice. A third limitation is the tumor diameter measurement method. Because EUS was not performed in all cases, some measurement error is expected. Despite those limitations, this study has several important strengths. This study is the first describing a study investigating the long-term natural history of small gastric SELs with a large sample size of 824 cases. Moreover, data for those cases were collected not only from high volume centers but also from clinics at which EUS had not been introduced. Therefore, the data presented herein reflect the natural history of gastric SELs more realistically in accordance with clinical practice. Long-term prospective studies should be conducted to prepare clear guidance for managing small SELs.

Acknowledgments

The authors are grateful to the doctors who replied to the questionnaires. We thank Sanae Iizuka, Miyako Ishida, and Naoko Nishimoto (Department of Gastroenterology, Dokkyo Medical University) for technical assistance. Members of the NUTSHELL20 study group (name and affiliation) are Satoshi Masuyama, Ken Kashima, Fumi Sakuma, Mimari Kanazawa, Yasuhito Kunogi, Takanao Tanaka, Masamichi Yamaura, Yoshitsugu Yoshida, Takahito Minaguchi, Kazunori Nagashima, Shoko Watanabe, Naoya Izawa, Yoichi Takimoto, Akane Yamabe, Takahiro Arisaka, Koki Hoshi, Yuichi Majima, Takeshi Sugaya, Makoto Iijima (Department of Gastroenterology, Dokkyo Medical University School of Medicine), Mutsumi Ishikawa, Koh Fukushi, Yu Okada, Fumihiko Urushibara, Toshimitsu Murohisa (Department of Internal Medicine, Japanese Red Cross Ashikaga Hospital), Mari Iwasaki, Kohei Tsuchida, Yoko Sugaya, Mitsunori Maeda (National Hospital Organization Utsunomiya Medical Center), Shigeo Tano (Shin-Oyama City Hospital), Okamichi Morikawa (Morikawa Internal Medicine/Surgery Clinic), Yukihiro Ichihara (Ichihara Family Clinic), Keiko Takeda (Keyakizaka Clinic), Jun Ishikawa (Ishikawa Clinic), Syusaku Kamei (Kamei Clinic), Koji Yoshizawa (Yoshizawa Clinic), Bunzaburo Ishikawa (Ishikawa Naikasyonika Clinic), Tetsuo Furukawa (Mashiko Medical Clinic), Takahide Shiba (Shiba Hospital), Toru Takahashi (Takahashi Toru Clinic), Shingo Senba (Senba Clinic), and Kazuo Kojima (Kojima Clinic).

Statement of Ethics

The study was conducted at Dokkyo Medical University Hospital as a retrospective observational study approved by the Institutional Ethics Committee (approval no. R-35-6J). This study was performed in accordance with ethical principles associated the World Medical Association Declaration of Helsinki update 2013 and registered at the University Hospital Medical Network Clinical Trials Registry [UMIN000050088]. Based on the study's retrospective nature, the Ethics Committee of the Dokkyo Medical University Hospital decided that written informed consent was replaced by the obligation of information to the participants and the right of participants to opt out approach. The opt-out is available on the website of the Department of Gastroenterology, Dokkyo Medical University.

Conflict of Interest Statement

Atsushi Irisawa is an associate editor of Digestion. The other authors have no conflict of interest to declare.

Funding Sources

The authors did not receive any funding.

Author Contributions

Keiichiro Abe and Atsushi Irisawa designed this study. Keiichiro Abe and Keiichi Tominaga collected and analyzed the data and drafted the manuscript. Keiichi Tominaga, Akira Yamamiya, and Atsushi Irisawa checked the manuscript and approved the final version. Akira Kanamori, Masayuki Kondo, Tsunehiro Suzuki, Hidetaka Watanabe, Masaki Kawano, Takashi Sato, Naoto Yoshitake, Tsuneo Ohwada, Maki Konno, Kazunobu Hanatsuka, and Hironori Masuyama analyzed the data. Keiichiro Abe, Yasunori Inaba, and Kenichi Goda created the figures and tables. Yasuo Haruyama analyzed the data as an expert in statistics.

Data Availability Statement

All data generated or analyzed during this study are included in this article and its online supplementary material. Further inquiries can be directed to the corresponding author.

References

1 Hedenbro JL, Ekelund M, Wetterberg P. Endoscopic diagnosis of submucosal gastric lesions. The results after routine endoscopy. Surg Endosc. 1991;5(1):20–3.
2 Nilsson B, Bümming P, Meis-Kindblom JM, Odén A, Dortok A, Gustavsson B, et al. Gastrointestinal stromal tumors: the incidence, prevalence, clinical course, and prognostication in the preimatinib mesylate era – a population-based study in western Sweden. Cancer. 2005;103(4):821–9.
3 Faulx AL, Acosta RD, Kothari S, Bruining DH, Agrawal D, Eloubeidi MA, et al. The role of endoscopy in subepithelial lesions of the GI tract. Gastrointest Endosc. 2017;85(6):1117–32.
4 Ang TL. Endoscopic ultrasound: moving from diagnostics to therapeutics. J Dig Dis. 2008;9(3):117–28.
5 Seo SW, Hong SJ, Han JP, Choi MH, Song JY, Kim HK, et al. Accuracy of a scoring system for the differential diagnosis of common gastric subepithelial tumors based on endoscopic ultrasonography. J Dig Dis. 2013;14(12):647–53.
6 McCarty TR, Ryou M. Endoscopic diagnosis and management of gastric subepithelial lesions. Curr Opin Gastroenterol. 2020;36(6):530–7.
7 Akahoshi K, Oya M, Koga T, Koga H, Motomura Y, Kubokawa M, 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(4):405–12.
8 Yamabe A, Irisawa A, Bhutani MS, Shibukawa G, Abe Y, Saito A, et al. Usefulness of endoscopic ultrasound-guided fine-needle aspiration with a forward-viewing and curved linear-array echoendoscope for small gastrointestinal subepithelial lesions. Endosc Int Open. 2015;03(02):E161–4.
9 Matsuzaki I, Miyahara R, Hirooka Y, Funasaka K, Ohno E, Nakamura M, et al. Forward-viewing versus oblique-viewing echoendoscopes in the diagnosis of upper GI subepithelial lesions with EUS-guided FNA: a prospective, randomized, crossover study. Gastrointest Endosc. 2015;82(2):287–95.
10 Sekine M, Miura T, Fujiwara J, Uehara T, Asano T, Matsumoto S, et al. Utility of endoscopic ultrasonography-guided fine-needle biopsy (EUS-FNB) for diagnosing small subepithelial lesions (<20 mm). J Ultrasound. 2022;25(1):35–40.
11 Nishida T, Hirota S, Yanagisawa A, Sugino Y, Minami M, Yamamura Y, et al. Clinical practice guidelines for gastrointestinal stromal tumor (GIST) in Japan: english version. Int J Clin Oncol. 2008;13(5):416–30.
12 Tanaka J, Oshima T, Hori K, Tomita T, Kim Y, Watari J, et al. Small gastrointestinal stromal tumor of the stomach showing rapid growth and early metastasis to the liver. Dig Endosc. 2010;22(4):354–6.
13 Sawaki A, Mizuno N, Takahashi K, Nakamura T, Tajika M, Kawai H, et al. Long-term follow up of patients with small gastrointestinal stromal tumors in the stomach using endoscopic ultrasonography-guided fine-needle aspiration biopsy. Dig Endosc. 2006;18(1):40–4.
14 Aso A, Ihara E, Kubo H, Osoegawa T, Oono T, Nakamura K, et al. Gastric gastrointestinal stromal tumor smaller than 20 mm with liver metastasis. Clin J Gastroenterol. 2013;6(1):29–32.
15 Nakajima T, Ushijima T, Kihara A, Murata K, Sugiyama T, Tsuneyama K, et al. A gastrointestinal stromal tumor of the stomach demonstrating a stepwise progression from low- to high-grade malignancy. Case Rep Gastrointest Med. 2012;2012:1–3.
16 Nishida T, Yoshinaga S, Takahashi T, Naito Y. Recent progress and challenges in the diagnosis and treatment of gastrointestinal stromal tumors. Cancers. 2021;13(13):3158.
17 Therasse P, Arbuck SG, Eisenhauer EA, Wanders J, Kaplan RS, Rubinstein L, et al. New guidelines to evaluate the response to treatment in solid tumors. J Natl Cancer Inst. 2000;92(3):205–16.
18 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(5):479–89.
19 Fletcher CD, Berman JJ, Corless C, Gorstein F, Lasota J, Longley BJ, et al. Diagnosis of gastrointestinal stromal tumors: a consensus approach. Hum Pathol. 2002;33(5):459–65.
20 Miyazaki Y, Nakajima K, Kurokawa Y, Takahashi T, Takiguchi S, Miyata H, et al. Clinical significance of surgery for gastric submucosal tumours with size enlargement during watchful waiting period. Eur J Cancer. 2013;49(12):2681–8.
21 Rossi S, Gasparotto D, Toffolatti L, Pastrello C, Gallina G, Marzotto A, et al. Molecular and clinicopathologic characterization of gastrointestinal stromal tumors (GISTs) of small size. Am J Surg Pathol. 2010;34(10):1480–91.
22 Leung WK, Wu MS, Kakugawa Y, Kim JJ, Yeoh KG, Goh KL, et al. Screening for gastric cancer in Asia: current evidence and practice. Lancet Oncol. 2008;9(3):279–87.
23 Otani Y, Furukawa T, Yoshida M, Saikawa Y, Wada N, Ueda M, et al. Operative indications for relatively small (2–5 cm) gastrointestinal stromal tumor of the stomach based on analysis of 60 operated cases. Surgery. 2006;139(4):484–92.
24 Dematteo RP, Heinrich MC, El-Rifai WM, Demetri G. Clinical management of gastrointestinal stromal tumors: before and after STI-571. Hum Pathol. 2002;33(5):466–77.

25 Lim YJ, Son HJ, Lee JS, Byun YH, Suh HJ, Rhee PL. Clinical course of subepithelial lesions detected on upper gastrointestinal endoscopy. World J Gastroenterol. 2010;16(4):439–44.
26 Ye LS, Li Y, Liu W, Yao MH, Khan N, Hu B. Clinical course of suspected small gastrointestinal stromal tumors in the stomach. World J Gastrointest Surg. 2020;12(4):171–7.
27 Demetri GD, von Mehren M, Antonescu CR, DeMatteo RP, Ganjoo KN, Maki RG, et al. NCCN Task Force report: update on the management of patients with gastrointestinal stromal tumors. J Natl Compr Canc Netw. 2010;8(Suppl 2):S1–41.
28 Casali PG, Abecassis N, Bonvalot S, Bauer S, Biagini R, Bielack S, et al. Gastrointestinal stromal tumours: ESMO–EURACAN Clinical Practice Guidelines for diagnosis, treatment and follow-up. Ann Oncol. 2018;29(Suppl 4):iv68–78.
29 Kim MC, Yook JH, Yang HK, Lee HJ, Sohn TS, Hyung WJ, et al. Long-term surgical outcome of 1057 gastric GISTs according to seventh UICC/AJCC TNM system: multicenter observational study from korea and Japan. Medicine. 2015;94(41):e1526.
30 Sekine M, Imaoka H, Mizuno N, Hara K, Hijioka S, Niwa Y, et al. Clinical course of gastrointestinal stromal tumor diagnosed by endoscopic ultrasound-guided fine-needle aspiration. Dig Endosc. 2015;27(1):44–52.
31 Onishi M, Tominaga K, Sugimori S, Machida H, Okazaki H, Yamagami H, 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(4):731–8.
32 Polkowski M. Endoscopic ultrasound and endoscopic ultrasound-guided fine-needle biopsy for the diagnosis of malignant submucosal tumors. Endoscopy. 2005;37(7):635–45.