学位論文

「 Clinical Implications of Doubling Time of Gastrointestinal Submucosal Tumors 」

（消化管粘膜下腫瘍の腫瘍倍加時間の臨床的意義）

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著者の宣言

本学位論文は、著者の責任において実験を遂行し、得られた真実の結果に基づいて正確に作成したものに相違ないことをここに宣言する。

論文要旨

【背景】

消化管粘膜下腫瘍（Submucosal tumor:SMT）は大多数が無症状で、検診のX線検査や通常内視鏡検査で偶然発見されることが多い。しかしGastrointestinal stromal tumor(GIST）はmalignant potentialを有するため切除術を要する。診断には超音波内視鏡ガイド下穿刺吸引法（EUS-FNA）が用いられることが多いが、小病変への対応には苦慮することが多い。GISTとそれ以外の腫瘍で発育速度が異なることがわかれば、治療方針決定に役立つと考えられる。我々は消化管SMTの発育速度を明らかにするため、超音波内視鏡検査（EUS）の経時的所見を用いて消化管SMTの腫瘍倍加時間（Doubling Time: DT）を算出し、新知見を得たので報告する。

【対象】

1987年から2012年11月までに北里東病院、北里大学病院で最終的に外科的切除術もしくはEUS-FNAで病理組織学的診断がなされた消化管SMTは323例であった。そのうち経過中にEUSが2回以上施行され、EUS所見で病変の計測が可能であった53例（切除34例、非切除19例）を対象とし、DTをretrospectiveに検討した。

【結果】

症例の内訳は、男/女:26/27、年齢:中央値63.0（31～83）歳、発生部位は食道/胃/十二指腸:4/47/2、観察期間は中央値31.7（6.6～210）ヶ月、EUS回数は中央値3（2～13）回であった。初回EUS時の腫瘍径は中央値19.1mm(10～44.8mm)であった。疾患別内訳はGIST34例、平滑筋腫5例、神経鞘腫3例、異所性膵1例、過誤腫1例、cyst1例、Brunner腺腫1例、spindle cell tumor7例であった。疾患別DTはGIST17.2ヶ月に対し、平滑筋腫/神経鞘腫/異所性膵/過誤腫/cyst/Brunner腺腫: 231.2/104.7/274.9/61.2/49.0/134.7であった。GISTのリスク分類別のDTは超低・低/中間/高リスク:24.0/17.1/3.9であった。GISTは平滑筋腫+神経鞘腫に比べ有意にDTが短く（$p<0.05$）、高リスクGISTは超低・低リスクGISTと比べ有意にDTが短かった（$p<0.05$）。

【考察】

EUSでは脂肪腫、cystなどと間葉系腫瘍の鑑別は比較的容易と思われるが、共に第4層に位置する低エコー腫瘍として同定されるGIST、平滑筋腫、神経鞘

腫の鑑別は困難である。

腫瘍径と核分裂像に発生部位を考慮に入れたリスク分類では 2cm 以下の病変であれば術後転移を認めないとされているが、腫瘍径の小さい GIST でも転移を示すことがあり、腫瘍径が小さいから良性であると断定することは困難であるとされる。病理診断には EUS-FNA が重要な役割を果たしており、一般的に 2cm 以上が適応とされ、一方、潰瘍形成、辺縁不整、急速増大などの悪性所見を認めない 2cm 以下の病変は年に 1～2 回の経過観察が行われている。しかし通常内視鏡検査では、明らかにサイズが増大した場合や胃内型発育の場合を除いて、詳細なサイズ評価は困難であるため、経過観察には EUS の使用が推奨される。また EUS は小病変の評価も可能であり、CT よりも小病変に対する経過観察には簡便と思われる。

一般的に malignant potential が大きいほど増大速度も速いと推測されているが、実際に各 SMT の増大速度を検討した報告はほとんどない。その理由として、EUS で得られる断層像を用いると、一般的に類円形である SMT の DT の推定は可能だが、時に分葉状に発育する症例もあり、正確な DT を算出するのは困難な場合がある。本検討でも SMT の DT を算出するに当たり、SMT が球体発育すると仮定して計算した。probe type ではない通常型 EUS による 3D-EUS の使用ができれば正確な腫瘍体積の測定が可能となり、今後の課題である。

今回の検討で、SMT は疾患毎に DT が異なることが確認された。特に GIST の DT は 17.2 ヶ月と他の SMT と比較して短く、malignant potential が高いことが確認された。GIST と GIST 以外の間葉系腫瘍（平滑筋腫、神経鞘腫）では DT に差を認めたことから、共に第 4 層に発生する GIST と平滑筋腫、神経鞘腫の鑑別がある程度可能であると考えられた。DT が長ければ malignant potential が低く、小 SMT は経過観察可能であると思われるが、超低・低リスクの GIST では DT が良性疾患よりも長い症例があり、また良性疾患でも GIST より DT が短いものも経験した。サイズの増大が緩徐でも経過中に病理組織学的診断を得ることは重要である。

GIST は病理組織学的に内部が heterogenious であり、EUS-FNA 検体の核分裂像のみで GIST を分類することは難しいとされているため、我々は 2cm 以上の病変あるいはそれ以下でも内部が不整で悪性を疑う病変に対しては積極的に EUS-FNA を施行している。GIST と診断された場合にはサイズが小さく、核分裂像に乏しくても速やかに切除術を施行すべきである。また、2cm 以上で診断がつかない場合には再度 EUS-FNA を行うか、厳重なフォローアップが必要と考えられた。

高リスクの GIST は発見時にすでにサイズが大きく症候性の場合が多く、EUS による経過観察はほとんど行われない。今回 GIST 全体の DT は 17.2 ヵ月であ

ったが、更なる症例の蓄積と検討が必要である。

【結論】

疾患によりDTが異なり、GISTのDTが有意に短いことが確認された。またGISTにおいては悪性度が高いほどDTが有意に短いことが確認された。さらにGISTの中リスクや高リスク群のDTは6か月未満であったため、2cm未満の小SMTでも初期は少なくとも6か月以内のフォローアップが必要と考えられた。

Contents

Introduction

In Japan, gastrointestinal submucosal tumors (SMTs) are often detected on radiographic and conventional endoscopic examinations during health checkups. SMTs are covered by mucosa, and the majority of lesions are nonepithelial tumors arising from the submucosa or muscularis propria. The presence of SMTs can be detected on radiography and conventional endoscopy, but qualitative diagnosis remains difficult on these imaging techniques. However, recent progress in endoscopic ultrasonography (EUS) and other diagnostic techniques has facilitated the qualitative evaluation of SMTs [1, 2]. In the differential diagnosis of gastrointestinal stromal tumors (GISTs), considered clinically important lesions, endoscopic ultrasound-guided fine-needle aspiration (EUS-FNA) plays a major role in deciding the treatment policy and is now widely used clinically [3, 4]. However, there remains room for improvement in the diagnostic accuracy of EUS-FNA for small lesions. Consequently, small SMTs yet to be definitively diagnosed are generally followed up once or twice per year [5]. To our knowledge, very few studies have evaluated the doubling time of SMTs, an index of the rate of tumor growth, according to diagnosis. We estimated the doubling time of different types of SMTs and report our findings.

Materials and methods

Patients

From April 1987 through November 2012, a total of 323 patients were given a final histopathological diagnosis of gastrointestinal SMT on surgical resection or EUS-FNA in our hospital. We studied 53 of these patients (34 with resected tumors and 19 with unresected tumors) whose tumors could be measured on EUS on at least two successive occasions. Tumor doubling time was estimated retrospectively. All examinations were carried out by endoscopists adequately experienced in EUS. Informed consent was obtained from each patient prior to the procedure. Regardless of the results, good clinical care was provided with consent of the patient. The longest and shortest tumor diameters were measured within the depicted range. The follow-up period was defined as the time between initial EUS and final EUS.

Endoscopes

Radial scanning echoendoscopes (GF-UM20, GF-UM240, GF-UM2000, UM-DP20, and UM-DP12; Olympus Co., Tokyo, Japan) were used to perform EUS. EUS-FNA was performed with the use of convex array echoendoscopes (GF-UCT260, GF-UCT240, XGF-UCT160, GF-UC2000P; Olympus Co., Ltd.). The following puncture needles were used: 19-gauge needles (Wilson-Cook, Winston Salem, NC, USA), 22-gauge needles (NA-200H, Olympus Co., Ltd.), and 25-gauge needles (Echochip, Wilson-Cook). The aspiration pressure was 10 to 20 cc, and "in-and-out motion" was continued for 20 strokes (occasionally, 10 strokes). Puncture was performed 2 to 6 time (median, 3 times).

Measurement methods

Three-dimensional EUS is more accurate than 2-dimensional EUS for the measurement of tumor volume. However, commercially available three-dimensional echoendoscopes are probe type, making it difficult to measure large lesions. In the present study, we therefore measured the longest and shortest diameters within the range depicted on

two-dimensional EUS. Few SMTs show a completely spherical growth pattern, and many grow in an oval fashion. In this study, however, we assumed that the tumors were spherical and used the mean value of the longest and shortest diameters as the tumor diameter to calculate tumor volume. The following equation was used to calculate doubling time: tumor growth rate (%) = (V1-V0)/ V0 × 100, in which V0 is the tumor volume (mm^3) at baseline EUS (□$d0^3/6$), V1 is the tumor volume (mm^3) at the second or subsequent sessions of EUS (□$d1^3/6$), d0 is the tumor diameter (mm) at baseline EUS, and d1 is the tumor diameter (mm) at the second or subsequent sessions of EUS.

The time courses of tumor growth rates were plotted on scattergrams with trend lines. The point at which the tumor growth rate became 100% was defined as the doubling time. For some SMTs with slow growth rates the doubling time was a negative value owing to the presence of measurement error. These lesions were excluded from the study.

Definition of diagnosis

On immunostaining of specimens obtained by surgical resection or FNA, tumors that stained positive for CD34 or KIT were diagnosed as GIST. Leiomyomas were diagnosed if immunostaining was positive for smooth-muscle antibodies (SMA) and negative for CD34 and KIT. Schwannomas were diagnosed if the tumor stained positive for S-100 and negative for CD34 and KIT. Spindle-cell tumors were diagnosed if spindle-shaped cells were confirmed on hematoxylin-eosin staining, but immunostaining was precluded by an inadequate sample size on FNA. GISTs were classified as extremely low risk, low risk, intermediate risk, and high risk on the basis of actual tumor diameters and mitotic figures in patients with resected tumors. In patients with unresected tumors, risk class was based on tumor diameter measured on EUS and mitotic figures.

Statistical analysis

For statistical analysis, the Mann-Whitney U test was used to compare doubling times. P values of less than 0.05 were considered to indicate statistical significance. SPSS statistical software, version 17.0 was

used for statistical analysis.

Results

The study group comprised 26 men and 27 women, with a median age of 63.0 years (range, 31 to 83). The tumor was located in the esophagus in 4 patients, the stomach in 47, and the duodenum in 2 (Table 1). The histopathological diagnosis was GIST in 34 patients, leiomyoma in 5, schwannoma in 3, ectopic pancreas in 1, hamartoma in 1, cyst in 1, Brunner's adenoma in 1, and spindle-cell tumor in 7 (Table 2). The median follow-up in the study group as a whole was 31.7 months (range, 6.6 to 210). The median number of EUS procedures performed during follow-up was 3 (range, 2 to 13). The median tumor diameter (mean of the longest and shortest diameters) was 19.1 mm (range, 10 to 44.8 mm) on initial EUS and 25.3 mm (range, 13 to 52.1 mm) on EUS before tumor resection or EUS-FNA for final diagnosis (Table 3).

Tumor resection was performed in 29 of the 34 patients with GIST. Among the 5 patients with unresectable tumors, surgery was precluded by poor general condition due to other diseases (neurologic diseases) in 2 patients, follow-up observation was requested by 1 patient, and the other 2 patients dropped out of the study. Of the 5 patients with leiomyoma, 1 underwent resection, and 4 were followed up. Of the 3 patients with neurinoma, 2 underwent resection, and 1 was followed up. The patient with ectopic pancreas and the patient with Brunner's adenoma were followed up. Among the 7 patients with spindle-cell tumors, 5 were followed up, and 2 dropped out of the study.

In the patents with resected tumors and those with unresected tumors, the median follow-up was 24.9 months and 36.5 months, the median number of EUS sessions during follow-up was 3 and 4, the median tumor diameter at initial EUS was 19.5 and 19.0 mm, and the median tumor diameter on EUS before surgery or EUS-FNA was 28.0 and 22.8 mm, respectively. In patients with resected tumors, the median interval from final EUS to surgery was 3.8 months (range, 22 days to 16.3 months). The median longest tumor diameter of the resected specimens was 35 mm (range, 20 to 60 mm) (Table 3). None of the patients who underwent follow-up observation or who were observed after surgery died or had recurrence (excluding

dropouts).

In the 34 patients with GIST, the median follow-up was 27.3 months (range, 6.6 to 210), and the median tumor diameter at initial EUS was 19.0 mm (range, 10.9 to 44.8). The GISTs were divided into risk classes on the basis of tumor diameters and mitotic figures (Fletcher's classification). The classification was extremely low risk or low risk in 28 patients, intermediate risk in 3, and high risk in 3. The median follow-up period was 31.0 months in patients with extremely low-risk and low-risk GISTs, 47.3 months in those with intermediate-risk GISTs, and 12.4 months in those with high-risk GISTs. The doubling time according to risk was 24.0 months for extremely low-risk plus low-risk GISTs, 17.1 months for intermediate-risk GISTs, and 3.9 months for high-risk GISTs (Table 4).

The median doubling time for GISTs as a whole was 17.2 months. In contrast, the doubling time was 231.2 months for leiomyoma, 104.7 months for schwannoma, 274.9 months for ectopic pancreas, 61.2 months for hamartoma, 49.0 months for intramural developmental cyst, and 134.7 months for Brunner's adenoma (Table 5). The doubling time of GISTs was significantly shorter than the doubling times of leiomyoma plus schwannoma ($p = 0.005$). When the doubling times of GISTs were compared according to risk class, the doubling time of high-risk GISTs was significantly shorter than that of extremely low-risk plus low-risk GISTs ($p = 0.033$). Moreover, the doubling time of high-risk plus intermediate-risk GISTs was significantly shorter than that of extremely low-risk plus low-risk GISTs ($p = 0.047$). Doubling times did not differ significantly between high-risk and intermediate-risk GISTs or between extremely low-risk plus low-risk GISTs and intermediate-risk GISTs (Table 6). The growth rates of individual GISTs during follow-up and the annual growth rates of GISTs according to risk class are shown in Figures 1 and 2, respectively.

We show some endoscopic and EUS findings of low-grade GIST (Figure 3a, 3b, 3c, 3d), high-grade GIST (Figure 4a, 4b, 4c) and ectopic pancreas (Figure 5a, 5b, 5c).

Discussion

Many gastrointestinal SMTs are asymptomatic and incidentally detected on radiographic examinations during health checkups or endoscopic or computed tomographic examinations performed to evaluate other diseases. Few studies have estimated the incidence of gastrointestinal SMTs, but most arise in the stomach, and the detection rate on endoscopy was reported to be 0.36% [3, 6]. Tumorous lesions presenting with the characteristics of SMTs include mesenchymal tumors, lipomas, carcinoids, granular-cell tumors, glomus tumors, and metastatic deposits. Nontumorous lesions include cysts, ectopic pancreas, Brunner's adenomas, and hamartomas [1]. Conventional endoscopy only provides information useful for the local diagnosis of SMTs, whereas EUS can depict the local structure and internal characteristics of the gastrointestinal wall, thereby facilitating qualitative diagnosis [7]. Although it is relatively easy to distinguish gastrointestinal mesenchymal tumors from tumors such as lipomas and cysts on EUS, it is difficult to differentially diagnose GISTs from leiomyomas and schwannomas, because all three of these lesions are depicted as hypoehoic tumors involving the fourth layer on EUS. The 2001 NIH GIST Consensus Meeting and the 2004 ESMO Consensus GIST Meeting proposed that GISTs are potentially malignant and recommended that surgical resection should be considered for all GISTs [8, 9, 10].

Miettinen et al. proposed a risk classification for GISTs, based on tumor diameter, mitotic figures, and location. They reported that tumors 2 cm or less in diameter have no risk of postoperative metastasis [11]. However, metastasis has been associated with even small GISTs [12]. It is therefore difficult to conclude that small tumors are benign. A histopathological diagnosis has an important role in formulating the treatment policy for SMTs. However, SMTs are covered by mucosa similar to that of the surrounding region, which often makes diagnosis challenging on conventional endoscopy with mucosal biopsy. EUS-FNA thus plays an important clinical role in the diagnosis of SMTs. In lesions measuring less than 2 cm, however, the rate of obtaining adequate specimens is generally low [13]. There is also the risk of tumor seeding caused by lesion rupture on puncture with an aspiration needle. Moreover, it is difficult to obtain adequate tissue specimens for immunostaining or other examination

techniques if adequate needle strokes cannot be taken. In general, EUS-FNA is indicated for lesions at least 2 cm in diameter. On the other hand, for lesions less than 2 cm in diameter with no findings suggesting malignancy, such as ulcer formation, irregular margins, or rapid growth [14], follow-up observation once or twice per year has been recommended [5]. However, with the exception of lesions showing distinct evidence of increasing size or an intragastric growth pattern, EUS is recommended for the follow-up of GISTs, particularly lesions showing an extragastric growth pattern precluding an accurate estimation of tumor size. EUS can be used to assess even small lesions and is simpler than computed tomography for the evaluation of small lesions.

Confirmation of differences in growth rate among specific types of SMTs during follow-up is expected to facilitate decision-making regarding the treatment policy. Similar to other types of tumors, a higher malignant potential of SMTs is generally assumed to be associated with a more rapid growth rate [15]. To date, however, few studies have investigated the growth rates of different types of SMTs. A previous study estimated the doubling time of SMTs on computed tomography [16]. To our knowledge, however, our study is the first to report the doubling time of SMTs on EUS. Because SMTs are generally oval tumors, EUS, which produces cross-sectional images, can be used to estimate the doubling time of most SMTs. However, some SMTs show a lobular growth pattern, making it difficult to accurately calculate the doubling time. In our study, we assumed that SMTs show a global growth pattern when we calculated the doubling time. The use of non-probe-type conventional three-dimensional EUS may allow tumor volumes to be more accurately estimated, but this issue must be addressed in future studies.

Our study confirmed that the growth rates of SMTs during follow-up differ according to the specific type of tumor. In particular, GIST had a shorter doubling time (17.2 months) and a higher malignant potential than did the other types of SMTs. The difference in the doubling time between GISTs and mesenchymal tumors other than GIST (leiomyoma and schwannoma) may facilitate the differential diagnosis of GISTs from leiomyomas and schwannomas, all of which arise in the fourth layer of the gastrointestinal wall. Among GISTs, a higher risk class tended to have shorter doubling times. Because our study group was small, further studies of larger numbers of patients are needed. In our study, the doubling times of

intermediate-risk and high-risk GISTs were less than 6 months. Initial follow-up examinations should be therefore performed at least within the first 6 months after diagnosis, even for small SMTs less than 2 cm in diameter.

GISTs, leiomyomas, schwannomas, and other SMTs arising in the fourth layer that have a prolonged doubling time are considered to have low malignant potential. Small SMTs can therefore undergo follow-up observation. Some extremely low-risk and low-risk GISTs have a longer doubling time than that of benign tumors, and we have encountered benign tumors with a shorter doubling time than that of GISTs. It is therefore important to obtain a histopathological diagnosis during follow-up, even for slowly growing tumors.

Although considerable progress has been made in techniques and devices for EUS-FNA, the diagnostic accuracy is not 100% [4, 17]. Patients in whom a histopathological diagnosis cannot be made should therefore be closely followed up. In our study, the median tumor diameter in patients who underwent EUS-FNA was 22.8 mm, which was adequate for EUS-FNA. For SMTs 20 mm or more in diameter that cannot be diagnosed, EUS-FNA should be repeated, and close follow-up is recommended.

In our study, the risk class of GIST was diagnosed on the basis of mitotic figures in specimens obtained by EUS-FNA in patients who did not undergo surgery. Histopathologically, GISTs are heterogeneous masses, making it difficult to classify GISTs solely on the basis of specimens obtained by EUS-FNA [18]. In our hospital, we aggressively perform EUS-FNA for lesions more than 2 cm in diameter as well as for lesions with heterogeneous contents suggestive of malignancy, even if the lesion diameter is less than 2 cm. If GIST is diagnosed, resection should be promptly performed, even if the tumor is small and shows few mitotic figures. For lesions that cannot be diagnosed and small lesions, other techniques [19, 20, 21] should be considered to obtain sufficient specimens.

Many SMTs are detected incidentally on upper gastrointestinal endoscopy, and many patients with small SMTs 1 to 2 cm in diameter are most likely followed up. The management of small lesions measuring less than 2 cm is often perplexing. Our study showed that the doubling time differed according to the type of SMT, and GISTs were confirmed to have a significantly shorter doubling time than other types of tumors. In addition, a

higher risk class of GIST was found to be associated with a significantly shorter doubling time. Our findings suggest that even small SMTs less than 2 cm in diameter should initially be followed up within at least 6 months after detection. In a limited number of patients, surgery or EUS-FNA is indicated. High-risk GISTs that are large and symptomatic are usually surgically resected at the time of detection. Our results demonstrated that SMTs showing evidence of rapid growth on follow-up EUS are likely to be high risk. The median doubling time for GISTs as a whole was 17.2 months, but further studies of larger groups of patients are needed to confirm our findings.

Conclusion

DT differed according to diagnosis. The DT of GIST was confirmed to be significantly shorter than that of other types of tumors. For GIST, a higher risk grade was associated with a significantly shorter DT. Our findings suggest that small SMTs should initially be followed up within at least 6 months after detection.

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Tables and Figures

Table 1. Demographic characteristics of all 53 patients

Characteristic	Value
Sex, No.	male/female: 26/27
Age, median (range), yr	63.0 (31-83)
Tumor location, No.	Esophagus/stomach/duodenum: 4/47/2

Table 2. Histopathological diagnosis

	Esophagus (n = 4)	Stomach (n = 47)	Duodenum (n = 2)	Total (n = 53)
GIMT	4	45	0	49
GIST	0	34	0	34
Leiomyoma	2	3	0	5
Schwannoma	1	2	0	3
Spindle-cell tumor	1	6	0	7
Ectopic pancreas	0	1	0	1
Hamartoma	0	0	1	1
Intramural developmental cyst	0	1	0	1
Brunner' s adenoma	0	0	1	1

Table 3. Details of 53 patients

	Resected tumors (n = 34)	Unresected tumors (n = 19)	Total (n = 53)	GIST (n = 34)
Follow-up period, median (range), mo	24.9 (6.6-210)	36.5 (11.2-183.6)	31.7 (6.6-210)	27.3 (6.6-210)
EUS sessions,median (range)	3 (2-8)	4 (2-13)	3 (2-13)	3 (2-11)
Tumor diameter at initial EUS, median (range), mm	19.5 (10-30)	19.0 (11.5-44.8)	19.1 (10-44.8)	19.0 (10.9-44.8)
Tumor diameter before surgery or FNA, median (range), mm	28.0 (20-43.1)	22.8 (15.2-52.1)	25.3 (13.7-52.1)	26.7 (13.7-52.1)
Time from the final EUS to surgery, median (range)	3.8 mo (22d-16.3 mo)	-	-	-

Table 4. Details of 34 patients with gastrointestinal submucosal tumors

	Extremely low plus low risk (n = 28)	Intermediate risk (n = 3)	High risk (n = 3)	Total (n = 34)
Follow-up period, median (range), mo	31.0 (6.6-210)	47.3 (11.2-49.9)	12.4 (7.4-16.7)	27.3 (6.6-210)
Initial tumor diameter, median (range), mm	18.6 (10.9-30.0)	28.5 (20.0-44.8)	25.5 (14.0-27.3)	19.0 (10.9-44.8)
Doubling time, median (range), mo	24.0 (2.0-183.6)	17.1 (6.1-19.4)	3.9 (0.8-10.4)	17.2 (0.8-183.6)

Table 5. Tumors other than gastrointestinal submucosal tumors

	No. of patient	Follow-up period, median (range), mo	Doubling time, median (range), mo
Leiomyoma	5	47.1 (10.7-137.2)	231.2 (21.3-1303.8)
Schwannoma	3	50.1 (24.3-71.7)	104.7 (3.9-305.4)
Ectopic pancreas	1	66.5	274.9
Hamartoma	1	99.6	61.2
Intramural developmental cyst	1	29.5	49.0
Brunner's adenoma	1	30.6	134.7

Table 6. Comparison according to diagnosis

	Doubling time (mo), median	P value
GIST vs Leiomyoma + schwannoma	17.2 vs 204.2	0.005
High risk vs Intermediate risk	3.9 vs 17.1	0.127
Intermediate risk vs Extremely low + low risk	17.1 vs 24.0	0.423
High risk vs Extremely low + low risk	3.9 vs 24.0	0.033
High + intermediate risk vs Extremely low + low risk	8.2 vs 24.0	0.047

Figure 1. Growth rates of individual gastrointestinal submucosal tumors during follow-up.

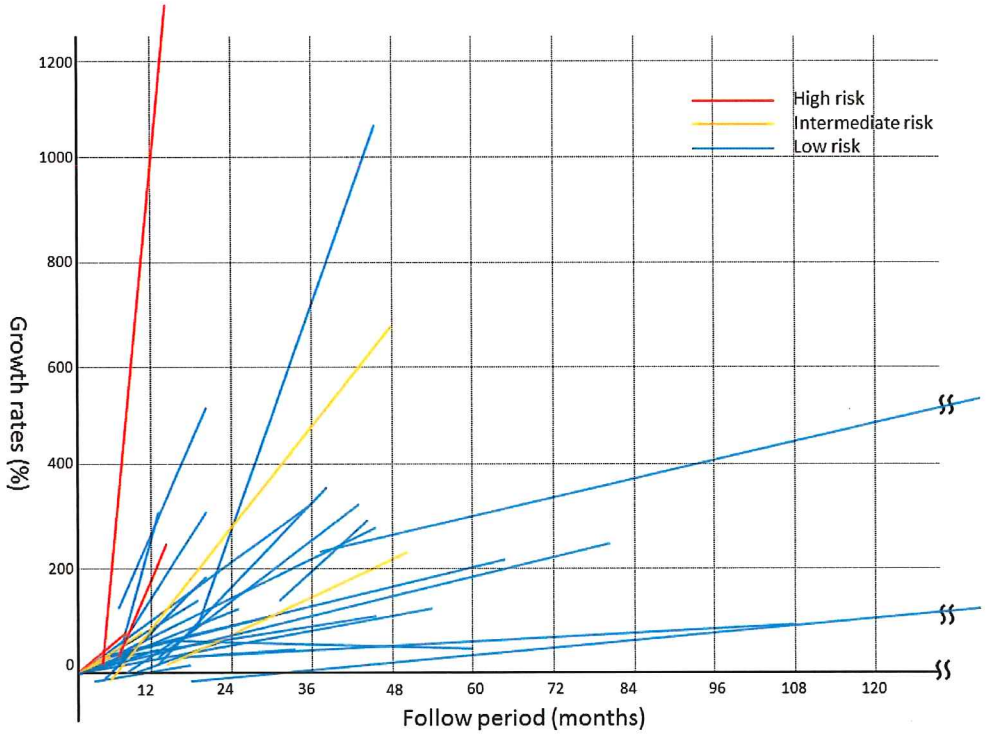


Figure 2, Annual growth rates of gastrointestinal submucosal tumors.

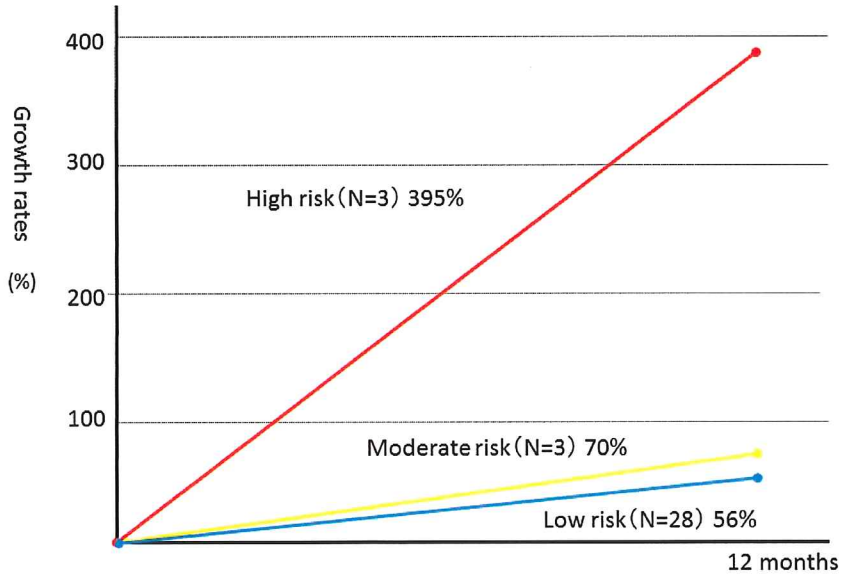


Figure 3, Gastrointestinal submucosal tumors low grade: Doubling time is 17.2 mo.

A: EUS finding at baseline, tumor diameter is 22.0 mm

B: EUS finding at four years later, tumor diameter is 34.0 mm

C: Endoscopic finding at baseline

D: Endoscopic finding at four years later

There is almost no change in endoscopic findings in four years. EUS: Endoscopic ultrasound.

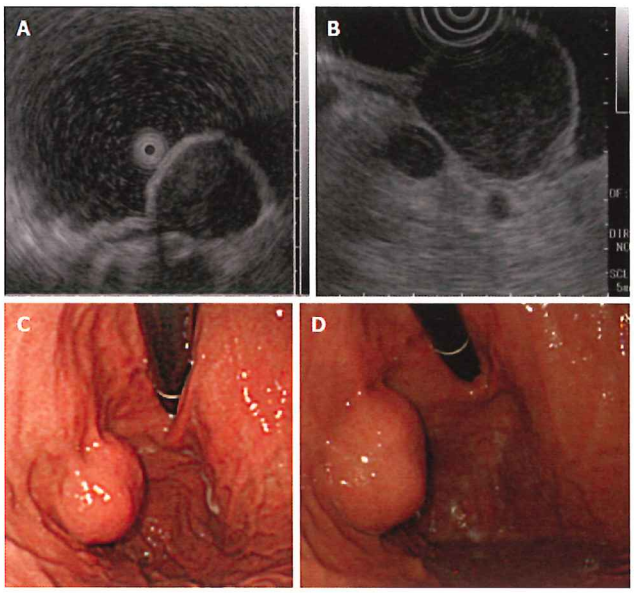


Figure 4. Gastrointestinal submucosal tumors high grade: Doubling time is 3.0 mo.

A: EUS finding at baseline, tumor diameter is 25.5 mm

B: EUS finding at 6 mo later, tumor diameter is 28 mm

C: EUS finding at 12 mo later, tumor diameter is 38.5 mm

There are remarkable changes in one year.

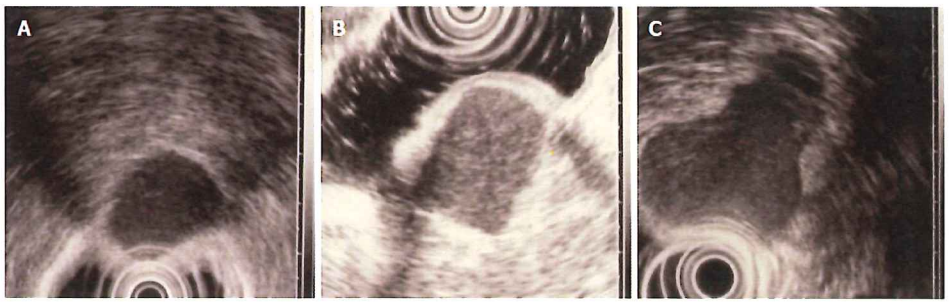


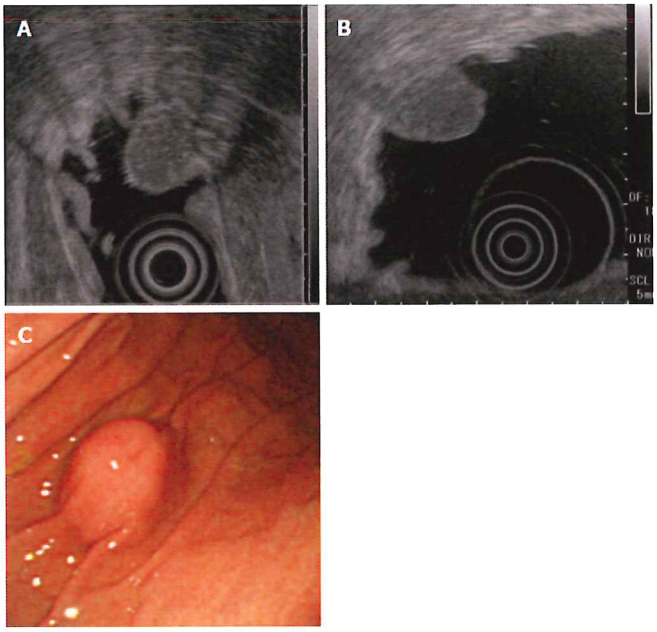
Figure 5. Ectopic pancreas

A: EUS finding at baseline, tumor diameter is 15.5 mm

B: EUS finding at five years later

C: Endoscopic finding

Ectopic pancreas has no change in five years.



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なし

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