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Clinical Usefulness of Endoscopic Ultrasound-Guided Fine Needle Aspiration for Gastric Subepithelial Lesions Smaller than 2 cm

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ABSTRACT

Background & Aims: There is no evidence of postoperative metastasis of gastric gastrointestinal stromal tumors (GISTs) smaller than 2 cm. The aim of this study was to evaluate the clinical usefulness of endoscopic ultrasound guided fine needle aspiration (EUS-FNA) for gastric subepithelial lesions (SELs) smaller than 2 cm.
Methods: Using a prospectively maintained EUS-FNA database, 90 consecutive EUS-FNAs of gastric hypoechoic solid SELs smaller than 2 cm diagnosed by EUS were evaluated retrospectively. The reference standards for the final diagnosis were surgery (n=44) and/or clinical follow-up (n=46) using esophagogastroduodenoscopy (EGD), CT, and/or ultrasonography (US). Additionally, immunophenotyping of specimens obtained by EUS-FNA and surgical resection specimens were compared.
Results: The diagnostic rate of EUS-FNA for gastric hypoechoic solid SELs smaller than 2 cm was 73% (66/90). Histological diagnosis of EUS-FNA showed 47 (52%) malignant SELs (44 GISTs, 1 glomus tumor, 1 SEL like cancer, and 1 malignant lymphoma), 19 (21%) benign SELs (14 leiomyomas, 4 ectopic pancreas, and 1 neurinoma), and 24 (27%) indeterminate SELs. In 44 surgically resected cases, the diagnostic accuracy of EUS-FNA using immunohistochemical analysis was 98% (43/44). There were no complications. Appropriate management was performed in 65 out of 66 SELs (98%) diagnosed by definitive EUS-FNA. After surgery, there was no recurrence of malignant SELs.
Conclusions: EUS-FNA is an accurate and safe method in the pre-therapeutic diagnosis of gastric SELs smaller than 2 cm. EUS-FNA for gastric SELs smaller than 2 cm is a promising way to permit early management of patients with gastric SELs including GIST.

Key words: EUS-FNA – GIST – SMT – subepithelial lesion – stomach – early diagnosis.

Abbreviations: EGD: esophagogastroduodenoscopy; EUS: endoscopic ultrasonography; EUS-FNA: endoscopic ultrasound-guided fine needle aspiration; GIST: gastrointestinal stromal tumor; HPF: high power field; SEL: subepithelial lesion; SMT: submucosal tumor.

INTRODUCTION

Gastrointestinal stromal tumor (GIST) is one of the most common malignant subepithelial lesions (SELs) of the stomach, and is pathologically defined by spindle cells, epitheloid cells or mixed findings with positive immunostaining for c-kit or CD34 [1-6]. Gastrointestinal stromal tumors have a risk of metastatic relapse, specifically in the liver and peritoneum, after initial surgery for localized disease [2-7]. The postoperative metastatic rate is related to tumor size and mitotic activity [5]. Usually, the larger the tumor size, the more frequent the mitosis of the resected specimen and the higher the postoperative metastatic rate. The nature and frequency of the GIST among gastric SELs smaller than 2 cm is unknown. Furthermore, strict discrimination between benign and malignant GIST is considered to be very difficult both by imaging investigations and by pathological examinations even though benign GIST may exist. Therefore, the European Society for Medical Oncology (ESMO) as well as the Japanese GIST guidelines recommend surgical resection when SEL is diagnosed as immunohistologically confirmed GIST even if < 2 cm [8-10]. Furthermore, at present, there is no reliable clinical management algorithm for gastric SELs smaller than 2 cm [2, 7-9]. Miettinen et al reported that gastric GISTs smaller than 2cm have a 0% metastatic rate after complete surgical resection irrespective of mitotic activity [5]. Theoretically, early diagnosis of tumors smaller than 2 cm and early surgical resection is a promising way of obtaining a permanent cure of this disease.

Unfortunately, all preoperative imaging modalities are unreliable for the accurate diagnosis of GIST. Therefore, tissue diagnosis with immunohistochemical analysis is required [7, 8]. At present, EUS-FNA is recognized as an accurate modality for the immunohistochemical diagnosis of GIST [11-14]. However, the clinical usefulness of EUS-FNA for gastric SELs smaller than 2 cm is unclear. Our objective was to evaluate the clinical usefulness of EUS-FNA for gastric hypoechoic solid SELs smaller than 2 cm.

METHODS

Patients

Patients with gastric SELs were managed according to our institutional diagnostic and therapeutic algorithm (Fig. 1) [7]. Surgical resection was recommended for patients with any size of histologically confirmed GIST (immunohistochemical analysis of the specimen obtained by EUS-FNA) according to the Japanese GIST guidelines [9] after discussion with each patient. In our algorithm, EUS-FNA is performed for all endosonographic hypoechoic solid SELs (suspected as GIST, leiomyoma, neurinoma, malignant lymphoma and SEL like gastric cancer, by standard EUS) larger than 1 cm. From February 2003 to October 2012, EUS-FNA was performed in 185 patients with gastric SELs at Aso Iizuka Hospital. In this study, 90 consecutive patients with subepithelial hypoechoic solid tumors smaller than 2 cm originating deeper than the second sonographic layer of the gastric wall by standard EUS were enrolled. There were 32 males and 58 females, and the mean age was 60 years (range 25 – 84).

EUS and EUS-FNA procedures

Standard EUS was performed on an outpatient basis, with the patient under conscious sedation, using a conventional radial scanner echoendoscope GF-UM20 (Olympus, Tokyo, Japan), EG-530UR2 (Fujifilm, Tokyo, Japan) or 12MHz ultrasound catheter probe SP-702 (Fujifilm, Tokyo, Japan). EUS-FNA was performed on a one day inpatient basis, with conscious sedation, using PEF-708FA (Toshiba-Fujinon, Tokyo, Japan) or EG-530UT2 (Fujifilm, Tokyo, Japan) convex array echoendoscope. The echoendoscope was connected to ultrasound scanner SSA-550A (Toshiba, Tokyo, Japan) or SU-8000 (Fujifilm, Tokyo, Japan). Color flow and Doppler sonography were performed to exclude intervening vascular structures and to select a vessel-free needle track. FNA procedures were performed using the 22G (NA-11J-KB, NA-200H, or EZ shot2, Olympus, Tokyo) or 25G needle (Expect, Boston Scientific, USA). Once the tip of the catheter was visualized, the needle was advanced from the catheter sheath through the gastric wall and into the target lesion under EUS guidance. The stylet was removed and continuous suction applied with a 20-ml syringe. The needle was moved back and forth within the lesion under ultrasonographic guidance. The suction was then released and the needle removed from the working channel. The aspirates were placed on glass slides, and both air-dried and alcohol-fixed smears were prepared. Air dried smears were stained with a modified Giemsa stain and reviewed immediately by a cytopathologist on site to ensure specimen adequacy. The remaining prepared histologic specimens were later processed for cell block in the pathology laboratory for hematoxylin and eosin staining and additional ancillary studies such as immunochemistry. The diagnosis of SEL using EUS-FNA in all cases was made by histologic assessment only. Subsequent hematocrit was obtained on the first day after EUS-FNA, and patients were assessed for hematemesis before discharge. If unsuccessful EUS-FNA was encountered, we performed the additional EUS-FNA session several months later to obtain an adequate sample. One attending endosonographer (KA) performed all EUS and EUS-FNA procedures. Technical data for EUS-FNA, including the date, age of the patients, type of needle, number of the needle pass, number of the session, location and size of the tumor, the

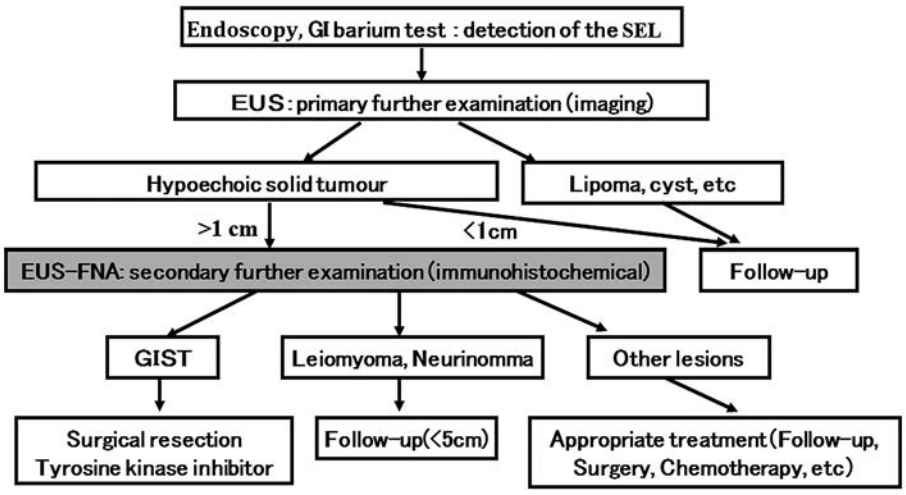

Fig. 1. Diagnostic and therapeutic algorithm for gastric subepithelial lesions (SELs) using endoscopic ultrasound-guided fine needle aspiration. Quoted and modified from Ref. [7]. In our institute, surgical resection is recommended for the patient with any size of histologically confirmed GIST (immunohistochemical analysis of the specimen obtained by EUS-FNA or bite-biopsy) according to the Japanese GIST guidelines [9] after discussion with each patient.

results of immunohistochemical analysis, and complications were recorded prospectively using our institutional formatted EUS-FNA reporting system.

Immunohistochemical analysis

Both the EUS-FNA and surgical resection specimens were fixed in 10% formaldehyde and tissue blocks were embedded in paraffin. Sections were stained with hematoxylin and eosin. Immunoperoxidase stains were subsequently made on the cell block and representative histologic sections of the tumor using commercially available antibodies. Details of the antibodies are described elsewhere [9]. A tumor with positive reaction to c-kit and/or CD34 was diagnosed as GIST. A tumor with a negative reaction to c-kit, CD34, and S-100 and a positive reaction for muscle actin was diagnosed as a myogenic tumor (leiomyoma). A tumor with a negative reaction to c-kit, CD34, and muscle actin and positive reaction for S-100 was diagnosed as a neurogenic tumor (neurinoma).

Assessment of clinical outcome

Clinical management was performed according to our institutional management algorithm for gastrointestinal (GI) tract SEL (Fig. 1) [7]. EUS-FNA diagnoses were compared with final diagnoses, which were based on the histologic examination of surgically resected pathology materials and/or clinical follow-up (mean: 35 months, range: 2 to 108 months) findings. A follow up study was performed using esophagogastroduodenoscopy (EGD) and US and/or CT. Histological diagnostic rate, complications, and the results of the follow-up study were evaluated in all 90 cases. Accuracy for the differential diagnosis of SEL was calculated in 44 surgically resected cases which were conclusively diagnosed by preoperative EUS-FNA. The appropriate decision-making rate for management was calculated in the 66 diagnostic cases (excluding 24 unsuccessful EUS-FNA cases, as they were non-diagnostic).

Ethical considerations

This study was carried out only at Aso Iizuka Hospital and was approved by its Ethics Committee. Written informed consent was obtained from all the patients in accordance with the Declaration of Helsinki.

RESULTS

Clinicopathological characteristics of the lesions are summarized in Table I. Histological diagnosis of gastric SELs smaller than 2 cm by EUS-FNA were 47 malignant SELs (71%) consisting of 44 GISTs (Fig. 2), 1 SEL-like cancer, 1 glomus tumor, and 1 malignant lymphoma (Fig. 3), and 19 benign SELs (29%) consisting of 14 leiomyomas, 4 ectopic pancreas (Fig. 4), and 1 neurinoma. The remaining 24 SELs were not concluded by EUS-FNA. Forty-three out of 90 cases were diagnosed as GIST by postoperative immunohistochemical analysis. Their mitotic count were < 5/50 high power field (HPF) (very low risk according to modified-Fletcher's classification) in 33 cases (77%) and >5/50 HPF (moderate risk according to modified-Fletcher's classification) in 10 cases (23%) [15].

Table I. Clinicopathological characteristics of the patients with small subepithelial lesions (N=90)

Gender, n	
Male : Female	32:58
Age, years	
Range : 25~84	Mean : 60
Anatomic sites of the lesions, n (%)	
Fundus	10 (11)
Cardia	12 (13)
Body	50 (56)
Angulus	13 (14)
Antrum	5 (6)
Tumor size	
Range : 1~2 cm	Mean ± SD: 1.5 ± 0.3 cm
Histological diagnosis (N=66*) by EUS-FNA, n (%)	
Malignant SEL	47 (71)
GIST	44 (67)
SEL like cancer	1 (2)
Glomus tumor	1 (2)
Malignant lymphoma	1 (2)
Benign SEL	19 (29)
Leiomyoma	14 (21)
Ectopic pancreas	4 (6)
Neurinoma	1 (2)
Mitotic count in patients with GIST who have undergone surgery (N=43)	
< 5/50 HPF	33 (77%)
> 5/50 HPF	10 (23%)

*Excluding inadequate specimen (not diagnosed cases); GIST: gastrointestinal stromal tumor; HPF: high power field; SEL: subepithelial lesion.

Table II. Technical results of EUS-FNA

Puncture not performed* (rate)	1/90 (1%)
Mean number of EUS-FNA passes (range)	3.2 (1-6)
Mean number of EUS-FNA sessions (range)	1.2 (1-4)
Collection of diagnostic specimen, n/total (%)	
1st session	56/90 (62)
The 2nd or more sessions after failure of the 1st session	10/20 (50)
Overall	66/90 (73)
Complications, n/total (%)	0/90 (0)

*Poor visualization due to severe intratumoral calcification.

Technical results are shown in Table II. In one case, puncture was not performed because of poor EUS visualization due to severe intratumoral calcification. The diagnostic rate (first session only) was 62% (56 of 90 patients). The diagnostic rate including the additional sessions completed after previous failure was improved to 73% (66 of 90 patients). No complications were encountered.

In 44 surgically resected cases after conclusive EUS-FNA (excluding non-diagnostic EUS-FNA cases), the accuracy of the preoperative differential diagnosis of SEL by EUS-FNA using immunohistochemical analysis was 98% (43 of 44 patients).

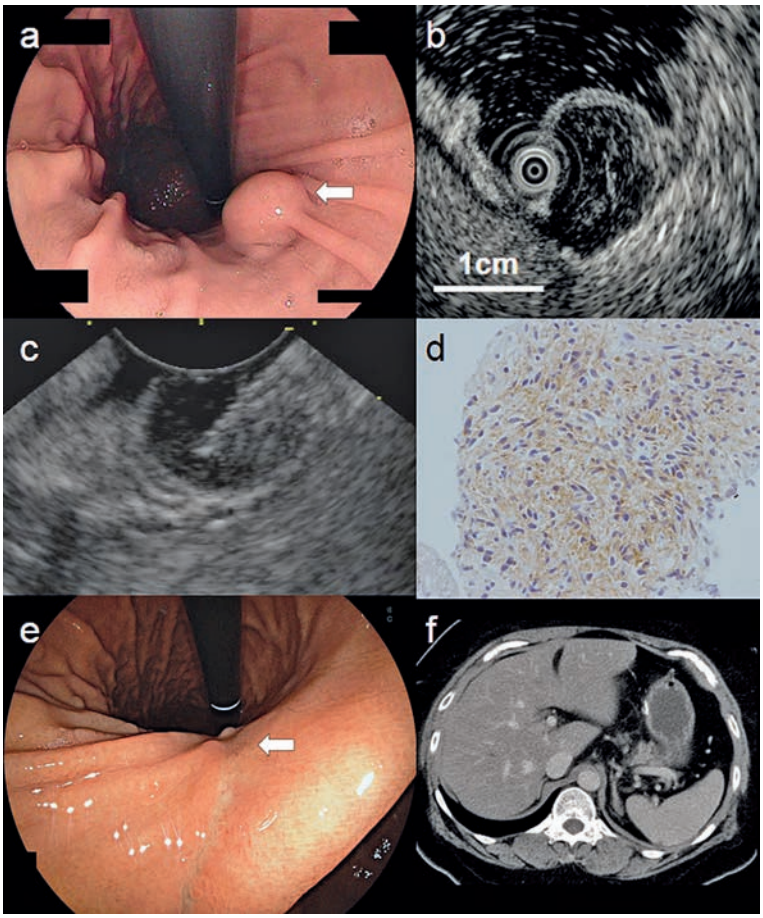

Fig. 2. Clinical course of small gastric GIST (surgically resected case). a. EGD shows a small SEL (arrow) in the lower body of the stomach. b. EUS reveals a 1.5 cm subepithelial hypoechoic solid tumor with continuity to proper muscle layer. c. Puncture of the small GIST under EUS guidance. d. The immunohistochemical finding of EUS-FNA specimen shows diffusely c-kit positive spindle tumor cells. e. Postoperative 6 years follow up EGD shows no recurrence (arrow). f. Postoperative 6 years follow up CT demonstrates no metastasis.

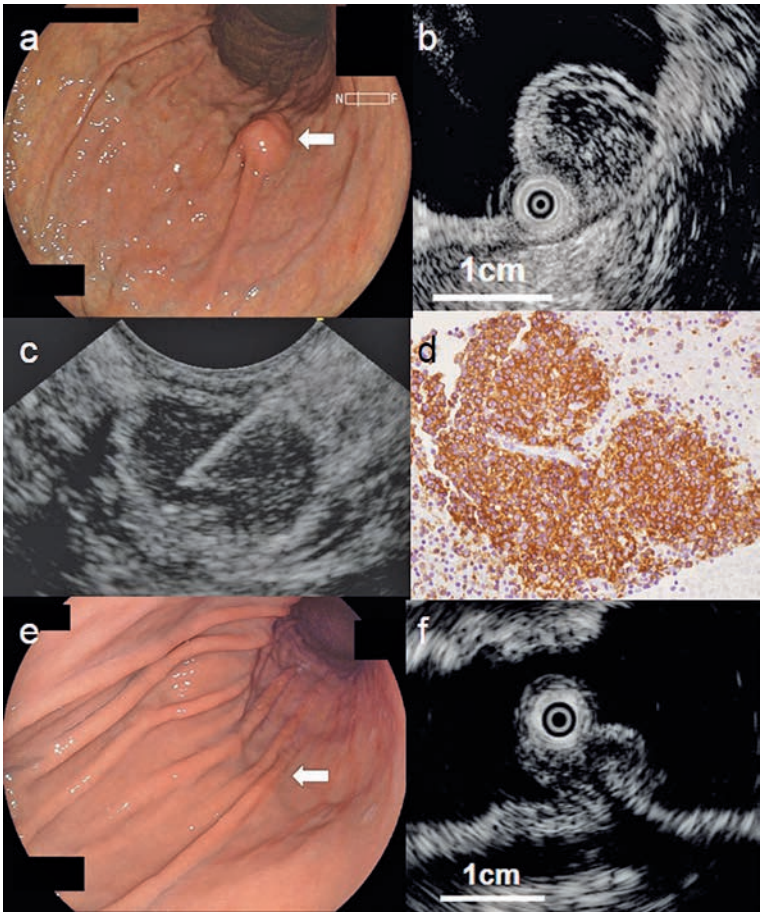

Fig. 3. Clinical course of small gastric malignant lymphoma (chemotherapy case). a. EGD shows small SEL (arrow) in the middle body of the stomach. b. EUS reveals a 1.5 cm subepithelial hypoechoic solid tumor within the submucosal layer. c. Puncture of the small SEL under EUS guidance. d. The immunohistochemical finding of EUS-FNA specimen reveals a CD20 positive diffuse large B cell lymphoma. e. Three years after chemotherapy plus radiation therapy EGD shows disappearance of the tumor (arrow). f. Three years after chemotherapy plus radiation therapy EUS demonstrating no subepithelial hypoechoic tumor.

Table III. Clinical impact on decision making for treatment plans of patients with gastric subepitelial lesions by EUS-FNA (N=90)

Number of patients	Size, cm	Location/layer/echogenicity	EUS-FNA diagnosis	Impact on decision making
8	mean 1.5	Fundus/4th/hypo	GIST	Plan for surgical local resection
3	mean 1.8	Cardia/4th/hypo	GIST	Plan for surgical local resection
24	mean 1.5	Body/4th/hypo	GIST	Plan for surgical local resection
6	mean 1.5	Angle/4th/hypo	GIST	Plan for surgical local resection
3	mean 1.4	Antrum/4th/hypo	GIST	Plan for surgical local resection
1	1.2	Body/4th/hypo	Glomus tumor	Plan for surgical local resection
1	1.5	Body/4th/hypo	Gastric cancer	Plan for partial gastrectomy with lymph node dissection
1	1.5	Body/3rd/hypo	Diffuse large B cell lymphoma	Plan for chemotherapy plus radiation
7	mean 1.4	Cardia/4th/hypo	Leiomyoma	Unnecessary resection avoided
7	mean 1.2	Body/4th/hypo	Leiomyoma	Unnecessary resection avoided
2	mean 1.5	Body/4th/hypo	Ectopic pancreas	Unnecessary resection avoided
1	1.5	Angle/4th/hypo	Ectopic pancreas	Unnecessary resection avoided
1	1.6	Angle/3rd/hypo	Ectopic pancreas	Unnecessary resection avoided
1	2	Body/4th/hypo	Neurinoma	Unnecessary resection avoided
2	mean 1.4	Fundus/4th/hypo	not conclusive*	None
2	mean 1.4	Cardia/4th/hypo	not conclusive*	None
12	mean 1.3	Body/4th/hypo	not conclusive*	None
1	1	Body/3rd/hypo	not conclusive*	None
5	mean 1.6	Angle/4th/hypo	not conclusive*	None
2	mean 1.2	Antrum/4th/hypo	not conclusive*	None

* Non-diagnostic cases due to inadequate specimens.

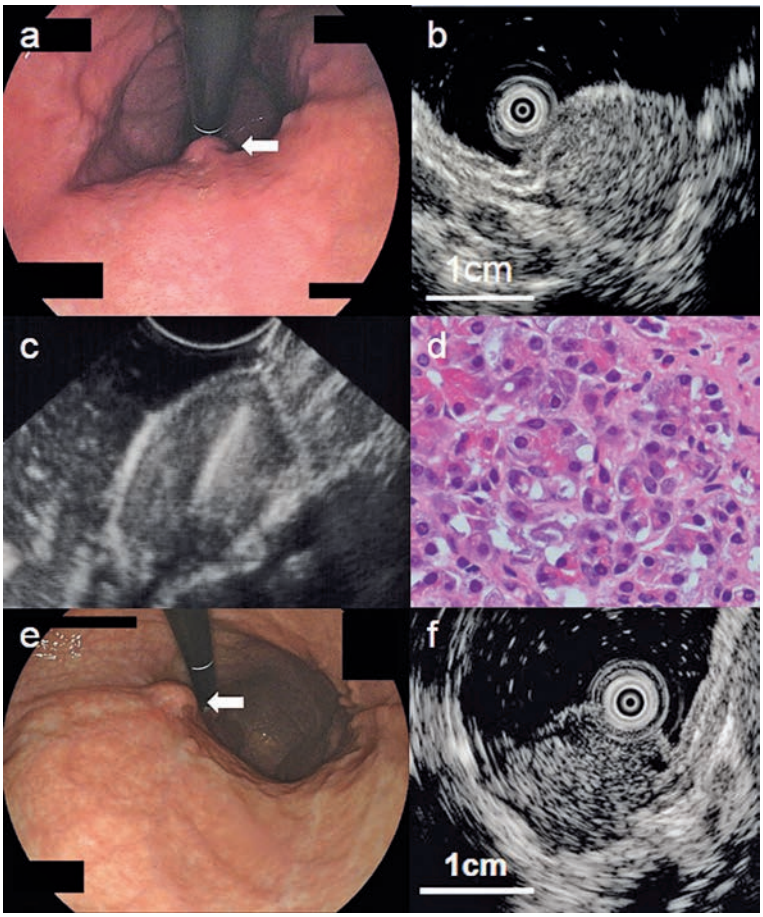

Fig. 4. Clinical course of small gastric ectopic pancreas (follow-up case). a. EGD shows small SEL (arrow) in the upper body of the stomach. b. EUS reveals 1.5 cm subepithelial hypoechoic solid tumor continuity to proper muscle layer. c. Puncture of the small SEL under EUS guidance. d. The EUS-FNA specimen revealing pancreatic acinar cells (H&E x200) e. Five years after EUS-FNA EGD showing no change of the tumor (arrow). f. EUS demonstrating no change in the tumor 5 years after EUS-FNA.

Figure 5 shows EUS-FNA diagnosis, the following management, and the clinical course. Local resection was performed in 42 out of 44 patients diagnosed as GIST by EUS-FNA (Fig. 2). Forty one out of 42 patients were diagnosed as GIST and the remaining patient was diagnosed as leiomyoma by postoperative immunohistochemical analysis. The 2 patients refused surgery. Appropriate management, including no need for treatment (Fig. 4), surgery, and chemotherapy (Fig. 3) was performed in all 22 patients diagnosed as non-GIST. After surgery, there was no recurrence in 47 malignant SELs. Appropriate management, including surgery, chemotherapy, and follow-up were performed in 65 out of 66 (98%) SELs diagnosed by definitive EUS-FNA (Table III). It was impossible to diagnose the remaining 24 patients because of insufficient material, but 22 patients were carefully followed up and two patients (patient's wish) received local resection (postoperative diagnosis for both was GIST). There was no tumor growth or metastasis in any of the 24 undiagnosed cases in the follow up study.

DISCUSSION

Gastrointestinal stromal tumors are the most commonly identified malignant SELs in the stomach. Their malignancy potential varies. Large GISTs and GISTs with a high mitosis count have a high recurrence rate, with metastases typically in the liver and abdominal cavity [1-7]. Miettinen et al reported that in small GISTs (< 2 cm) no metastasis occurred in 1765 cases, broken down into prognostic categories, with follow-up information [5]. In other words, it means that complete surgical resection of a GIST smaller than 2 cm has the potential to produce a 100% permanent cure without adjuvant therapy. However, not all gastric SELs are GISTs. Generally, most small gastric SELs were considered benign without sufficient evidence [2, 8, 16]. Therefore, the management of incidentally encountered gastric SELs smaller than 2cm remains controversial. Most gastric SELs smaller than 2 cm may be followed up endoscopically until they have grown or become symptomatic and the frequency of follow-up remains uncertain [16]. In this study, we found that malignant SELs have a 71% share of hypoechoic solid SELs measuring 1 to 2 cm, and that GISTs have a 67% share of them. Furthermore, postoperative risk assessment (modified-Fletcher's classification) of GISTs classified 23% as a moderate risk and 77% as a very low risk. Therefore, to perform early management, it is also desirable to pay special attention to small SEL groups as well as to the large ones.

In every kind of tumor including early gastric cancer, early diagnosis and early treatment is the best way to improve the quality of life of the patient. In early gastric cancer, histological confirmation is easily obtained using conventional endoscopic biopsy. However, it is difficult to obtain histologic diagnosis in the gastric SEL [7, 11, 16, 17]. Gastric SELs are frequently detected by EGD. However, the mucosal surface of SEL is usually normal, and the biopsy examination by conventional forceps at EGD is frequently negative. Deep biopsy procedures such as the unroofing technique [18, 19] or mucosal incision assisted biopsy [20] were attempted to obtain sufficient tissue sample, and showed a good diagnostic rate (85-100%) with sufficient tissue volume. Their shortcomings are as follows: 1) difficulty in obtaining a tissue sample of extraluminal growth pattern SEL, and 2) invasive and complicated procedures.

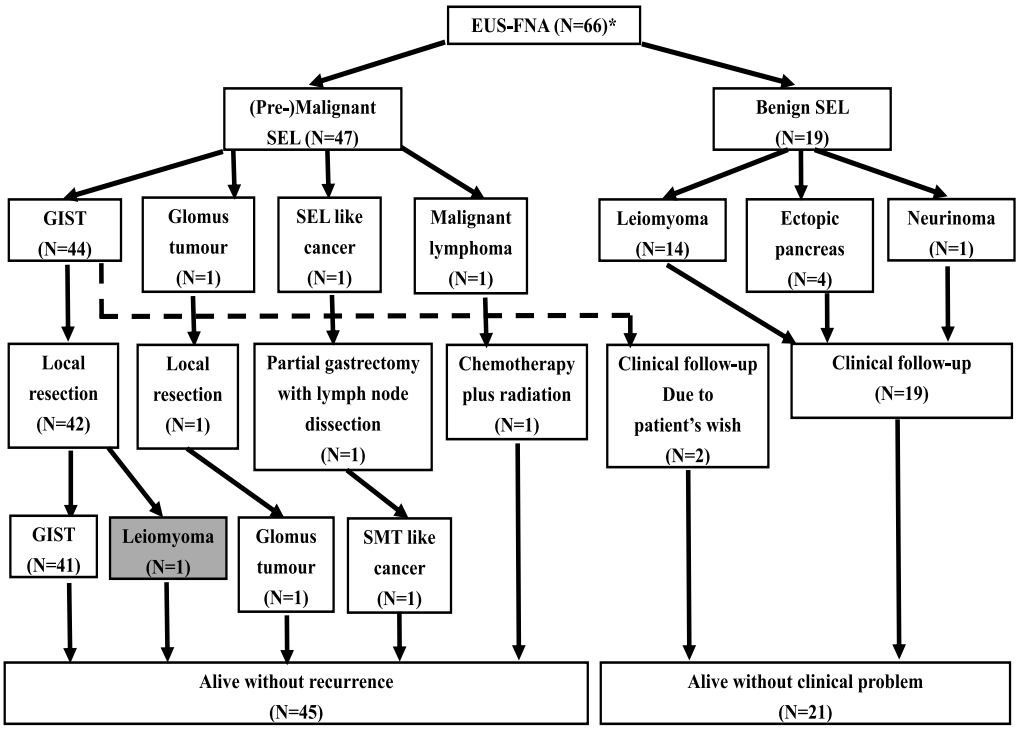

Fig. 5. EUS-FNA diagnosis and clinical course of gastric subepithelial lesions (SEL) smaller than 2cm. A grey square is incorrect diagnosis by EUS-FNA
*Excluding 24 non-diagnostic cases due to inadequate specimens.

Recently, Kannengiesser et al [21] reported that contrast-enhanced harmonic EUS can discriminate GIST from benign lesions with high accuracy. However, diagnosis on the basis of EUS imaging is presumptive and cannot replace a histological diagnosis of SEL. In the diagnostic process of GIST, immunohistochemical analysis of tissue sample such as c-kit is vital for confirmation of this disease. Therefore, at present EUS-FNA is a promising technique to obtain tissue samples from SELs with minimal risks [7, 11-14]. In this study, the diagnostic rate (first session only) was 62% in gastric SELs measuring 1 to 2 cm, and the diagnostic rate including the sessions completed after previous failure was improved to 73%. There were no complications. Although EUS-FNA for gastric SELs smaller than 2 cm was safe, the diagnostic rate (adequate sampling rate) was relatively low. To obtain more diagnostic tissue samples by EUS-FNA, various needles (25, 22, and19G needle sizes, trucut, procore, etc) have been developed. The reported diagnostic rate of EUS-FNA using such needles for GI tract SELs ranged from 52-93% [11-14, 22-26]. Larghi et al [26] reported a good diagnostic rate (81.5%) of EUS-FNA using 19G needle and forward viewing linear echoendoscope for small SELs (less than 2 cm) in 27 patients. However, differences in the EUS guided tissue sampling technique using various types of needles for tissue acquisition are still controversial. Further technical improvement and refinement of devices including needle and echoendoscope is needed to solve such problems.

In our 44 surgically resected cases (lesions smaller than 2 cm), the accuracy for EUS-FNA diagnosis using immunohistochemical analysis was 98%. The reported accuracy of preoperative diagnosis of EUS-FNA using immunohistochemical analysis for surgically resected GIST cases ranged from 85.2 to 97% without major complications [11-14]. The diagnostic accuracy and safety of EUS-FNA using immunohistochemical analysis is excellent irrespective of tumor size. At present, EUS-FNA is the most accurate and safe preoperative histological test for small gastric SELs including GIST. Polkowski and Bergman [27] pointed out that most previous retrospective studies tended to overestimate the yield of EUS-FNA. In fact, non-surgically resected cases (benign lesion diagnosed by EUS-FNA such as leiomyoma or neurinoma, etc) were judged as correct diagnosis cases by follow-up study using imaging tests (no advance of the lesion, i.e. size up or metastasis, etc). Therefore, there is a risk of malignant lesions such as GISTs to be misdiagnosed as benign lesions (leiomyoma or neurinoma, etc.), which leads to overestimating the diagnostic yield. However, diagnostic yield of EUS-FNA for surgically resected cases is accurate, because comparison between immunohistochemical analysis results of EUS-FNA specimen and that of surgically resected specimen is available.

In our institute, we previously designed an algorithm for early diagnosis of SELs using EUS-FNA, and have performed decision making according to this algorithm in the daily clinical setting (Fig. 1) [7]. In our algorithm, the indication for EUS-FNA is subepithelial hypoechoic solid tumor larger than 1 cm. The larger than 1 cm limit was determined by technical issues. Using the current EUS-FNA system including needles, it is difficult to puncture an intramural solid tumor smaller than 1 cm, and there is also a risk of seeding due to needle penetration of the small tumor. Surgical planning, including the type of surgery to be conducted, varies dramatically in relation to the histological diagnosis [7, 11-14]. Accurate preoperative histological proof of gastric SELs using EUS-FNA facilitates the surgeon's decision-making for early local resection. For example, a patient with localized GIST can be cured with a wedge resection, or if the GIST is extensive, he can receive imatinib; however, a patient with SEL-like gastric cancer would undergo gastrectomy with lymph-node dissection. A patient with benign SEL could avoid surgery completely because of the confirmation of histological benignancy such as ectopic pancreas. In this study, appropriate decision making using EUS-FNA was made in 98% of patients. EUS-FNA thus evidently has a significant positive impact on the clinical management of patients by providing a definitive histological diagnosis [11]. From the point of view of curability of gastric GIST, 2 cm is a promising line for obtaining a permanent cure using local resection [5]. We previously reported a postoperative hepatic metastasis case with 2.5 cm gastric GIST [7]. This patient died 6 years after surgery, even after using imatinib. In our gastric GIST series smaller than 2 cm, pre-therapeutic imaging modalities revealed no metastasis. Furthermore, there was no post-operative local or distant recurrence in the follow-up study. Therefore, we believe that early diagnosis of 1 to 2 cm gastric SEL using EUS-FNA is an encouraging approach to improving the management of patients with gastric GIST.

However, the majority of GISTs < 2 cm simply do not evolve to metastatic disease at follow-up [16]. A recent update of the National Comprehensive Cancer Network Guidelines on the management of GISTs recommends that incidentally encountered small asymptomatic gastric GISTs (less than 2 cm) with no high-risk EUS features can be managed conservatively with endoscopic surveillance at 6 to 12 months intervals [2, 24]. On the contrary, accurate differential diagnosis between benign and malignant GIST is considered to be very difficult both by imaging tests and by pathological examinations. Thus, European (ESMO) and Japanese GIST guidelines recommend surgical resection when SEL is diagnosed as an immunohistologically confirmed GIST even if < 2 cm [8-10]. At the moment, the decision to indicate surgery or watch and wait are both reasonable after sufficient discussion with the patient. Further extensive clinical studies are needed to clarify this point.

CONCLUSION

EUS-FNA with immunohistochemical analysis is a safe and accurate histological test in the pre-therapeutic diagnosis of gastric SELs smaller than 2 cm. EUS-FNA for gastric SELs smaller than 2 cm is a promising option that enables us to perform early diagnosis and early treatment of this condition.

Conflicts of interest. None.

Authors' contribution: A.K. performed EUS-FNA and designed this study. O.M. performed histological analysis. K.T. performed the surgical treatment. K.H. performed statistical analysis. A.K., M.Y., K.M., G.J., and N.K. wrote the paper. All the authors approved the final manuscript.

REFERENCES

1. Hirota S, Isozaki K, Moriyama Y, et al. Gain-of-function mutations of c-kit in human gastrointestinal stromal tumors. Science 1998;279:577-580.
2. Von Mehren M, Randall RL, Benjamin RS, et al. Soft tissue sarcoma, version 2. 2014. J Natl Compr Cancer Netw 2014;12:473-483.
3. Blay JY, Bonvalot S, Casali P, et al; GIST consensus meeting panelists. Consensus meeting for the management of gastrointestinal stromal tumors. Report of the GIST consensus conference of 20-21 March 2004, under the auspices of ESMO. Ann Oncol 2005;16:566-578.
4. Reichardt P, Blay JY, Von Mehren M. Towards global consensus in the treatment of gastrointestinal stromal tumor. Expert Rev Anticancer Ther 2010;10:221-232.
5. Miettinen M, Sobin LH, Lasota J. Gastrointestinal stromal tumors of the stomach: a clinicopathologic, immunohistochemical, and molecular genetic study of 1765 cases with long-term follow-up. Am J Surg Pathol 2005;29:52-68.
6. Casali PG, Jost L, Reichardt P, Schlemmer M, Blay JY; ESMO Guidelines Working Group. Gastrointestinal stromal tumors: ESMO clinical recommendations for diagnosis, treatment and follow-up. Ann Oncol 2009;20 (Suppl 4):64-67.
7. Akahoshi K, Oya M. Gastrointestinal stromal tumor of the stomach: How to manage? World J Gastrointest Endosc 2010;2;271-277.
8. Nishida T, Kawai N, Yamaguchi S, Nishida Y. Submucosal tumors: Comprehensive guide for the diagnosis and therapy of gastrointestinal Submucosal tumors. Dig Endosc 2013;25:479-489.
9. Nishida T, Hirota S, Yanagisawa A, et al. Clinical practice guideline for gastrointestinal stromal tumor (GIST) in Japan: English version. Int J Clin Oncol 2008;13:416–430.
10. ESMO/European Sarcoma Network Working Group. Gastrointestinal stromal tumors: ESMO Clinical Practice Guidelines for diagnosis, treatment and follow-up. Ann Oncol 2012;23 (Suppl 7):vii49–vii55.
11. Akahoshi K, Sumida Y, Matsui N, et al. Preoperative diagnosis of gastrointestinal stromal tumor by endoscopic ultrasound-guided fine needle aspiration. World J Gastroenterol 2007;14:2077-2082.
12. Ando N, Goto H, Niwa Y, et al. The diagnosis of GI stromal tumors with EUS-guided fine needle aspiration with immunohistochemical diagnosis. Gastrointest Endosc 2002;55:37-43.
13. Okubo K, Yamao K, Nakamura T, et al. Endoscopic ultrasound-guided fine-needle aspiration biopsy for the diagnosis of gastrointestinal stromal tumors in the stomach. J Gastroenterol 2004;39:747-753.
14. Chatzipantelis P, Salla C, Karoumpalis I, et al. Endoscopic ultrasound-guided fine needle aspiration biopsy in the diagnosis of gastrointestinal stromal tumors of the stomach. A study of 17 cases. J Gastrointest Liver Dis 2008;17:15-20.
15. Joensuu H, Vehtari A, Riihimäki J, et al. Risk of recurrence of gastrointestinal stromal tumour after surgery: an analysis of pooled population-based cohorts. Lancet Oncol 2012;13:265-274.
16. Sawaki A, Mizuno N, Takahashi K, 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;18:40-44.
17. Rösch T, Kapfer B, Will U, et al; German EUS Club. Endoscopic ultrasonography. Accuracy of endoscopic ultrasonography in upper gastrointestinal submucosal lesions: a prospective multicenter study. Scand J Gastroenterol 2002;37:856-862.
18. Lee CK, Chung IK, Lee SH, et al. Endoscopic partial resection with the unroofing technique for reliable tissue diagnosis of upper GI subepithelial tumors originating from the muscularis propria on EUS (with video). Gastrointest Endosc 2010;71:188-194.
19. Binmoeller KF, Shah JN, Bhat YM, Kane SD. Suck-ligate-unroof-biopsy by using a detachable 20-mm loop for the diagnosis and therapy of small subepithelial tumors (with video). Gastrointest Endosc 2014;79:750-755.
20. Ihara E, Matsuzaka H, Honda K, et al. Mucosal-incision assisted biopsy for suspected gastric gastrointestinal stromal tumors. World J Gastrointest Endosc 2013;5:191-196.
21. Kannengiesser K, Mahlke R, Petersen F, et al. Contrast-enhanced harmonic endoscopic ultrasound is able to discriminate benign submucosal lesions from gastrointestinal stromal tumors. Scand J Gastroenterol 2012;47:1515-1520.
22. Polkowski M, Gerke W, Jarosz D, et al. Diagnostic yield and safety of endoscopic ultrasound-guided trucut biopsy in patients with gastric submucosal tumors: a prospective study. Endoscopy 2009;41:329-334.
23. Eckardt AJ, Adler A, Gomes EM, et al. Endosonographic large-bore biopsy of gastric subepithelial tumors: a prospective multicenter study. Eur J Gastroenterol Hepatol 2012;24:1135-1144.
24. Sepe PS, Moparty B, Pitman MB, Saltzman JR, Brugge WR. EUS-guided FNA for the diagnosis of GI stromal cell tumors; sensivity and cytologic yield. Gastrointest Endosc 2009;70:254-261.
25. Iglesias-Garcia J, Poley JW, Larghi A, et al. Feasibility and yield of a new EUS histology needle: results from a multicenter, pooled, cohort study. Gastrointest Endosc 2011;73:1189-1196.
26. Larghi A, Fuccio L, Chiarello G, et al. Fine-needle tissue acquisition from subepithelial lesions using a forward-viewing linear echoendoscope. Endoscopy 2014;46:39-45.
27. Polkowski M, Bergman JJ. Endoscopic ultrasonography-guided biopsy for submucosal tumors: needless needling? Endoscopy 2010;42:324-326.