Endoscopic ultrasound-guided forceps biopsy from upper gastrointestinal subepithelial lesions using a forward-viewing echoendoscope

Authors Ippei Matsuzaki[1], Ryoji Miyahara[1], Yoshiki Hirooka[2], Kohei Funasaka[2], Takeshi Yamamura[2], Eizaburo Ohno[1], Masanao Nakamura[1], Hiroki Kawashima[1], Osamu Watanabe[1], Makoto Kobayashi[3], Yoshie Shimoyama[4], Shigeo Nakamura[4], Hidemi Goto[1]

Institutions Institutions are listed at the end of article.

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Corresponding author
Ryoji Miyahara, MD PhD
Department of Gastroenterology and Hepatology
Nagoya University Graduate School of Medicine
65
Tsurumai-cho
Showa-ku
Nagoya
466-8550
Japan
Fax: +81-52-7442180
myhr@med.nagoya-u.ac.jp

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Background and study aims: Endoscopic tissue acquisition techniques using needle-knife and biopsy forceps allow abundant tissue acquisition from upper gastrointestinal subepithelial lesions; however, these techniques cannot capture real-time intratumor information. The aim of this study was to evaluate the feasibility of endoscopic ultrasound-guided forceps biopsy (EUS-FB) from upper gastrointestinal subepithelial lesions using a forward-viewing echoendoscope.

Patients and methods: This study was a prospective case series. After mucosal cuts, several specimens were taken using a hot biopsy forceps under real-time EUS visualization. The incision was closed using hemoclips. Diagnostic yield, rate of diagnosable samples obtained under EUS visualization, procedure time, and adverse events were assessed.

Results: Ten patients (median lesion size 16 mm, range 15 – 44 mm) underwent EUS-FB. The overall rate of histological diagnosis by EUS-FB was 100 % (10/10). The rate of diagnosable samples among all cases was 97.6 % (41/42). The median procedure times for EUS-FB and complete closure were 28.5 and 4.5 minutes, respectively. No adverse events occurred.

Conclusions: This newly developed EUS-FB is feasible and allowed forceps biopsy from upper gastrointestinal subepithelial lesions.
Study registration: UMIN000015364

Introduction

Endoscopic ultrasound-guided fine-needle aspiration (EUS-FNA) has become accepted as an accurate technique for tissue acquisition from upper gastrointestinal subepithelial lesions [1 – 3]. We have also reported the usefulness of a newly developed forward-viewing echoendoscope with regard to sample area [4]. On the other hand, endoscopic tissue acquisition techniques using snare, needle-knife and biopsy forceps allow abundant tissue acquisition; however, these techniques cannot capture real-time intratumor information [5 – 7].

We hypothesized that a forceps biopsy using a forward-viewing echoendoscope could be a useful new endoscopic tissue acquisition technique under EUS visualization. The aim of this study was to evaluate the feasibility of EUS-guided forceps biopsy (EUS-FB) from upper gastrointestinal subepithelial lesions.

Materials and methods

This prospective trial was conducted at the Nagoya University Hospital in Japan. Between January 2015 and April 2015, all 10 patients with upper gastrointestinal subepithelial lesions were examined with a radial scanner (GF-UM2000; Olympus Medical Systems Corp., Tokyo, Japan) before EUS-FB.

The inclusion criterion for the study was the presence of an upper gastrointestinal subepithelial lesion. Exclusion criteria were as follows: age > 90 years; tumor size < 1.5 cm; diagnosis of lipoma or cyst by EUS; and lack of patient's consent. This study was approved by the institutional review board of Nagoya University (IRB No. 2014-0300), and written informed consent was obtained from all participating patients. This study was registered in the University Hospital Medical Information Network Clinical Trials Registry (UMIN-CTR) as study number: UMIN0000015364.

Echoendoscope

All EUS-FB procedures were performed using a forward-viewing echoendoscope (TGF-UC260J; Olympus) by an experienced endoscopist (I. M.)

Fig. 1 Forward-viewing echoendoscope with a hot biopsy forceps.

who had performed both endoscopic submucosal dissection (ESD) and EUS on more than 200 upper gastrointestinal lesions. This echoendoscope provides a forward endoscopic view, allows device deployment along the axis of the scope, and has a larger tip angulation compared with the oblique-viewing echoendoscope.

EUS-FB procedure

All patients were placed in the left lateral position under conscious or deep sedation with intravenous anesthesia using midazolam and pentazocine.

First, the lesion was observed and color flow mapping was applied to avoid thick vessels using a forward-viewing echoendoscope and an ultrasound processor with color Doppler function (EU-ME2; Olympus). Second, a mucosal cut was made by hot biopsy forceps (FD-210U; Olympus) with a PulseCut Fast mode setting of 40 W using an electrosurgical unit (ESG-100; Olympus) after injection of saline into the submucosa (**Fig. 1**). After mucosal and submucosal cuts, several specimens were taken within the lesion using this forceps without coagulation under real-time EUS visualization. The forceps biopsies were repeated until two whitish tissues were obtained macroscopically, with a maximum of six biopsies. On-site pathologists were not present to determine the adequacy of specimens in this study. Finally, the incision site was closed using hemoclips (HX-610-090L; Olympus) to achieve hemostasis and to avoid exposure of tumor. A broad-spectrum antibiotic and a proton pump inhibitor were administered for 5 days. Patients were hospitalized for 3 days.

Histological assessment

The collected specimens were immediately placed in formalin and embedded in paraffin for histological examination. The pathological diagnosis was made on the basis of hematoxylin-eosin staining and immunopathological stains by expert pathologists (Y.S., S.N).

Outcome measures

The primary end point was the diagnostic yield of the EUS-FB. The secondary end points were the number of mucosal cuts before biopsy of the lesion, the rates of diagnosable samples obtained under EUS visualization, and the procedure times for both EUS-FB and complete closure. Adverse events were defined as any deviation from the clinical course after EUS-FB. All patients were contacted within 1 month of the procedure to assess whether there had been any late adverse events.

Statistical analysis

Continuous variables such as patients' age and tumor size were reported as median and range. Comparisons of proportions such as diagnostic yield, rates of diagnosable samples, and adverse events were expressed as frequencies and proportions.

Results

During this study period, 10 patients (7 males and 3 females; median age 63 years, range 31 – 77 years) underwent EUS-FB. Tumor locations were esophagus in two cases, stomach in five cases, and duodenum in three cases. The median tumor size was 16 mm (range 15 – 44 mm). Layers of origin were the submucosa in two cases and the muscularis propria in eight cases. Patterns of growth were intraluminal in seven cases, extraluminal in one case, and mixed in two cases (**Table 1**). The overall rate of histological diagnosis of EUS-FB was 100 % (10/10). The median number of mucosal cut biopsies was 3.5 (range 1 – 11) and the rate of diagnosable samples among the 10 cases was 97.6 % (41/42). Abundant tissue fragments without cautery artifact and without blood contamination were obtained from all cases. The histologic results of EUS-FB were gastrointestinal stromal tumor (GIST), mitotic index < 5/50 (n = 1) (**Fig. 2**) (**Video 1**), leiomyoma (n = 4), schwannoma (n = 1), malignant lymphoma (n = 1), neuroendocrine tumor, Ki-67 3 – 5 % (n = 1), ectopic pancreas (n = 1), and Brunner's gland hyperplasia (n = 1). Median procedure times

Table 1 Characteristics of patients with subepithelial lesions.

Case	Age, years/sex	Tumor location	Tumor size, mm	Wall layer of origin on EUS	Pattern of growth on EUS
1	33/M	Duodenum, bulb, PW	16	Muscularis propria	Intraluminal
2	77/F	Stomach, middle body, LC	21	Muscularis propria	Extraluminal
3	66/M	Duodenum, bulb, AW	15	Submucosa	Intraluminal
4	31/M	Stomach, upper body, GC	44	Muscularis propria	Intraluminal
5	72/M	Stomach, upper body, LC	15	Muscularis propria	Intraluminal
6	75/M	Duodenum, bulb, PW	15	Submucosa	Intraluminal
7	71/M	Stomach, middle body, GC	16	Muscularis propria	Mixed
8	35/M	Esophagus, middle, AW	31	Muscularis propria	Mixed
9	34/F	Stomach, lower body, GC	20	Muscularis propria	Intraluminal
10	60/F	Esophagus, cervical, AW	15	Muscularis propria	Intraluminal

PW, posterior wall; LC, lesser curvature; AW, anterior wall; GC, greater curvature.

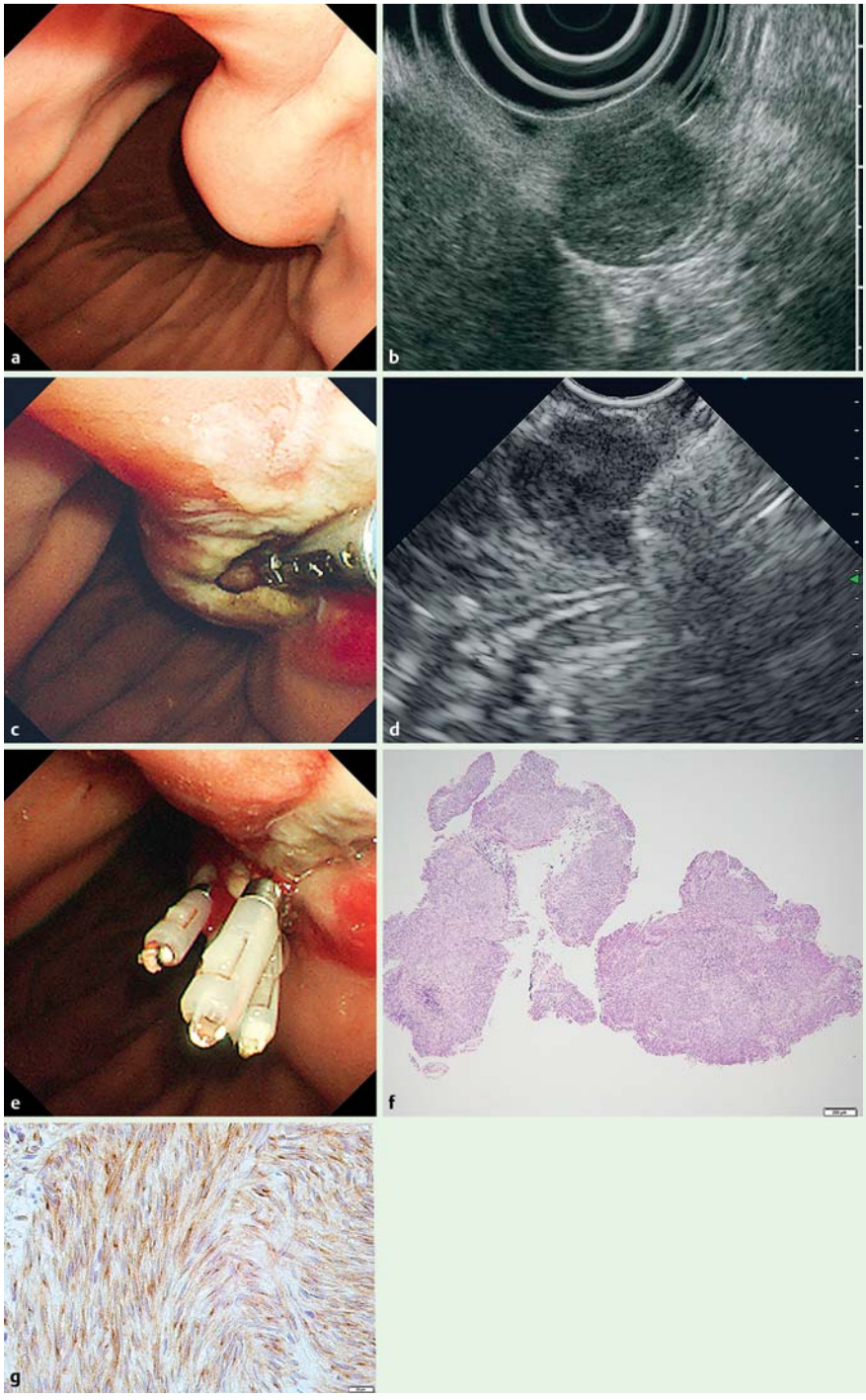


Fig. 2 Representative case of a gastrointestinal stromal tumor (case 5) diagnosed using EUS-FB. **a** Endoscopy showing subepithelial lesion in the upper body of the stomach. **b** EUS image with radial scanner. The hypoechoic tumor was 15 mm and a heterogeneous echo pattern was located in the muscularis propria. **c** Endoscopic view of the EUS-FB shows the forceps entering the subepithelial lesion after mucosal cut. **d** EUS image showing the open forceps within the subepithelial lesion. **e** Incision closed using hemoclips. **f** Abundant tissue fragments without contamination showing a spindle-cell neoplasm (hematoxylin and eosin stain; magnification × 40). **g** Tumor is diffusely positive for c-kit (immunohistochemical stain for c-kit; magnification × 400).

for EUS-FB and complete closure were 28.5 minutes (range 9 – 46 minutes) and 4.5 minutes (range 3 – 32 minutes), respectively (**Table 2**). No adverse events occurred.

Discussion

EUS-FBs using the forward-viewing echoendoscope for upper gastrointestinal subepithelial lesions were successfully performed without adverse events. Histopathological diagnoses including immunopathological stains and mitotic index assessments were obtained in all cases.

The prognostication of GISTs is based on the mitotic index, and gastrointestinal subepithelial lesions less than 2 cm have a low risk of malignant behavior [8,9]. Theoretically, early diagnosis and early treatment are promising means of obtaining a permanent cure. All six subepithelial lesions less than 2 cm were diagnosed in this study. A small tumor size was thought to be one of the factors related to a nondiagnostic result for EUS-FNA [2,4]. Therefore, the EUS-FB technique is thought to be suitable for all gastrointestinal subepithelial lesions including small tumor sizes. The diagnostic yield from EUS-FNA ranged from 83 % to 93 % [1 – 3]. Recently, we reported the usefulness of EUS-FNA using a forward-viewing echoendoscope with regard to sample area [4]. However, the mitotic and proliferative assessments using FNA are thought to be difficult. On the other hand, unroofing and cutting biopsy techniques allowed abundant tissue acquisition safely (**Table 3**) [5 – 7]; however, these reported techniques could not

Table 2 Outcome of EUS-guided forceps biopsy.

Case	Number of mucosal cuts before biopsy of lesion	Number of samples within tumor*	Number of diagnosable samples by pathology	Procedure time for EUS-FB, min	Procedure time for complete closure, min	EUS-FB diagnosis
1	3	5	5	44	32	Heterotopic pancreas
2	5	6	6	34	4	Malignant lymphoma
3	1	2	2	28	4	Brunner's gland hyperplasia
4	1	5	5	29	4	Leiomyoma
5	7	2	2	19	5	GIST, mitotic index < 5/50 HPF
6	1	4	3	9	14	Neuroendocrine tumor, Ki-67 3 – 5 %
7	9	3	3	31	3	Leiomyoma
8	4	6	6	19	9	Leiomyoma
9	11	5	5	46	3	Schwannoma
10	1	4	4	13	11	Leiomyoma

GIST, gastrointestinal stromal tumor; HPF, high power field.
* Tissue samples were taken under EUS visualization.

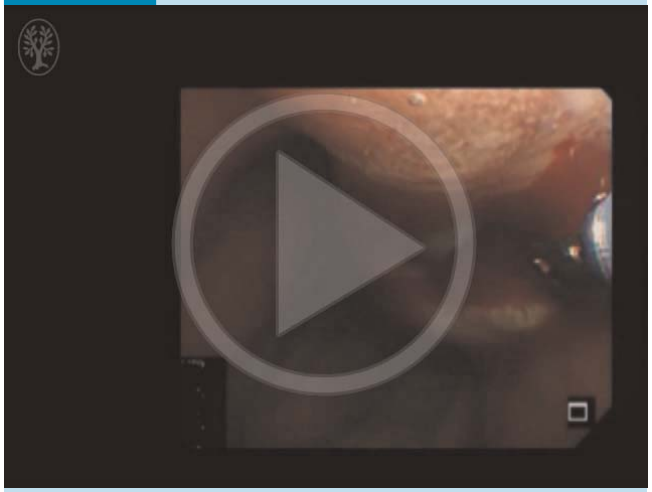
Table 3 Comparison of endoscopic tissue acquisition techniques from subepithelial lesions apart from EUS-guided FNA.

Author, year	Technique	Devices	No. of patients	Tumor size, median (range), mm	Diagnostic yield	Rates of mitotic index evaluation	Adverse events
Lee et al. [5], 2010	Unroofing technique	Electrosurgical snare	16	16 (11 – 25)	93.8 % (15/16)	100 % (6/6)	0 %
de la Serna-Higuera et al. [6], 2011	EUS-guided single-incision; needle-knife biopsy	Needle-knife, biopsy forceps	14	31 (12 – 64)	92.9 % (13/14)	62.5 % (5/8)	0 %
Kobara et al. [7], 2013	Bloc biopsy	Needle-knife	8	20 (8 – 40)	100 % (8/8)	100 % (6/6)	0 %
Matsuzaki et al., this study	EUS-guided forceps biopsy	Hot biopsy forceps	10	16 (15 – 44)	100 % (10/10)	100 % (1/1)	0 %

capture real-time intratumor information using an echoendoscope.

Recently, EUS-guided through-the-needle forceps biopsy was reported [10]. This technique allows tissue acquisition within the lesion using forceps under EUS guidance. However, this technique required 19 gauge needle puncture and miniforceps. Furthermore, the feasibility with regard to diagnosis of subepithelial lesions was not clarified. In this study, forward endoscopic view and device deployment along the axis of the scope could allow forceps biopsy from subepithelial lesions under real-time EUS guidance using the forward-viewing echoendoscope. The real-time intratumor information and the depth of forceps within the tumor could be confirmed using this echoendoscope. On the other hand, care should be taken not to burn the distal end of the echoendoscope when using hot biopsy forceps. This technique cannot be easily and safely performed using an oblique-viewing echoendoscope.

Video 1



EUS-guided forceps biopsy from upper gastrointestinal subepithelial lesion. Online content including video sequences viewable at: http://dx.doi.org/10.1055/s-0042-106204

In this study, adequate tissues were obtained using hot biopsy forceps in all cases including eight subepithelial lesions originating from muscularis propria. Furthermore, the rate of diagnosable samples was 97.6 % (41/42) in this study. The diagnostic accuracy of EUS-guided forceps biopsy may be higher than for conventional endoscopic tissue acquisition techniques including EUS-FNA; however, in some cases, several mucosal cutting biopsies were performed to insert the forceps into tumors because of slip. The improved prehensile hot biopsy forceps or needle-knife may be suitable for this technique.

Procedural blood oozing was common and was treated using unroofing and cutting biopsy techniques [5 – 7]. In our study, electrosurgical current using hot biopsy forceps and complete closure of the incision sites could prevent this adverse event. Furthermore, no infectious adverse events occurred. This technique may not require antibiotics and hospitalization.

Theoretically, this EUS-FB technique is suitable for all subepithelial lesions. This may be especially advantageous for small lesions less than 2 cm and extraluminal growth lesions.

In conclusion, this study clearly demonstrated the feasibility of this newly developed EUS-FB using a forward-viewing echoendoscope for upper gastrointestinal subepithelial lesions. Stud-

ies with a larger sample size are needed to further evaluate this procedure.

Competing interests: None

Institutions
[1] Department of Gastroenterology and Hepatology, Nagoya University Graduate School of Medicine, Nagoya, Japan
[2] Department of Endoscopy, Nagoya University Hospital, Nagoya, Japan
[3] Department of Gastroenterology, Yokkaichi Municipal Hospital, Mie, Japan
[4] Department of Pathology and Clinical Laboratories, Nagoya University Hospital, Nagoya, Japan

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