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BRIEF REPORT

Boring biopsy with rapid on-site evaluation for gastric gastrointestinal stromal tumor: A pilot study

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Introduction

A gastrointestinal stromal tumor (GIST) is a mesenchymal tumor with potential for malignancy. Given that the endoscopic findings of gastric GIST are quite similar to those of benign mesenchymal tumors, for example, schwannoma and leiomyoma, histopathological examination using immunohistochemistry is required to distinguish them.[1] Currently, endoscopic ultrasonography-guided fine-needle aspiration (EUS-FNA) is the standard sampling method for GIST[1–3]; however, it requires specific devices and expertise. Submucosal tunneling biopsy (also known as mucosal incision-assisted biopsy) is a sampling method option.[4–6] Nonetheless, it is time consuming.[4] Boring biopsy is a simple sampling method that obtains the tissue after digging into the submucosa,[7,8] and rapid on-site evaluation (ROSE) is used to confirm the specimen's adequacy in EUS-FNA.[9] This study aimed to assess the feasibility of boring biopsy with ROSE for gastric GIST.

Methods

Patients. Among 16 consecutive patients who underwent boring biopsy in combination with ROSE for gastric subepithelial lesions between July 2020 and February 2021, 12 patients with 12 lesions, which were connected with the fourth layer (muscularis propria) identified on EUS, were retrospectively reviewed. The patients underwent boring biopsy after EUS for tissue sampling of gastric subepithelial lesions when the lesions were identified with a conventional endoscope and measured ≥15 mm by EUS, regardless of the growth morphology. Conventional boring biopsy was performed until October 2020,

and hot boring biopsy was performed thereafter. The study protocol was approved by the Institutional Review Board of Osaka International Cancer Institute on 25 June 2021 (No. 21056).

Endoscopic procedure. Conventional boring biopsy was performed using a biopsy forceps (Radial Jaw 4 Standard Capacity, Boston Scientific, Marlborough, MA, USA). The first two mucosal specimens were discarded, and the next 2–5 specimens were taken for the routine histopathological examination. ROSE was then performed for the next specimen. If ROSE was negative, the same procedure was repeated up to two times. Finally, two specimens were taken for routine histopathological examination after positive results of ROSE.

Hot boring biopsy was performed using a coagulation forceps (Radial Jaw 4 Hot Biopsy Forceps, Boston Scientific). The first two mucosal specimens were discarded, and then submucosal tissues were removed by electrical cutting. ROSE was performed for the next obtained specimen. If ROSE was negative, ROSE was repeated up to two times after removing the submucosal tissues additionally. Finally, two specimens were taken for routine histopathological examination after positive ROSE results (Fig. 1).

All procedures were performed under moderate sedation using midazolam and pethidine in the outpatient setting. An endoscope with a soft transparent hood was used for boring biopsy. An electrosurgical unit (VIO300D; Erbe, Tübingen, Germany) was used for electrical cutting and coagulation during hot boring biopsy. Endoclips (SureClip; Micro-Tech Co., Ltd., Nanjing, China) were used to close the wound after completion of the biopsy.

ROSE. ROSE was performed by a cytotechnologist and was used to check the adequacy of the specimen. A biopsy specimen was prepared using the touch imprint technique on the slides. One of the two slides was prepared using both air-dried and wet-fixed (placed in 95% ethyl alcohol) techniques. It was stained with hematoxylin staining and then with Shorr staining. The other slide was placed in 95% ethyl alcohol without air-drying and then stained with Papanicolaou staining later. When a cluster of spindle cells was identified on the slide, the specimen was considered adequate, that is, ROSE positive.

Histopathological examination. Histopathological examination was carried out based on H&E staining and immunohistochemistry. When the spindle cells were positive for c-kit, CD34, or DOG1, the lesion was diagnosed as GIST. When the spindle cells were positive for S-100 and negative for the aforementioned molecular markers, it was diagnosed as schwannoma. When the spindle cells were positive for desmin and negative for the aforementioned molecular markers, the diagnosis was "controversial" because muscularis mucosae or muscularis propria could not be ruled out.

Adverse events. Adverse events (grade ≥ 3) were investigated to evaluate the safety of these procedures in accordance with the Common Toxicity Criteria for Adverse Events v5.0.

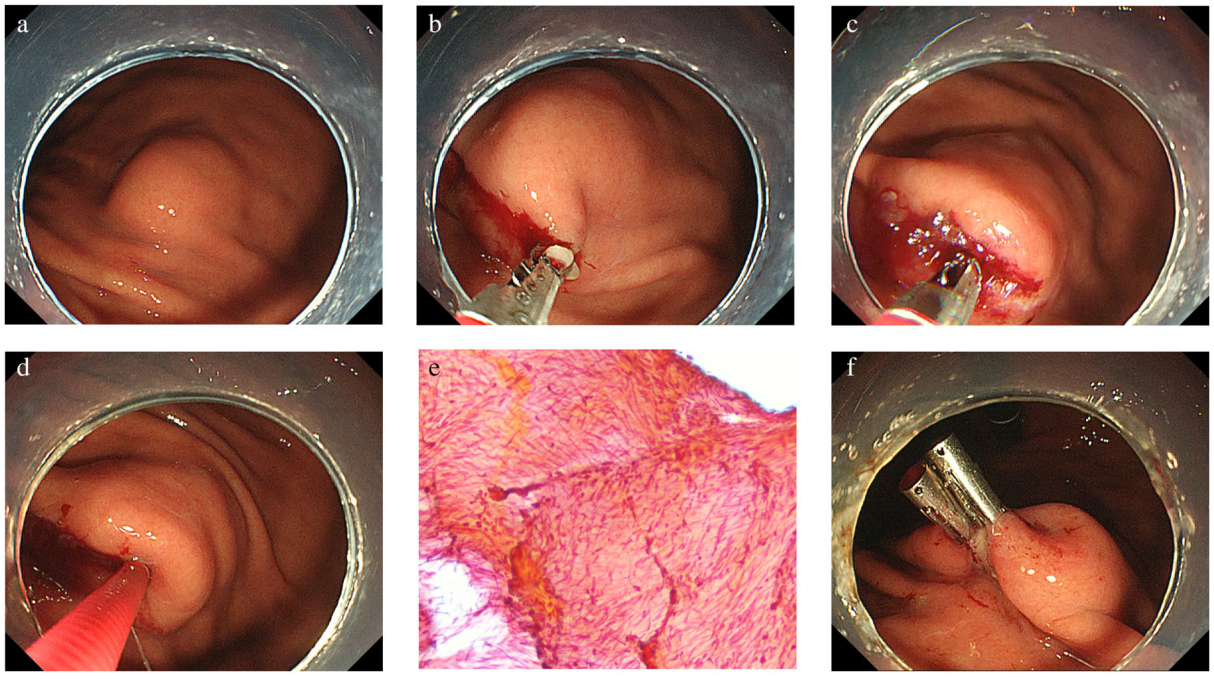

Figure 1 (a) Endoscopic image before hot boring biopsy. A 16-mm subepithelial lesion was located in the anterior wall of the lower gastric body. (b) the first two mucosal specimens were discarded. (c) Submucosal tissues were removed by electrical cutting. (d) Specimens were taken. (e) Rapid on-site evaluation revealed a cluster of spindle cells. (f) the biopsy wound was closed with endoclips after biopsy completion.

Table 1 Clinical characteristics and results of procedure in 12 patients who underwent boring biopsy with ROSE

Case	Age, years	Sex	Tumor location	EUS: Tumor size, mm	EUS: Relationship of lesion with muscle layer	Method	ROSE	Number of biopsy specimens	Procedure time, min	Dx of biopsy specimens	Dx of resected specimen
1	77	Male	U AW	21	Inside	CBB	N	6	22	Small amount of smooth muscle	NA
2	35	Male	M AW	35	Inside	CBB	N/P	10	21	Smooth muscle	GIST
3	80	Female	U LC	24	Outside	CBB	N/P	7	21	GIST	GIST
4	65	Female	U LC	15	Outside	CBB	N/P	8	27	Small amount of smooth muscle	GIST
5	65	Male	U GC	25	Outside	CBB	N/P	10	34	Stromal tissue	GIST
6	64	Female	U AW	17	Outside	CBB	P	4	13	Small amount of smooth muscle	NA
7	68	Female	U AW	19	inside	CBB	N/P	9	24	Stromal tissue	Schwannoma
8	60	Male	M AW	16	Inside	HBB	P	4	22	GIST	GIST
9	64	Female	U GC	21	Outside	HBB	N	2	18	Smooth muscle	NA
10	78	Female	U PW	21	Outside	HBB	P	3	20	Smooth muscle	NA
11	66	Female	U LC	18	Outside	HBB	N/N	5	23	Small amount of smooth muscle	GIST
12	61	Male	L LC	28	Inside	HBB	P	2	18	GIST	GIST

Procedure time is defined as the time from insertion to removal of an endoscope.
AW, anterior wall; CBB, conventional boring biopsy; Dx, diagnosis; EUS, endoscopic ultrasonography; GC, greater curvature; GIST, gastrointestinal stromal tumor; HBB, hot boring biopsy; L, lower third; LC, lesser curvature; M, middle third; N, negative; NA, not applicable; P, positive; PW, posterior wall; ROSE, rapid on-site evaluation; U, upper third.

Statistical analysis. Continuous variables are presented as median and range. Procedure time was defined as the time from the start of boring biopsy to the completion of clip closure. The diagnostic yields of boring biopsy in combination with ROSE among patients who were diagnosed with GIST by resected specimens were calculated. The positive and negative predictive values of ROSE for the diagnosis of GIST were also calculated when the diagnosis of subsequently taken biopsy was defined as a reference standard. All statistical analyses were conducted using R software, version 3.6.3 (R Foundation for Statistical Computing, Vienna, Austria; http://cran.r-project.org/).

Results

Clinical data of the 12 patients are shown in Table 1. The procedure was complete when ROSE positive results were obtained in nine patients, but it was discontinued in three patients (Figure S1). The reasons for discontinuation were loss of tumor orientation due to edematous changes in the surrounding mucosa during the procedure ($n = 2$) and a preset limit on the number of ROSE ($n = 1$). Among patients with histopathologically proven GISTs, one of four patients (25%) was correctly diagnosed by conventional boring biopsy and two of three patients (67%) were correctly diagnosed by hot boring biopsy. The median procedure time for conventional boring biopsy and hot boring biopsy was 21 (range, 13–33) and 17 (range, 16–23) min, respectively.

ROSE. ROSE was performed for a total of 12 times in seven GIST patients. Histopathological examinations of subsequently taken biopsy specimens showed GIST in three of six sessions (50%) of positive ROSE results. However, the biopsy specimens did not show GIST in the other three sessions of positive ROSE results and all six sessions of negative ROSE results. The positive and negative predictive values of ROSE for the diagnosis of GIST in subsequent biopsy were 0.5 (95% confidential interval, 0.12–0.88) and 1.0 (95% confidential interval, 0.42–1.00), respectively.

Adverse events. Among 12 patients, delayed bleeding occurred in one patient who underwent hot boring biopsy 2 days after the procedure. He underwent gastroscopy for melena, and the biopsy wound was reclosed with endoclips; blood transfusion was performed thereafter. No severe abdominal pain was reported.

Discussion

In this study, conventional boring biopsy showed a diagnostic yield of only 25% even when ROSE was used in combination, whereas hot boring biopsy showed a diagnostic yield of 67%.

The diagnostic yield of EUS-FNA for GIST was reported to be 50%–87.5% and that of submucosal tunneling biopsy or mucosal incision-assisted biopsy was 92.9%–100%.[5,6] It is difficult to demonstrate the superiority of boring biopsy over these methods, but boring biopsy could be performed in the outpatient setting without requiring any special techniques. If 67% of GIST can be diagnosed by this outpatient procedure, it would be clinically meaningful. Moreover, the procedure time and cost are advantages over these methods. Kobara et al.[5] reported that the median procedure time of EUS-FNA and submucosal tunneling biopsy was 18 (range, 13–34; only for technically successful cases) and 37 (range, 19–90) min, respectively, whereas Osoegawa et al.[6]

reported that the median procedure time of EUS-FNA and mucosal incision-assisted biopsy was 26 (range, 18.75–31) and 34 (range, 24–58) min, respectively. The costs of disposable devices are shown in Table S1, with boring biopsy having the lowest cost.

Regarding ROSE in combination with boring biopsy, there was no case wherein biopsy showed GIST with negative ROSE results, indicating that it is necessary to continue the procedure at least until positive ROSE results are obtained. In contrast, the positive predictive value of ROSE was insufficient, possibly because of obtaining tissues of the muscularis mucosae or muscularis propria and sampling errors. These are the disadvantages of this blind technique. If smooth muscle and tumor tissues can be distinguished visually, false positives may be avoided. To avoid sampling errors, it may be necessary to insert the forceps deeply (approximately 1 cm). Lesions larger than 20 mm may be appropriate for this method as recommended in the Japanese guideline. It is also important to ensure the safety of the procedure.

Our study has several limitations. First, this was a pilot study with a small sample size, in which statistical analysis could not be performed. Verification of the findings in a larger prospective study is necessary. Since no detailed data have been reported on boring biopsy and ROSE previously, we believe that these findings will be useful in planning a prospective study. Second, histopathological diagnosis in some patients were unknown, because they did not undergo EUS-FNA or resection after negative test of this method. We excluded these cases from the evaluation of diagnostic yield. Third, the characteristics of unsuccessful cases could not be clarified in this study. Although quantitative evaluation was difficult, operability and visibility of the lesions during the procedure may be related to appropriate tissue sampling.

In conclusion, hot boring biopsy with ROSE may be a sampling method option for the diagnosis of gastric GIST, but low positive predictive value of ROSE remains a challenge.

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Supporting information

Additional supporting information may be found in the online version of this article at the publisher's website:

Figure S1. Patient selection flowchart.
Table S1. Comparison of cost for hot boring biopsy, EUS-FNA, and submucosal tunneling biopsy (mucosal incision-assisted biopsy).