How Can We Avoid Unnecessary Surgical Resection for Gastric Subepithelial Tumours? A Multicenter Retrospective Study in Korea

Il Hyun Baek¹, Kwang Ro Joo², and Kyeong Won Min³

Corresponding author:

Il Hyun Baek, M.D., Ph D
Department of Gastroenterology
Eulji University Hospital
Eulji University School of Medicine
1306, Dunsan-dong, Seo-gu
Daejeon, Republic of KOREA 35233
Telephone: +82-42-611-3063
E-mail: drandrea100@daum.net

¹Department of Gastroenterology, Eulji University Hospital, Eulji University School of Medicine Daejeon, Korea

²Department of Gastroenterology, Kyung Hee University Hospital at Gangdong Kyung Hee University, Seoul, Korea

³Department of Human Resource Development, Graduate School of Chung-Ang University Seoul, Korea

ABSTRACT

Background: Gastric subepithelial tumors (SETs) are often encountered in endoscopy without any special symptoms. The effectiveness of current diagnostic tissue sampling techniques for gastric SETs is limited. Better tissue acquisition methods are required to improve the diagnostic yield in patients with gastric SETs. The purpose of this study is to assess the safety and diagnostic effectiveness of an endoscopic incisional target biopsy technique for gastric SETs.

Methods: This study was intended for patients with gastric SETs with failed tissue diagnosis by conventional forceps biopsy. Gastric SETs were assessed by endoscopic incisional target biopsy in order to obtain preoperative pathological diagnosis. Endoscopic ultrasound (EUS) and abdominal CT, were also part of the assessment, in accordance with diagnostic management algorithms.

Results: Endoscopic incisional target biopsy provided sufficient tissue specimens for definite pathologic diagnosis in 17 of 19 cases (diagnostic yield 89.5%). Contrary to widely-held assumptions, there were so many benign SETs even in over 2 cm sized SET. Only three out of 19 cases (15.8%) were diagnosed as GIST. In all GISTs, the size of the incisional target biopsy samples enabled immunohistochemical analysis (100%) and the evaluation of malignancy risk was performed by measuring the mitotic index in two cases (66.7%). The mean procedure time for incisional target biopsy was 11.4 ± 5.0 minutes. Six procedure-related minor bleedings occurred during or after the procedure.

Conclusion: Endoscopic incisional target biopsy appears to be an easy to perform, effective, safe and less aggressive methods to determine the definitive pathological evaluation and malignant risk. It can be a reliable alternative to Fine Needle Aspiration (FNA) or (Trucut Biopsy) TCB, providing larger specimens that improve pathologic yields. To avoid unnecessary surgical resection of gastric SETs, we recommend tissue diagnosis by endoscopic incisional target biopsy.

Key words: subepithelial tumour, incisional biopsy, stomach

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INTRODUCTION

Gastric subepithelial tumours (SETs) with normal overlying mucosa are frequently encountered during oesophagogastrroduodenoscopy (OGD).

Endoscopic ultrasound (EUS) is used to evaluate the delineation, echo pattern, size, and layer of origin of SETs (1,2). Algorithms based on EUS images are instrumental in determining whether gastric SETs should be monitored or removed endoscopically or surgically (3). However, it is difficult to offer an exact assessment of the potential for malignancy by the EUS images alone, especially in the case of intramural masses with low echos (4).

Standard endoscopic forceps biopsy, jumbo forceps biopsy, and bite-on-bite methods generally do not provide suitable samples for the assessment of gastric SETs (5). EUS-guided Tru-Cut™ Needle biopsy (EUS-TCB) and EUS-guided fine-needle aspiration (EUS-FNA) are now considered standard technique for tissue diagnosis of gastric SETs. However, the diagnostic accuracy of EUS-FNA is relatively low, at 62% (6). Although the EUS-TCB can overcome some of the limitations of the EUS-FNA, the diagnostic accuracy is less than 60%, due to its high technical failure rate (7). In other words, EUS-TCB and EUS-FNA may not be able to provide enough tissue specimens in order to obtain the necessary information about immunohistochemistry (IHC) and the mitotic index, both of which are required for a detailed histopathological diagnosis of gastric SET. Therefore, better tissue acquisition methods are required to ameliorate the diagnostic yield in patients with gastric SETs. The endoscopic incisional biopsy technique is used to perform a deep forceps biopsy after planned incision in order to obtain enough tissue for histopathological diagnosis. Histopathological examination will include mitotic counts essential for

the differentiation between potentially malignant gastrointestinal stromal tumours (GIST) and benign leiomyomas.

The purpose of this preliminary study is to assess the safety and diagnostic effectiveness of endoscopic incisional target biopsy methods for histopathological diagnosis of gastric SETs.

METHODS

This study was designed to evaluate 19 consecutive gastric SETs patients who had failed histopathological assessment by conventional forceps biopsy. The ethics committee of Eulji University Hospital approved the research protocol and received informed consent from each patient (IRB No. EMC 2016-09-006-002, Clinical trial registration No. KCT 0002306). We retrospectively reviewed procedural and pathology reports of endoscopic incisional target biopsy for the evaluation of gastric SETs.

Fig. 1 illustrates the treatment approach strategy for gastric SETs at our institution. EUS with or without abdominal CT was initially performed for all gastric SETs. Conventional EUS (GF UM160; Olympus, Tokyo, Japan) was performed to assess gastric SETs' layer of origin, echogenicity, delineation, shape, location, and size. Gastric SETs were managed differently depending on size. Gastric SETs with a diameter less than 1 cm received EUS six months after the initial inspection, and then an additional follow-up EUS after twelve months if volume, echogenicity, or shape did not change significantly. Gastric SETs of 1~2 cm in diameter under-

Figure 1 - Treatment algorithm for the management of gastric subepithelial tumors. SET, subepithelial tumor; EUS, endoscopic ultrasound

went incisional biopsy. According to the pathological diagnosis, SETs were considered for surveillance, endoscopic resection, or surgical resection. Gastric SETs of ≥ 2 cm in diameter underwent incisional biopsy. According to the pathological diagnosis, SETs were considered for surveillance or surgical resection.

Experienced endoscopists performed all incisional

biopsies using standard single-channel endoscopes (GIF-Q260, Olympus Medical Systems Corporation, Tokyo, Japan). Endoscopic incisional target biopsy was conducted as follows: (fig. 2), epinephrine in hypertonic saline solution (10 mL, dilution 1:1000) was injected into the submucosal layer of the lesion. A 20-30 mm linear incision using Dual Knife (KD-650 L; Olympus Medical

Systems Corporation, Tokyo, Japan) and Endocut Q currents (cut interval 4, cut duration 3, and effect 2) was achieved at the highest convexity of the lesion while looking directly at the lesion with an endoscope. Then, a traditional pair of biopsy forceps (Radial Jaw 4; Boston Scientific) was inserted deeply and at least five biopsy samples were obtained. Finally, the incision site was prophylactically closed with two or three endoclips (Olympus Medical Systems Corporation, Tokyo, Japan).

Perforation was defined as free air visible on simple x-ray after procedure. Bleeding was defined as any oozing or active bleeding requiring endoclippping or electrocautery during or after the procedure. Pathological diagnosis included identification of cell types, cellularity, cytoplasmic features, nuclear atypia, immunohistochemistry, and mitotic index of sample. The mitotic index was determined on 50 consecutive high-power fields (HPF) (8). The characteristics of mesenchymal origin were determined by conventional cytological analysis. Immunohistochemical staining was performed for further differentiation between gastrointestinal stromal tumours and non-gastrointestinal stromal tumours. With commercially available monoclonal/polyclonal primary antibodies, the most particular immunohistochemical markers for gastrointestinal stromal tumours (c-KIT, CD34, smooth muscle actin, Ki-67, S-100) were analysed.

Statistical analysis

Lesion properties and patient demographics were analysed using PASW for Windows, version 20.0 (Statistics 20, SPSS, IBM, Armonk, NY). Continuous variables were expressed as mean $\pm$ standard deviation. Categorical variables were analysed by Chi-square test and expressed as frequency (%).

RESULTS

During the study period, a total of 19 patients (9 men and 10 women) were included. Mean age was 53.2 years (range 39-64 years). Depending on EUS assessment, gastric SETs were divided as 14 (73.7%) small (< 2 cm in diameter) and 5 (26.3%) large ($\geq$ 2 cm) SETs. SETs were located in the fundus and cardia in 3 cases (15.8%), body of the stomach in 12 cases (63.2%), and the antrum in 4 cases (21.0%). The degree of tumour involvement by the SETs was: second layer (3 patients - 15.8%), third layer (4 patients, 21.0%), and fourth layer, respectively (12 cases, 63.2%). In terms of echogenicity, SETs were either hypoechoic in 16 cases (84.2%) or mixed in the remaining 3 cases (15.8%). Clinical, demographic, and endoscopic features of the

GSETs and patients are summarized in *table 1*.

Endoscopic incision target biopsy provided sufficient tissue specimens for definitive pathological diagnosis in 17 of the 19 cases (diagnostic yield rate 89.5%). The pathological diagnosis was GIST in 3 cases (15.8%), leiomyoma in 7 patients (36.8%), heterotopic pancreas in 2 patients (10.5%), glomus tumours (2 cases - 10.5%), polyps (2 patients - 10.5%), 1 vascular malformation (5.4%), and 2 not diagnostic (10.5%). Of the 19 patients, 14 (73.7%) were diagnosed with benign gastric SET such as ectopic pancreas or leiomyoma, and thus an unnecessary operation was avoided. The size of incisional biopsy samples was sufficient to allow immunohistochemistry in

Table 1 - Endoscopic, demographic, and clinical characteristics of the patients and lesions

Characteristics	n (%)
Patients, n	19
Age, average (range), years	53.2 (39-64)
Sex, n (%)	
Male	9 (47.4)
Female	10 (52.6)
Size of SET on EUS, average(range), n (%)	15.1 (5-30)
< 2 cm	14 (73.7)
$\geq$ 2cm	5 (26.3)
Location, n (%)	
Fundus	1 (5.3)
Cardia	2 (10.5)
Body (upper)	10 (52.6)
Body (mid)	1 (5.3)
Body (lower)	1 (5.3)
Antrum	4 (21.0)
Layer, n (%)	
2nd	3 (15.8)
3rd	4 (21.0)
4th	12 (63.2)
Echogenicity, n (%)	
Hypoechoic	16 (84.2)
Hyperechoic	0 (0.0)
Mixed	3 (15.8)
Pathologic Diagnosis, n (%)	
GIST	3 (15.8)
Leiomyoma	7 (36.8)
Heterotopic pancreas	2 (10.5)
Glomus tumour	2 (10.5)
Polyp	2 (10.5)
Vascular malformation	1 (5.4)
Not diagnostic	2 (10.5)

SET, subepithelial tumour; EUS, endoscopic ultrasound; GIST, gastrointestinal stromal tumour.

all (100%) GISTs. Malignant potential was assessed in two cases (66.7%) by measuring mitotic index (table 2).

The mean procedure time for incisional biopsy was 11.4±5.0 minutes. Six (31.6%) procedure-related minor bleedings occurred during or after the procedure.

DISCUSSION

Gastric SETs are generally found incidentally during routine endoscopy. The differential diagnosis of various types of gastric SETs is important because they can benefit from different treatment options and also have a different prognosis. The American Gastroenterological Association recommends surgical resection of gastric SETs larger than 3 cm in size with a low or heterogeneous echo originating from the fourth layer. Conversely, gastric SETs less than 3 cm in size without the characteristics of malignancy can be evaluated periodically by EUS (3,9,10). The National Comprehensive Cancer Network recommends surgical resection for all GISTs greater than 2 cm in diameter due to malignant potential, and resection or follow-up for GISTs with a diameter of less than 2 cm (11). However, even small GISTs (< 1 cm) have malignant potential and can metastasize to distant organs (12,13). EUS morphological

findings alone cannot replace histopathological diagnosis and cannot accurately predict malignant potential of gastric subepithelial neoplasms (3, 4). Current management guidelines for gastric subepithelial tumors based on EUS findings without pathological diagnosis are likely to lead to unnecessary surgery for benign gastric SET patients. Therefore, it is essential to obtain appropriate samples for cytological and immunohistochemical analysis for the accurate diagnosis and evaluation of potential malignancy (14-16). EUS-FNA is used to get specimens from gastric SETs, but its diagnostic yield varies from 38% to 82% (17-19). EUS-FNA has a high incidence of complications (21.7%), such as bleeding and even one death after biopsy (20). IHC staining, such as CD117, CD34, Ki-67, S-100, smooth muscle actin, or desmin, is important to distinguish SETs. IHC staining is only possible when a sufficient amount of tissue sample is available. For this reason, there is a limit to distinguishing gastric SETs, taking in consideration that the amount of tissue samples obtained with EUS-FNA is often not sufficient for IHC staining (21). The reason for the low diagnosis rate of EUS-FNA is that it is difficult to insert the needle deeply due to rubbery consistency of mesenchymal tumour and the stiffness of FNA itself. Moreover, it is difficult to aspirate the necessary

Table 2 - The results of incisional biopsy for gastric subepithelial tumours

Patient	Size, mm	Location	layer	echogenicity	Pathologic Dx	Ki-67	mitosis
1	20	upper body	4th	hypo	Not diagnostic		
2	7	upper body	4th	hypo	leiomyoma		
3	15	upper body	3rd	hypo	glomus tumour		
4	30	mid body	3rd	mixed	heterotopic pancreas		
5	5	lower body	4th	hypo	Not diagnostic		
6	20	cardia	4th	hypo	leiomyoma	< 1%	
7	12	antrum	2nd	hypo	hamartomatous polyp		
8	12	upper body	4th	hypo	glomus tumour		
9	12	fundus	2nd	hypo	fibroid polyp		
10	17	antrum	4th	hypo	GIST	< 1%	0~1/50 HPF
11	10	cardia	4th	hypo	GIST	< 1%	0~1/50 HPF
12	20	antrum	4th	hypo	leiomyoma	< 1%	
13	15	upper body	2nd	hypo	leiomyoma	< 2%	
14	17	upper body	4th	hypo	GIST	< 1%	
15	15	upper body	4th	hypo	leiomyoma		
16	12	upper body	3rd	mixed	vascular malformation		
17	15	upper body	4th	hypo	leiomyoma		
18	20	antrum	3rd	mixed	heterotopic pancreas		
19	15	upper body	4th	hypo	leiomyoma		

EUS, endoscopic ultrasound; hypo, hypoechoic; hyper, hyperechoic; mixed, mixed echogenicity; GIST, gastrointestinal stromal tumour. IHC (immunohistochemistry)

amount of cells because a small gauge needle is used. EUS-guided TCB (trucut biopsy), designed to overcome these problems, has been able to obtain a larger tissue specimen that retains the morphology of the tissue, enabling more accurate histological diagnosis than cytological diagnosis. However, even in recent studies, the diagnostic yield of TCB in gastric SETs is moderate (47% -63%) and is not superior to EUS-FNA (6,7,22). This is because it is difficult to aim and penetrate small gastric SETs covered with normal elastic mucosa. Also, a straight and stiff needle cannot pass through the channel of the bended endoscope to aim lesions in difficult-to-reach areas such as gastric cardia or fundus and duodenum (7, 11). When assessing the malignancy potential of GIST, information about the mitotic index of the tumour is important. Nevertheless, the EUS-TCB tissue specimen is too small to reliably provide information about the mitotic index to determine the malignant potential of gastric stromal tumours (14,22). There are also concerns about safety. Of the 52 procedures performed for gastric SETs, there were 2 cases of sepsis (22). Also, there is a risk of malignant cells spreading into the abdominal cavity after the lesion was punctured (23). Although endoscopic partial resection (the "unroofing" technique) has been advocated as an efficient measure, preliminary studies have shown that the risk of haemorrhage following endoscopic snare resection was as high as 56%, despite providing sufficient tissue specimens for mitotic analysis (21). There are also technical restrictions, because it is difficult to snare the skiddy lesion when gastric the SET is of rubbery consistency or grows extraluminally. Therefore, a breakthrough EUS-based tissue acquisition methods such as the endoscopic incisional target biopsy technique used in this study is needed. 17 (diagnostic yield 89.5%) out of 19 of our patients, who underwent endoscopic incisional target biopsy, had enough tissue samples for definite pathologic diagnosis, immunohistochemical analysis, and mitotic index of GISTs. In this study, endoscopic incisional target biopsy shows some advantages over the EUS-FNA or EUS-TCB, providing sufficiently large tissue specimens for final diagnosis in a cost-effective manner, reducing unnecessary surgical resection due to insufficient specimens or avoiding needless follow-up study. In addition, endoscopic incisional target biopsy can be made easier and safer regardless of the location of the gastric SET. Since conventional biopsy forceps are used to perform biopsy while looking directly at the lesion, there were less bleeding complications in comparison to other invasive methods. That has to do with the fact that frank bleeding or exposed blood vessels can be

immediately treated during the procedure. Moreover, delayed hemorrhage was also prevented by clipping of the incised mucosa as a prophylactic manoeuvre. In this study, six (31.6%) procedure-related minor bleedings occurred during or after the procedure. However, there was no infection or perforation related morbidity during or after incisional biopsy.

This study has some limitations, such as its retrospective nature, small sample size, and also the fact that it has not been directly compared to other methods such as conventional or EUS-TCB or EUS-FNA. Further studies involving more patients are required to compare endoscopic incisional target biopsy with other tissue sampling methods.

CONCLUSIONS

In conclusion, endoscopic incisional target biopsy seems to be a safe, simple, effective and less aggressive methods for the assessment of potential malignancy and establishment of a management plan for gastric subepithelial tumours. It can be a dependable substitute to traditional TCB and FNA, providing a larger specimen that improves pathologic yields. Contrary to widely-held assumptions, there are numerous benign SETs even in over 2cm sized SET. In order to avoid unnecessary surgical resection, we recommend decisive tissue diagnosis by endoscopic incisional target biopsy in gastric SETs.

Conflict of interest

The authors declare that there is no conflict of interest.

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