Editorial

Is a "wait-and-see" policy the best for small gastric gastrointestinal stromal tumor (GIST)?

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Several months ago, a middle-aged female patient presenting with a gastrointestinal stromal tumor (GIST) visited me at Sanjo General Hospital to seek a second opinion of her disease. The patient was asymptomatic and a diagnosis of submucosal tumor (SMT) in the stomach was made on the basis of barium swallow in a health examination. The incidentally found SMT was located at the gastric fornix and not associated with ulceration. Endoscopic ultrasonography (EUS) and computed tomography (CT) both showed that the tumor had a homogenous content and measured approximately 1.8 cm in maximal diameter. EUS-guided fine-needle aspiration (FNA) disclosed KIT-positive spindle cells. A diagnosis of GIST was made, and the attending physician recommended that she undergo surgical resection of the tumor. The query of the patient was whether surgery was mandatory or not although she preferred not to. I informed her of the potentially malignant nature of GIST and the very low risk of metastasis in her case and advised that resection was essentially recommended although she could take a wait-and-see strategy with regular follow-up. The patient finally chose watchful waiting and was scheduled for another CT 6 months later.

With gastric surveillance becoming more widespread, asymptomatic, incidentally found GISTs are becoming more common, and we occasionally encounter gastric GISTs smaller than 2 cm in diameter, named "small gastric GISTs" (SGGs). Owing to the lack of clinicopathological data, however, an unanswered clinical question remains: how can we manage SGGs?

In a study published in Medicine, Shen and colleagues offered new evidence for managing patients with SGGs (1). They analyzed the clinical outcomes of 54 patients who underwent endoscopic and surgical resections of gastric GISTs measuring 2 cm or smaller at the authors' institution. The study of Shen *et al.* provided two pieces of clinically useful information. First, endoscopic resection was safe and feasible. Second, SGGs included a considerable number of tumors with significant metastatic risk. By comparing two patient groups divided according to selected treatment, Shen *et al.* showed that endoscopic resection was a more preferable procedure than surgical resection in terms of operative time, blood loss, use of analgesics, time of nasogastric tube retention, and hospital stay. Conventional open surgery was selected in all patients of the surgical group. The results are, therefore, not surprising. Nevertheless, the data of 32 SGG patients who underwent endoscopic resection were regarded as clinically valuable.

Advances in endoscopic technology, including endoscopic submucosal dissection (ESD), have enabled the resection of large and submucosa-invasive gastric carcinomas. Nevertheless, concerns remain whether or not endoscopic resection is applicable to gastric SMTs, because in such cases, the tumors are mainly located beneath the mucosa, which presumably increases the risk of operative morbidities, including perforation and bleeding. Indeed, the reported incidence of perforation ranged from zero to 28% in early studies of endoscopic resection of gastric SMTs (2-6). In the current study by Shen *et al.*, perforation and postoperative bleeding occurred in one (3%) and two patients (6%), respectively. The findings suggested that endoscopic resection for SGGs was relatively safe and feasible. It should be noted, however, that the authors selectively used endoscopic resection in patients with tumors exhibiting intraluminal growth, not in patients with extramural and mixed-type GISTs. Ye *et al.* (5) have reported a higher risk of perforation in tumors located at

the deep muscular layer than in those at the superficial muscular layer (70% *vs.* 1.3%). Careful selection of patients according to intramural location may be critical for achieving safe endoscopic resection of GISTs.

Despite increasing evidence pointing to the safety of endoscopic resection, it also should be noted that the current study of Shen *et al.* has corroborated the technical feasibility of endoscopic resection for SGGs but has not ensured an oncological one. They made no mention of the histological status of the endoscopically excised tumors although they reported no macroscopic tumor residue. Joo *et al.* (6) reported conducting endoscopic resection in 90 GIST patients, 23 (25.6%) of whom microscopic complete resection with histologically negative margins was achieved. Although only one patient showed recurrence after the median follow-up of 31.5 months in Shen *et al.*'s study, delayed local recurrence is not rare in GIST (7). We should wait longer to determine whether endoscopic resection with possible microscopic injury of tumor capsules increases the risk of *in situ* recurrence or not.

The clinicopathology of SGGs was another important finding in Shen *et al.*'s study. Of the 54 SGGs that were endoscopically or surgically excised, of which median tumor size was 1.7 or 1.82 cm, respectively, seven tumors showed 6–10 mitoses per 50 high power fields (HPF) and four showed more than 10 mitoses per 50 HPF. Patients presenting with tumors showing high mitotic activities should be regarded as being at a significant risk of metastasis, and tumor resection should be recommended. Studies by refined histopathological analysis have revealed that subclinical minute GISTs (micro GISTs), which are smaller than 10 mm in diameter, are unexpectedly common in the general population. Micro GISTs were found in 22.5% of autopsy cases (8) and 35% of gastric cancer patients who underwent stomach resection (9). On the contrary, population-based studies have estimated that the annual incidence of clinically diagnosed GISTs is 11–14.5 per million (10-12). According to observations of the large differences between the incidences of micro and clinical GISTs, there is widespread understanding that many of the micro GISTs are self-limiting and only a small population of micro GISTs develop into clinically diagnosed GISTs. Thus, it remains undetermined how earnestly we should remove asymptomatic SGGs, which are borderline lesions of the two categories. According to expert consensus, clinical guidelines recommend that endoscopic surveillance be conducted at 6- to 12-month intervals (wait-and-see approach) for SGGs that show no possible high-risk features based on endoscopy and ultrasonography, because data on SGG pathology are limited (13,14).

The current study of Shen *et al.* has shown that SGGs include a considerable number of GISTs with significant metastatic potential. In a recent study from Italy (15) in which 170 GISTs measuring 2 cm or smaller were analyzed, mitotic activity was found to be very low in tumors smaller than 1 cm, but the activity dramatically increased once the tumor size exceeded 1 cm. These findings suggested that SGGs were not self-limiting lesions in contrast to micro GISTs, strongly supporting that timely histological diagnosis should be made even in small SMTs. On the other hand, Sekine *et al.* (16) reported a significant increase in the mean diameter of SGGs from 1.14 cm to 2.27 cm after a 12-month follow-up of 18 patients with tumors histologically diagnosed by FNA. The wait-and-see approach could be a practical choice for making decisions on the necessity and timing of tumor resection as EUS-FNA is difficult for small gastric SMTs. Patients who select regular follow-up would have to continue undergoing endoscopic examinations at 6- to 12-month intervals and sustain psychological and financial burden because their disease has yet to be essentially eradicated. Endoscopic resection may be suitable for the management of patients with small gastric SMTs because the procedure is not only diagnostically useful but also potentially curable. Although more data are needed, the study of Shen *et al.* has opened doors to a new approach for small gastric SMTs.

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Footnote

Conflicts of Interest: The author has no conflicts of interest to declare.

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