

Necessity for Resection of Gastric Gastrointestinal Stromal Tumors ≤ 20 mm

TADASHI KOGA¹, YOSHIE HIRAYAMA¹, SYOHEI YOSHIYA¹, KENJI TAKETANI¹,
TOMONORI NAKANOKO¹, RINTARO YOSHIDA¹, RYOSUKE MINAGAWA¹, MASANORI KAI¹,
KIYOSHI KAJIYAMA¹, KAZUYA AKAHOSHI² and YOSHIHIKO MAEHARA³

Departments of ¹Surgery and ²Gastroenterology, Iizuka Hospital, Fukuoka, Japan;

³Department of Surgery and Science, Graduate School of Medical Sciences, Kyushu University, Fukuoka, Japan

Abstract. *Background/Aim: To evaluate whether surgical intervention was useful in patients undergoing surgery for gastric gastrointestinal stromal tumors (GISTs), for tumors ≤ 20 mm in size. Patients and Methods: Between August 2002 and July 2014, 138 patients with GIST underwent surgery at our Hospital, including 112 patients with gastric GISTs. The medical records of these patients were retrospectively reviewed. Results: Postoperative recurrence was observed in three patients, each having tumors with high mitotic rates and ≥ 21 mm in size. In 89 patients undergoing gastric wedge resection, the incidence of postoperative complications was 10.1%; 5.6% of the patients developed late sequelae, all of which were mild. The group classified as having tumors ≥ 21 mm in size had a higher proportion of elderly patients ($p=0.0010$), more complications ($p=0.0152$), and longer hospital stay ($p=0.0589$). Conclusion: To prevent recurrence, definitive diagnosis and aggressive resection while the tumor size is 20 mm or less is recommended. However, because some patients also carry surgical risks, sufficient consideration must be given to the needs of individual patients.*

At present, gastric submucosal tumors (SMTs) are occasionally encountered during the widely practiced health check-ups in Japan. The majority of the detected gastric SMTs are classified as gastrointestinal stromal tumors (GISTs). According to Japanese guidelines, gastric SMTs measuring more than 20 mm in size are recommended for surgery, whereas those measuring 51 mm or more are absolutely indicated for surgery. Moreover, tumors with malignant features

or those definitively diagnosed as GISTs are also absolutely indicated for surgery (1, 2). However, because gastric GISTs have relatively good prognoses (3-5), the risks associated with the tests required to make a definitive diagnosis, the subsequent surgical interventions required, and the patient's prognosis also need to be considered. Although endoscopic ultrasound-guided fine-needle aspirations (EUS-FNAs) enable generally safe definitive diagnoses (6-8), the procedure requires for specific devices and skills. At the Department of Gastroenterology of our hospital, EUS-FNA has been aggressively introduced and performed on many surgical patients with GISTs 20 mm or less in size to make definitive diagnoses. In addition, emergent surgeries have not been necessary for EUS-FNA-induced perforations during the same period. On the other hand, the surgical risks have not been well-examined.

In the present study, we retrospectively assessed the current status of patients who had undergone surgery for gastric GISTs at our Hospital in order to determine whether intervention (resection) is absolutely necessary for gastric GISTs of 20 mm or less in size.

Patients and Methods

Between August 2002 and July 2014, 138 patients with GIST underwent surgery at our hospital, including 112 with gastric GISTs. The medical records of these patients were retrospectively reviewed. Forty-nine (43.8%) patients had tumors 20 mm or less in size, 46 (41.0%) had tumors 21-50 mm, and 17 (15.2%) had tumors 51 mm or more in size. Tumors in seven (14.3%) patients with tumors 20 mm or less in size had high mitotic rates [$\geq 6/50$ high-power fields (HPF)]. This relatively large number indicates that even if the tumor size was small, there were some recurrence risks after resection. Moreover, similarly high mitotic rates were observed in 10 (21.7%) patients with 21-50 mm tumors and in two (11.8%) patients with ≥ 51 mm tumors (Table I). Twelve patients in this study met the criteria for a recurrence rate of $\geq 10\%$, based on the 2006 Miettinen classification(4). For prevention of recurrence in such patients, resection while the tumor is 20 mm in size or less seems preferable.

Correspondence to: Tadashi Koga, Department of Surgery, Iizuka Hospital, 3-83 Yoshio Town, Iizuka City, Fukuoka 820-8505, Japan. Tel: +81 948223800; Fax: +81 948298747, e-mail: tkogah1@aih-net.com

Key Words: Gastric gastrointestinal stromal tumor, tumor size, post-operative sequelae.

Table I. The relationship between tumor size and the number of mitoses among all resected gastric GISTs. There was no definitive difference between the ≤ 20 mm tumor size group and the 21-50 mm group regarding the frequency of mitoses $\geq 6/50$ HPF ($p=0.3436$). On the other hand, the ≥ 51 -mm group had fewer mitosis ($p=0.5351$).

Tumor size	Number of mitoses/50 HPF		Total
	≤ 5	≥ 6	
≤ 20 mm	42	7	49
21-50 mm	36	10	46
≥ 51 mm	15	2	17
Total	93	19	112

HPF: Microscopic high-power field.

Health checkup was the most common reason leading to tumor detection (90 patients, 80.4%). Other reasons included self-awareness of symptoms, such as hemorrhagic stool due to tumor hemorrhage, and abdominal masses (Table II). In each of the patients with tumors of ≤ 20 mm, the definitive diagnosis was made using EUS-FNA.

Out of the 112 patients, recurrence was observed in three, all of whom had a tumor mitotic rate of $\geq 6/50$ HPF. The tumor sizes in these patients were 21-50 mm (one patient; recurrence rate of 10%) and ≥ 51 mm (two patients; recurrence rate of 100%).

The surgical procedures were gastric wedge resection in 105 patients, total gastrectomy or distal gastrectomy or proximal gastrectomy in six, and an exploratory laparotomy in one. The reason why gastric wedge resection was not applicable to patients undergoing total gastrectomy or distal gastrectomy or proximal gastrectomy was assumed to be a concern because wedge resection might cause stomach deformities and dysfunction due to the large tumor size (≥ 42 mm, all patients), intraductal or intramural tumor morphology (five patients), or tumors located near the esophagogastric junction (two patients).

To elucidate the intra- and postoperative impact of surgery, various clinical factors were evaluated in 89 patients, excluding those simultaneously undergoing surgery for other diseases (cholecystectomy, hepatectomy, mastectomy, inguinal hernia, etc.), among the 112 patients who underwent gastric wedge resection due to gastric GIST. Laparoscopic surgery was performed in 58 patients. The techniques employed for the gastric wedge resection were mechanical resection-anastomosis using a linear stapler or fullthickness resection with manual suturing.

For statistical analysis, χ^2 tests were performed to analyze sex, sequelae, and complications; t-tests were performed to analyze age; and Wilcoxon rank sum tests were performed for operative time, volume of blood loss, length of hospital stay, and follow-up period.

Results

The mean intraoperative blood loss was 53.1 (± 173.3) g, with a mean operative time of 104 (± 61.0) min. Only one patient developed an intraoperative complication (poor bleeding

Table II. Chief complaint leading to diagnosis.

No symptoms (health check) Upper gastrointestinal study (fiber or radioscapy), US, CT, MRI	90 cases	80.4%	(≤ 20 mm: 43 cases)
Symptomatic tumor bleeding hematemesis, melena, blackish feces, anemia	9 cases	8.0%	(≤ 20 mm: 0 cases)
Probable abdominal mass	1 case	0.9%	(≤ 20 mm: 0 cases)
Other symptoms abdominal pain, epigastralgia, body weight loss, etc.	12 cases	10.7%	(≤ 20 mm: 6 cases)

US, Ultrasonography; CT, computed tomography; MRI, magnetic resonance imaging.

control) and required conversion from a laparoscopic procedure to a laparotomy. The mean postoperative hospital stay was 11 (± 8.7) days. Postoperative complications were observed in nine patients. Except for an intraabdominal abscess in one patient and wound infections in two, the postoperative complications were those affecting systemic conditions: pneumonia (n=2), urinary tract infection (n=2), adhesive ileus at a previous appendectomy site (n=1), and a rib fracture due to a fall during hospitalization (n=1). According to the Clavien-Dindo postoperative complication classification criteria, four patients had grade I, four had grade II, and one had grade IIIa complications. In the patient with a grade IIIa complication, intra-abdominal abscess drainage, under EUS guidance, into the stomach was performed.

Data on postoperative sequelae were collected from medical records. The mean follow-up period was 802.3 (± 671.0) days. At discharge, none of the patients had any sequelae. On the day of the last outpatient visit, five patients (5.6%) presented with complaints. Because one patient with complaints was not followed-up, the patient's long-term course remains unknown. The remaining four patients had reflux esophagitis (one patient) and a hiatal hernia (one patient), but no abnormalities were found in the other two patients by gastrointestinoscopy. Moreover, oral medications were administered only to the patient with a hiatal hernia, which was relieved by Kampo preparations. In the four patients followed-up, none of the sequelae were considered to be consequences of surgeries.

Patient outcomes were also compared between those with ≤ 20 mm tumors (n=41) and those with ≥ 21 -mm tumors (n=48) (Table III). The mean ages were 61.5 (± 11.2) years and 69.6 (± 11.0) years, respectively, with the latter being significantly older ($p=0.001$). The mean intraoperative blood loss were 16.5 (± 25.7) g and 84.9 (± 233.7) g, respectively, showing that the blood loss tended to be larger in patients

Table III. Clinical characteristics of 89 patients undergoing gastric wedge resection. Data are frequencies or the mean±SD

Tumor size	≤20 mm N=41	≥21 mm N=48	p-Value
Sex, Male:Female	11:30	18:30	0.2824
Age (years)	61.5±11.2	69.6±11.0	0.0010
Operative time (min)	98.4±66.0	108.2±56.6	0.4182
Blood loss (g)	16.5±25.7	84.9±233.7	0.1572
Hospitalization (days)	9.6±3.6	12.1±11.4	0.0589

with larger tumors. The mean operative times were 98.4 (±66.0) min and 108.2 (±56.6) min, respectively, showing that the operative time also tended to be longer for these patients. The mean length of postoperative hospitalization was 9.6 (±3.6) days and 12.1 (±11.4) days, respectively, showing that the hospital stay also tended to be longer ($p=0.0589$). Significantly more intra- and postoperative complications were observed in the group with larger tumors (9 vs. 1 patient; (Table IV, $p<0.016$). Sequelae were observed in four patients of the small tumor group and in one patient of those with large tumors, with the incidence being higher in the former, but not significantly so. Detailed examinations of individual patients revealed that four patients had lesions located near the cardia or on the lesser curvature and one patient had a lesion located on the fundus among those who had undergone resection of the short gastric arteries.

Discussion

In Japan, gastric SMTs, especially gastric GIST, are often detected and treated according to the Japanese guidelines (1). These guidelines state that surgery is indicated even for small SMTs if they present with malignant findings or are definitively diagnosed as GIST. The examination of patients with recurrence, based on the Miettinen classification (1, 4) and our data, suggests that GIST resections, even when the tumor is 20 mm in size or less, may be useful for preventing recurrence, as also reported previously (2). Advances (non-resectable or recurrent GIST) in drug therapy have yielded relatively long-term survival, as demonstrated by 5-year survival rates of 50% or higher (9-11). Nevertheless, recurrence makes achieving a cure difficult.

In assessing the validity of treating gastric GISTs measuring 20 mm in size or less, the risks associated with the tests required to make a definitive diagnosis (EUS-FNA, *etc.* at present) (6-8) and surgical risks should be considered.

In the present study, which targeted patients undergoing surgery for gastric GISTs, we examined 89 patients undergoing gastric wedge resection, excluding those simultaneously treated for other diseases. Considering the

Table IV. Complications in the 89 patients undergoing gastric wedge resection.

Tumor size	≤20 mm N=41	≥21 mm N=48	p-Value
Operative or perioperative complications	1	9	0.0152
Postoperative complication			
Prior to discharge	0	0	
After discharge	4	1	0.1171
Follow-up interval (days)	790.0±656.1	812.9±697.2	0.9639

operative time, volume of blood loss, length of hospital stay, and other findings, no major risks were identified that suggest a need to avoid surgery, and the postoperative sequelae were mild. Even small tumors may have an impact on sequelae, depending on their location (12); thus, attention to the tumor sites (proximity of the cardia and lesser curvature) is also required. However, if tumors grow during a follow-up period without resection, gastric wedge resection may become inadequate, and the need for distal, proximal or total gastrectomy, and the incidence of sequelae will increase (13, 14). Thus, surgical intervention for tumors of 20 mm in size or less seems to be of significance.

The comparison between patients with tumors ≤20 mm and those with tumors ≥21 mm (Table III) showed that tumors of 21 mm or more were more common in elderly patients. This might be because elderly patients are less likely to undergo health check-ups, or that they may have been only monitored until the tumors became large; however, neither possibility is certain. Tumors of 21 mm or more were associated with a higher incidence of postoperative complications and thus with a longer hospital stay, although there might have been an impact of the large number of elderly patients. Because postoperative complications are more likely in elderly patients, surgery should be performed, giving sufficient consideration to the patient's preoperative general condition and the balance between gastric GIST recurrence and survival prognosis.

Conclusion

Gastric GISTs that are of 21 mm or larger in size have higher rates of recurrence. Prior to the follow-up of gastric SMTs of 20 mm or less, detected during health checkups, definitive diagnoses using EUS-FNA are useful. The preferable therapeutic strategy is gastric wedge resection. However, even if gastric wedge resection is indicated, depending on the tumor site, complications or mild sequelae may occur, particularly in elderly patients. When surgical intervention is performed, the risks and prognosis should be sufficiently considered.

References

- 1 Japanese Clinical Practice Guidelines for Gastrointestinal Stromal Tumors (GIST) Third Edition. Kanehara & Co., Ltd. Tokyo, Japan, 2014.
- 2 Miyazaki Y, Nakajima K, Kurokawa Y, Takahashi T, Takiguchi S, Miyata H, Yamasaki M, Hirota S, Nishida T, Mori M and Doki Y: Clinical significance of surgery for gastric submucosal tumours with size enlargement during watchful waiting period. *Eur J Cancer* 49: 2681-2688, 2013.
- 3 DeMatteo RP, Lewis JJ, Leung D, Mudan SS, Woodruff JM and Brennan MF: Two hundred gastrointestinal stromal tumors: recurrence patterns and prognostic factors for survival. *Ann Surg* Jan 231: 51-58, 2000.
- 4 Miettinen M and Lasota J: Gastrointestinal stromal tumors: pathology and prognosis at different sites. *Semin Diag Pathol* 23: 70-83, 2006.
- 5 Corless CL, Ballman KV, Antonescu CR, Kolesnikova V, Maki RG, Pisters PW, Blackstein ME, Blanke CD, Demetri GD, Heinrich MC, von Mehren M, Patel S, McCarter MD, Owzar K and DeMatteo RP: Pathologic and molecular features correlate with long-term outcome after adjuvant therapy of resected primary GI stromal tumor: the ACOSOG Z9001 trial. *J Clin Oncol* 32: 1563-70, 2014.
- 6 Akahoshi K, Sumida Y, Matsui N, Oya M, Akinaga R, Kubokawa M, Motomura Y, Honda K, Watanabe M and Nagaie T: Preoperative diagnosis of gastrointestinal stromal tumor by endoscopic ultrasound-guided fine-needle aspiration. *World J Gastroenterol* 13: 2077-2082, 2007.
- 7 Akahoshi K and Oya M: Gastrointestinal stromal tumor of the stomach: How to manage? *World J Gastrointest Endosc* 2: 271-277, 2010.
- 8 Ito H, Inoue H, Ryozaawa S, Ikeda H, Odaka N, Eleftheriadis N, Maselli R, Sando N, Kimura S, Kudo SE: Fine-needle aspiration biopsy and endoscopic ultrasound for pretreatment pathological diagnosis of gastric gastrointestinal stromal tumors. *Gastroenterol Res Pract*. 2012:139083, 2012.9 Ogata K, Mochiki E, Ojima H, Haga N, Fukuchi M, Aihara R, Ando H, Uchida N, Toyomasu Y, Suzuki M, Kimura A, Kogure N, Yokobori T, Ohno T and Kuwano H: A multicenter long-term study of imatinib treatment for Japanese patients with unresectable or recurrent gastrointestinal stromal tumors. *J Surg Oncol* 110: 942-946, 2014.
- 10 Demetri GD, van Oosterom AT, Garrett CR, Blackstein ME, Shah MH, Verweij J, McArthur G, Judson IR, Heinrich MC, Morgan JA, Desai J, Fletcher CD, George S, Bello CL, Huang X, Baum CM and Casali PG: Efficacy and safety of sunitinib in patients with advanced gastrointestinal stromal tumour after failure of imatinib: a randomised controlled trial. *Lancet* 14: 1329-1338, 2006.
- 11 Demetri GD, Reichardt P, Kang YK, Blay JY, Rutkowski P, Gelderblom H, Hohenberger P, Leahy M, von Mehren M, Joensuu H, Badalamenti G, Blackstein M, Le Cesne A, Schöffski P, Maki RG, Bauer S, Nguyen BB, Xu J, Nishida T, Chung J, Kappeler C, Kuss I, Laurent D and Casali PG: GRID study investigators. Efficacy and safety of regorafenib for advanced gastrointestinal stromal tumours after failure of imatinib and sunitinib (GRID): an international, multicentre, randomised, placebo-controlled, phase III trial. *Lancet* 26: 295-302, 2013.
- 12 Sakamoto Y, Sakaguchi Y, Akimoto H, Chinen Y, Kojo M, Sugiyama M, Morita K, Saeki H, Minami K, Soejima Y, Toh Y and Okamura T: Safe laparoscopic resection of a gastric gastrointestinal stromal tumor close to the esophagogastric junction. *Surg Today* 42: 708-711, 2012.
- 13 Loffeld RJ: Prevalence of upper abdominal complaints in patients who have undergone partial gastrectomy. *Can J Gastroenterol* 14: 681-684, 2000.
- 14 Terashima M, Tanabe K, Yoshida M, Kawahira H, Inada T, Okabe H, Urushihara T, Kawashima Y, Fukushima N and Nakada K: Postgastrectomy Syndrome Assessment Scale (PGSAS)-45 and changes in body weight are useful tools for evaluation of reconstruction methods following distal gastrectomy. *Ann Surg Oncol* 21: S370-378, 2014.

Received January 6, 2015
Revised January 23, 2015
Accepted January 26, 2015