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CLINICOPATHOLOGICAL STUDY OF SMALL BOWEL GASTROINTESTINAL STROMAL TUMOR WITH SURGICAL INTERVENTION

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Abstract – *Objective:* *Gastrointestinal stromal tumors (GISTs) present with different clinical and immunohistochemical characteristics depending on the anatomic site. The present study clarified the clinicopathological characteristics of small bowel (SB) GISTs, which are relatively infrequent.*

Patients and methods: *The clinicopathological characteristics of 15 cases of small intestinal GISTs resected at our hospital were reviewed. SBGISTs were divided into duodenal (d) GISTs and jejunal/ ileal (ji) GISTs for the comparison.*

Results: *The tumors included six cases in the duodenum, six in the jejunum, and three in ileum. All patients underwent duodenal wedge resection for dGIST and partial SB resection for jiGIST. The stage was I in seven patients, II in two patients, IIIB in five patients, and IV in one patient. The median postoperative observation period was 67 (11-175) months. Ten patients had no recurrence, two had hepatic and peritoneal recurrence, one had multiple hepatic recurrence, one had peritoneal recurrence, and one had lymph node recurrence. On comparing dGISTs and jiGISTs, recurrence was significantly more frequent in jiGISTs than in dGISTs.*

Conclusions: *In five cases of recurrence, chemotherapy and surgery at the appropriate time seemed effective for achieving a long-term survival. Recurrence was significantly more frequent in jiGISTs than in dGISTs.*

KEYWORDS: *Small bowel, Gastrointestinal stromal tumors, Diagnosis, Surgical procedure, Chemotherapy.*

INTRODUCTION

Primary gastrointestinal stromal tumors (GISTs) can appear anywhere in the gastrointestinal (GI) tract, stomach (40%-60%), jejunum and ileum (ji) (30%), duodenum (d) (5%), colon (15%), and very rarely in the esophagus and appendix. Extra-GI tract GISTs have been reported in the omentum, mesentery, retroperitoneum, gallbladder, and urinary bladder[1-3]. The diagnosis of small bowel (SB) GISTs may be delayed for several reasons, including its relatively low incidence, nonspecific and variable symptoms, the wide spectrum of radiological appearances, intestinal thickening, and the presence of overlapping loops of intestine, which make imaging studies difficult; all of these lead to a delayed diagnosis or misdiagnosis of SB-GIST[4,5]. The risk stratification of GIST depends on its mitotic index (MI), size and anatomic site or origin, with MI being the strongest predictor of

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recurrence[6-8]. The surgical technique depends on the size of the tumor and its site of origin, and a variety of techniques are possible.

The prognosis of SB GISTs is reported to be worse than that of tumors of equivalent size and MI elsewhere[6,8]. Many papers have been published describing the treatment and characteristics of patients with GIST; however, only a few are available regarding the subpopulation of patients with SBGIST.

We herein reviewed the clinical, pathological, and imaging characteristics of 15 cases of SB-GIST following surgical resection.

PATIENTS AND METHODS

The clinicopathological characteristics of 15 cases of small intestinal GISTs resected at our hospital between January 1998 and August 2021 were reviewed. The TNM classification and staging were described according to the TNM classification of malignant tumors, 8th edition.

All procedures were in accordance with the Ethical Standards of the responsible Committee on Human Experimentation (institutional and national) and with the 1964 Declaration of Helsinki and later versions. This study was approved by the Ethics Committee of the Mitoyo General Hospital (approval number, 21-CR01-172; approval date, September 7, 2021).

SBGISTs were divided into duodenal (dGISTs) and jejunum and ileum (jiGISTs) lesions and compared in terms of the age, sex, tumor size, mitosis, T factor, N factor, stage, recurrence, and tumor rupture.

STATISTICAL ANALYSIS

Statistical analyses were performed using the IBM SPSS software program, version 24 (IBM Corp., Armonk, NY, USA). The chi-square and Fisher's exact tests were used to compare categorical variables, and Student's *t*-test or the Mann-Whitney test was used to compare continuous variables. All tests were 2-sided, and *p*-values of <0.05 were considered statistically significant.

RESULTS

Clinical Characteristics

The mean age of the 15 patients (10 men, 5 women) was 66.4 (43-83) years old.

The chief complaint was melena in three cases, tarry stool in three cases, abdominal pain in three cases, hematemesis in one case, vomiting in one case, anemia in one case, weight loss in one case, and detection by medical examination in two cases. The sites were the duodenum in six cases, jejunum in six cases, and ileum in three cases.

Computed tomography (CT) showed contrast-enhanced tumor images in the small intestine in 14 of 15 cases (93.3%) (Figure 1). The remaining patient had a non-enhanced CT scan showing free air and an SB tumor (Figure 2). For the preoperative diagnosis, all patients underwent upper endoscopy for their duodenal lesions, and one patient was diagnosed with a GIST by a biopsy (Figure 3a), while another patient with a jejunal lesion was found to have a tumor with ulceration as confirmed by double-balloon SB endoscopy

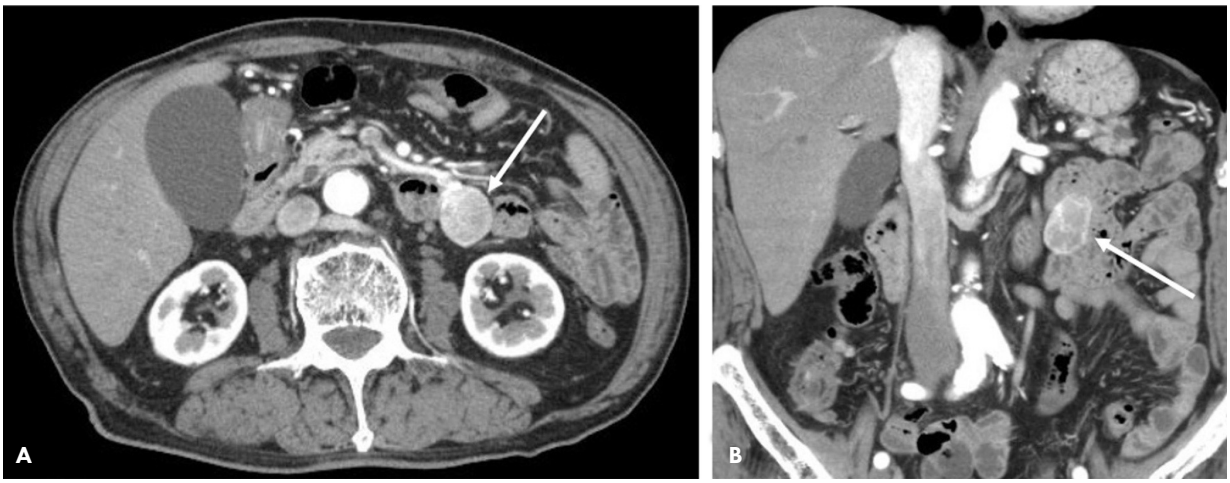

Fig. 1. Case 8) Contrast-enhanced computed tomography showed a heterogeneous tumor in the jejunum (arrow). *A,* Horizontal slice. *B,* Sagittal slice.

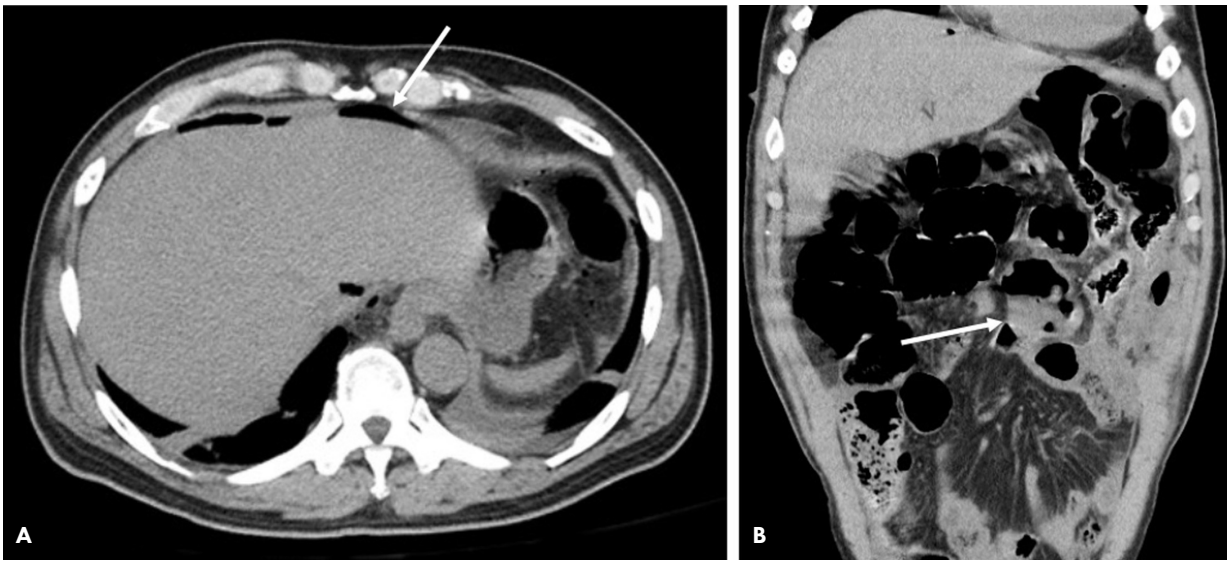

Fig. 2. The non-enhanced computed tomography findings of Case 15. *A,* Computed tomography showed a free air (arrow). *B,* Computed tomography showed a small bowel tumor *(arrow)*.

(Figure 3b). A preoperative diagnosis of GIST was confirmed in 1 patient, suspicion of GIST was diagnosed in 13 patients, and SB tumor perforation was determined in the remaining 1 patient (Table 1).

Surgical Procedure

Emergency surgery was performed in 3 patients, while the other 12 received standby surgery. Rupture of GISTs was observed in 2 of 15 patients (13.3%) (Figure 4). Six patients with dGIST underwent duodenal wedge resection and direct suture. Four jejunal GISTs were treated with partial segmental jejunal resection, one with laparoscopic partial segmental jejunal resection, and one with wedge resection. Three patients with ileal GIST underwent partial segmental ileal resection. The average size of the tumors was 50.3 (25-100) mm.

Histopathological and Immunohistochemical Findings

The MI indicated low mitosis (≤5 per 5 mm^2) in 9 cases and high mitosis (≥6 per 5 mm^2) in 6 cases.

The T classification was T1 in 1 case, T2 in 9 cases, and T3 in 5 cases. In the N classification, N0 in 14 cases and N1 in 1 case. The stage was stage I in 7 cases, stage II in 2 cases, stage IIIB in 5 cases, and stage IV in 1 case. The histopathological results were R0 in all cases. Staining for Kit was positive in all patients, CD34 was positive in 11, S100 was positive in 1 and Desmin was positive in none (Table 2).

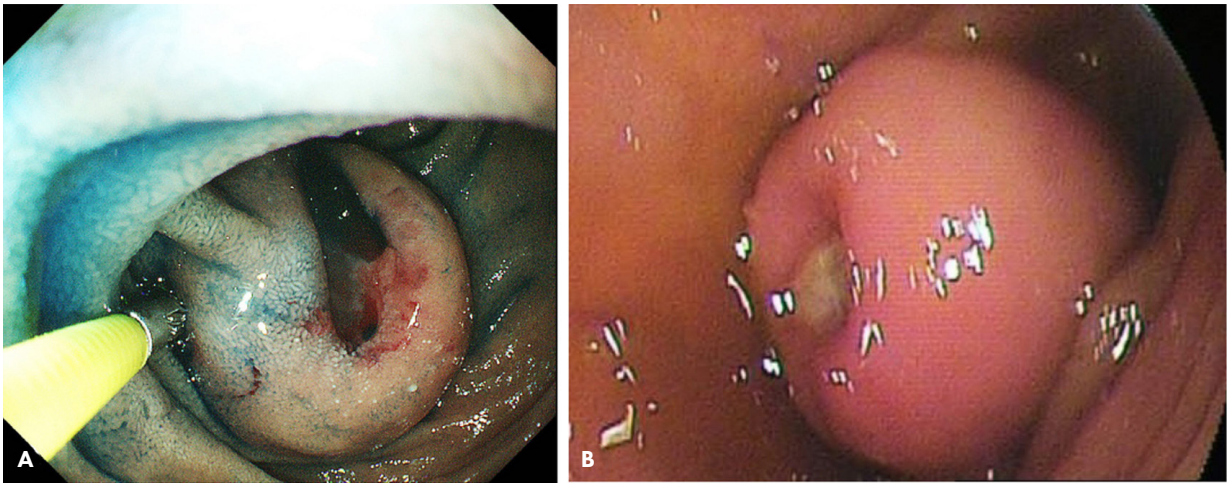

Fig. 3. Endoscopy findings. *A,* Upper endoscopy showed a tumor with ulceration in the second portion of the duodenum, which was definitely diagnosed by a biopsy. *B,* Double-balloon small bowel endoscopy showed a tumor with ulceration in the jejunum.

TABLE 1. Clinical characteristics

Case	*Age*	*Sex*	*Symptoms*	*Site*	*CT Findings*	*Endoscopic Findings*	*Preoperative Diagnosis*
1	43	M	Tarry stool	Duodenum	Well-defined, superficially irregular masse	Tumor with sessile, irregular surface and depressed apex	GIST on biopsy
2	75	F	Melena	–	–	Stalked, smooth-surfaced tumor	Suspected GIST
3	83	M	Hematemesis	–	Well-defined, smooth-surfaced mass with contrast effect	Tumor with sessile, irregular surface and depressed apex	–
4	57	M	Tarry stool	–	Mass protruding into the lumen in the shape of a ball with contrast effect	Tumor that protrudes into the lumen and is depressed at the apex, seeping blood	–
5	70	M	Tarry stool	–	Well-defined, smooth-surfaced mass with contrast effect	Tumor with gourd-shaped protrusion into the lumen and ulceration at the apex	–
6	54	M	Melena	–	A well-defined mass projecting outside the wall with contrast effect	Tumor with basal vascularity and shallow ulceration at the apex	–
7	70	F	None	Jejunum	Small bowel tumor to be contrasted	None	–
8	74	M	Anemia	–	–	–	–
9	65	M	Abdominal pain	–	Heterogeneously contrasted small bowel tumor	–	–
10	63	F	Melena	–	Small bowel tumor to be contrasted	Submucosal tumor with ulcer	–
11	71	F	Vomiting	–	–	None	–
12	75	F	None	–	–	–	–
13	62	M	Abdominal pain	Ileum	–	–	–
14	69	M	Weight loss	–	–	–	–
15	65	M	Abdominal pain	–	Free air, small bowel extramural tumor	–	Small bowel tumor perforation

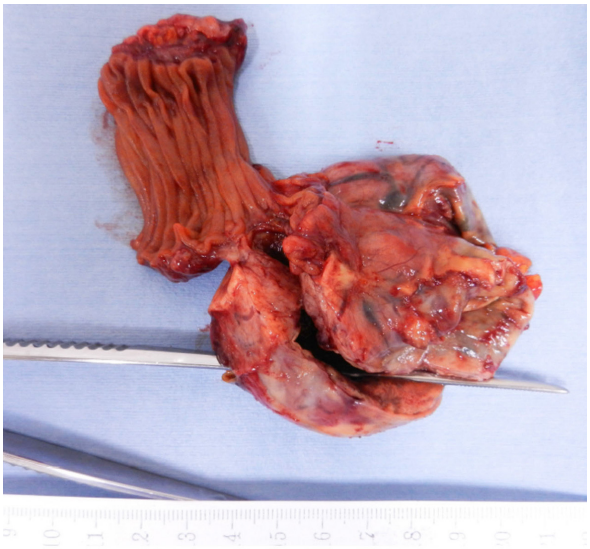

Fig. 4. A resected specimen revealed rupture of the ileal GISTs (Case 15). The forceps were inserted into the perforation.

Postoperatively, one patient with jejunal GIST had anastomotic stenosis, and the other patient with ileal GIST and tumor perforation had wound infection; however, both recovered with conservative treatment. All patients were discharged from the hospital after a median of 12 (8-47) days (Table 2).

Chemotherapy, the Outcome, and Survival

The median postoperative observation period was 67 (1-175) months. Ten patients had without recurrence, two had hepatic and peritoneal recurrence, one had multiple hepatic metastases, one had peritoneal recurrence, and one had lymph node recurrence and multiple hepatic metastases. Five of the patients with an MI of ≥6 had recurrence.

Nine patients received no postoperative treatments. Case 1 was treated with adjuvant chemotherapy by imatinib for three years and had no recurrence. Case 8 was diagnosed with multiple liver metastases and was treated with imatinib for eight months, and CT showed a reduced size of liver metastases; however, he died three years and nine months after surgery because of discontinuation of imatinib after eight months due to side effects. Case 9 and Case 15 had a rupture of GIST and underwent peritoneal recurrence and hepatic recurrence after surgery. Case 9 underwent peritoneal recurrence surgery for repeated peritoneal recurrence and partial hepatectomy for hepatic metastasis. He is currently taking imatinib after surgery. Case 15 underwent peritoneal recurrence surgery for peritoneal recurrence. Postoperative hepatic metastasis was observed while the patient was taking imatinib, and hepatectomy was performed. After surgery, hepatic metastasis was observed during postoperative imatinib therapy, so he was treated with sunitinib. Case 11 was unable to receive chemotherapy due to postoperative weakness and ultimately died of lymph node recurrence and multiple liver metastases 11 months after surgery. Case 13 experienced peritoneal recurrence that was treated with imatinib. The lesion was judged to be resectable and sunitinib was administered after resection of the peritoneal recurrence. Thirteen patients remain alive (Table 3).

The Comparison of dGISTs and ji GISTs

There were no significant differences in the age or gender between dGISTs and jiGISTs. jiGISTs tended to be more advanced than dGISTs in terms of the tumor size, MI, T factor, N factor, and stage. The rate of tumor rupture was also higher in jiGISTs than in dGISTs, but the difference was not statistically significant. Recurrence was significantly more frequent in jiGISTs than in dGISTs (p= 0.0253) (Table 4).

DISCUSSION

GISTs are one of the most common submucosal tumors of the GI tract encountered in daily practice. They arise from the interstitial cells of Cajal, the intestinal pacemaker cells present in the myenteric plexus in the muscularis propria, which likely accounts for their more commonly exophytic rather than intralumenal growth[9-12]. SBGISTs account for 35% of all GISTs, making them the second-most common lesion after those of the stomach[1].

SBGISTs tend to cause intermittent bleeding, and the presence of SBGISTs should be considered in cases without a source of bleeding in the stomach or colon. In the present study, 8 of 15 patients (53%) had symptoms due to bleeding from the tumor. On a preoperative examination, contrast-enhanced CT showed contrast-enhanced tumors in 14 of 15 cases, and in the remaining 1 case, an SB tumor and free air was seen.

Contrast-enhanced CT seemed to be effective in diagnosing the presence of tumors. Upper gastrointestinal endoscopy was able to confirm the presence of dGIST in all patients, and a biopsy was able to diagnose GIST in one patient. For jejunal GIST, double-balloon SB endoscopy showed the presence of jejunal GIST in one patient. Recently, the availability of double-balloon SB endoscopy has made the examination and biopsy of jiGISTs relatively easy.

TABLE 2. Tumor location, surgical procedure, and histopathological and immunohistochemical findings.

Case	Reason for surgery	Tumor rupture	Surgical Procedure	Tumor size (mm)	Mitosis (/5 mm²)	TNM	Stage	Margin status	KIT	CD34	S100	Desmin	Postoperative complications	Postoperative hospital stay (days)
1	Planned	None	Wedge resection	30	≥6	T2N0M0	IIIB	R0	(+)	(+)	(-)	(-)	None	11
2	–	–	–	25	≤5	T2N0M0	I	–	(+)	(+)	(-)	(-)	–	13
3	–	–	–	35	–	T2N0M0	I	–	(+)	(+)	(-)	(-)	–	14
4	Emergency	–	–	29	–	T2N0M0	I	–	(+)	(-)	(-)	(-)	–	10
5	Planned	–	–	38	–	T2N0M0	I	–	(+)	(-)	(+)	(-)	–	16
6	–	–	–	75	–	T3N0M0	II	–	(+)	(+)	(-)	(-)	–	12
7	–	–	Segmental resection	50	–	T2N0M0	I	–	(+)	(+)	(-)	(-)	Stenosis of anastomosis	47
8	–	–	Wedge resection	28	≥6	T2N0M0	IIIB	–	(+)	(+)	(-)	(-)	None	8
9	Emergency	Presence	Segmental resection	80	–	T3N0M0	IIIB	–	(+)	(+)	(-)	(-)	–	12
10	Planned	None	–	20	≤5	T1N0M0	I	–	(+)	(+)	(-)	(-)	–	12
11	–	–	–	50	≥6	T2N1M0	IV	–	(+)	(+)	(-)	(-)	–	12
12	–	–	Laparoscopic segmental resection	85	≤5	T3N0M0	II	–	(+)	(+)	(-)	(-)	–	12
13	–	–	Segmental resection	60	≥6	T3N0M0	IIIB	–	(+)	(-)	(-)	(-)	–	10
14	–	–	–	50	≤5	T2N0M0	I	–	(+)	(-)	(-)	(-)	–	10
15	Emergency	Presence	–	100	≥6	T3N0M0	IIIB	–	(+)	(+)	(-)	(-)	Wound infection	25

TABLE 3. Treatment with chemotherapy and/or re-surgical operation, the outcome, and the survival.

Case	*Recurrence*	*Treatment*	*Outcome*
1	None	Postoperative adjuvant chemotherapy with imatinib	4Y alive
2	–	None	6Y alive
3	–	–	6Y4M alive
4	–	–	6Y3M alive
5	–	–	12Y alive
6	–	–	14Y9M alive
7	–	–	1Y alive
8	Liver	Chemotherapy with imatinib for 8 months	3Y9M dead
9	Peritoneum and liver	Peritoneal recurrence surgery, peritoneal recurrence surgery and partial hepatectomy, imatinib after surgery	14Y7M alive
10	None	None	13Y alive
11	Lymph node and liver	–	11M dead
12	None	–	14Y alive
13	Peritoneum	Imatinib, sunitinib, peritoneal recurrence surgery, sunitinib	14Y alive
14	None	None	9Y4M alive
15	Peritoneum and liver	Peritoneal recurrence surgery, imatinib, and hepatectomy, sunitinib for hepatic metastasis	5Y9M alive

Surgery is the standard treatment for non-metastatic GIST[13]. The main objectives of surgical treatment are to achieve negative surgical resection margins (R0) and to resect the tumor without causing tumor rupture[14]. Lymphadenectomy is usually not needed, since GISTs rarely metastasize to local or regional lymph nodes[15]. Pancreaticoduodenectomy is the procedure of choice for patients with GISTs of the duodenum, depending on the localization, size, and nature of the tumor, due to its anatomical specificity. Pancreas-sparing duodenal segmental resection or duodenal wedge resection is performed for tumors that do not extend into the ampulla of Vater, regardless of whether the ampulla of Vater a is on the oral or anal side. As reported in our previous paper[16],

TABLE 4. A comparison of duodenal GISTs and jejunal/ ileal GISTs.

Variables	*Anatomical location of GIST*		
	Duodenum (6)	*Jejunum/Ileum (9)*	p-*value*
Age (years)	63.7±14.9	68.2±4.7	0.679
Sex (Male/Female)	5/1	5/4	0.576
Size (mm)	38.7±18.4	58.1±26.3	0.174
Mitosis (/5 mm²)			0.282
0-5	5	4	
6≤	1	5	
T factor			0.300
1	0	1	
2	5	4	
3	1	4	
N factor			0.291
0	6	8	
1	0	1	
Stage			0.486
I	4	3	
II	1	1	
IIIB	1	4	
IV	0	1	
Recurrence			0.0253
Presence	0	5	
Absence	6	4	
Tumor rupture			0.431
Presence	0	2	
Absence	6	9	

dGISTs do not invade the pancreas. Therefore, we performed a duodenal wedge resection to remove the GISTs and sutured the duodenum in the short-axis direction without causing anastomotic stenosis. One patient with jejunal GIST underwent wedge resection, and the remaining five patients underwent segmental resection. In one case, a laparoscopic segmental resection was performed. Laparoscopic surgery is indicated when the tumor can be easily extracted through a small laparotomy wound. All patients with ileal GIST underwent segmental resection. Basically, open laparotomy is chosen, but laparoscopic surgery is indicated when the small intestine, including the GIST, can be easily resected without touching the GIST.

In the future, laparoscopic surgery is expected to be used increasingly frequently for small GISTs in the jejunum and ileum without peritoneal recurrence.

Estimating the risk of recurrence is important for managing operable GIST. The tumor size, mitosis count, and tumor rupture are considered established risk factors for recurrence[17-20]. Recurrence was not seen in any dGISTs in our study but was seen in 5 (55.6%) of the 9 jiGISTs.

Imatinib, a small-molecule tyrosine kinase inhibitor (TKI) with activity against the KIT proto-oncogene receptor tyrosine kinase (KIT) and platelet-derived growth factor receptor (PDGFR), has played a major role in the management of GIST[21,22]. The administration of imatinib strongly influences the outcomes in high-risk groups[23-26]. The Scandinavian Sarcoma Group XVIII trial established a three-years postoperative therapy regimen involving imatinib for high-risk GISTs[27]. Sunitinb (TKI) is used to treat imatinib-refractory GIST and in patients unable to tolerate imatinib. Sunitinb targets multiple kinases, including vascular endothelial growth factor receptors, PDGFR, KIT, and FLt3. Other newer drugs in development include sorafenib, dasatinib, nilotinib, and regorafenib[27]. Case 8 showed multiple liver metastases after surgery and took imatinib for eight months. Case 9 was a patient with peritoneal recurrence who underwent peritoneal recurrence surgery. During follow-up, repeated peritoneal recurrence and hepatic metastasis occurred, so the patient underwent additional peritoneal recurrence surgery and partial hepatectomy. In Case 13, after taking imatinib and sunitinib for peritoneal recurrence, a peritoneal recurrence surgery was performed because it was judged to be resectable, and sunitinib was subsequently administered. Case 15 underwent peritoneal recurrence surgery for peritoneal recurrence, and liver metastasis occurred during imatinib therapy, resulting in hepatectomy. He was taking sunitinib for liver and peritoneal metastasis previously and is now taking sunitinib. Thus, even in the cases of peritoneal or hepatic recurrence, a long-term survival may be achieved with appropriate chemotherapy and surgical treatment.

Regarding the prognosis of SBGIST, Case 11 died of lymph node recurrence and multiple liver metastases 11 months after surgery at stage IV. The patient's poor general condition after surgery and inability to undergo postoperative chemotherapy were considered why her life was not prolonged. Case 8 was diagnosed with multiple liver metastases after surgery and was treated with imatinib for eight months. However, he died three years and nine months after surgery because of discontinuation of imatinib after eight months due to side effects.

GISTs may originate anywhere along the gastrointestinal tract, with SB being the second-most common site of involvement (30%-45%) after gastric GIST (50%-70%). SBGISTs have a worse prognosis than tumors or equivalent size and MI elsewhere[28-30]. We compared the risk of dGISTs and jiGISTs separately. jiGISTs tended to be more advanced than dGISTs in terms of the tumor size, MI, T factor, N factor, and stage. jiGISTs also showed tumor rupture more frequently than dGISTs, but there was no statistically significant difference. Furthermore, recurrence was significantly more frequent in jiGISTs than in dGISTs.

Several reports, including a recent multi-center study, have suggested that dGISTs may have a better prognosis than jiGISTs[31,32]. These reports insisted that dGISTs showed earlier presentation, smaller tumors, and a lower NIH risk classification than jiGIST. In contrast, Miki et al[33] reported that the prognosis of dGISTs was worse than that of non-dGISTs. Miettinen et al[8] analyzed 906 GISTs originating from the ileum and jejunum and concluded that jiGISTs seemed to have a similar prognosis to dGISTs, with a comparable size and mitosis parameters. In the present study, dGISTs tended to be smaller than jiGISTs in terms of the tumor size, MI, stage, and tumor rupture. The rate of recurrence of dGISTs was also significantly lower than that of jiGISTs. Guller et al[34] reported on 313 dGISTs and 1288 jiGISTs in the SEER database. The 3- and 5-year survival rates of dGISTs were 92.0% and 88.2%, respectively, and those of jiGISTs were 89.8% and 85.0%, respectively, with no significant difference. However, they concluded that GISTs larger than 10 cm had a poor prognosis. In the present study, jiGISTs tended to be larger than dGISTs, resulting in significantly more frequent recurrence of jiGISTs than dGISTs.

The present study is limited by its retrospective study design as well as the small study size (15 patients) and the fact that the study was performed at

a single center, which may have introduced some study bias. The statistical analyses were limited owing to the small number of patients included.

CONCLUSIONS

We have experienced 15 cases of SBGIST subjected to surgical intervention. Even if GISTs recur as peritoneal or hepatic metastases, a long-term survival can still be achieved with appropriate chemotherapy and surgery. The incidence of GIST recurrence was shown to be significantly higher for jiGISTs than for dGISTs.

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Authors' contributions:

Udaka T analyzed the data and wrote the manuscript. Udaka T, Endou I, Yoshida O, and Kubo M performed the surgery, and Asano H and Kubo M helped draft the manuscript. Nishiyama T, Watanabe N, Yoshida O, and Kubo M participated in revising the manuscript critically. All authors declare that they contributed to this article and that they read and approved the final version.

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Ethics Approval:

This study was approved by the Ethics Committee of the Mitoyo General Hospital (approval number, 21-CR01-172; approval date, September 7, 2021).

Conflict of interest:

All authors declare that there are no conflicts of interest.

Availability of data and materials:

All data generated or analyzed during this study are included in this published article.

Consent for publication:

Consent to publish was obtained from the patient.

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