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CASE REPORT

Madoka Hamada · Kazuhide Ozaki
Tadashi Horimi · Akihito Tsuji · Yoshitsugu Nasu
Jun Iwata · Yusuke Nagata

Recurrent rectal GIST resected successfully after preoperative chemotherapy with imatinib mesylate

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Abstract A 60-year-old-man underwent initial resection of a rectal tumor, with a transanal approach, on December 6, 2000. The tumor was diagnosed as a gastrointestinal stromal tumor(GIST) by KIT and CD34 immunohistochemistry. In June 2003, a third recurrence in the rectum was discovered, at the same location as the initial tumor, and he was referred to our hospital. Magnetic resonance imaging (MRI) revealed a tumor 3.0 cm in diameter, compressing the prostate anteriorly. After the oral administration of imatinib mesylate (Gleevec, Glivec) at a dose of 400 mg per day for 3 months, the size of the tumor had decreased to 1.2 cm in diameter. On December 12, 2003, a fourth operation was performed successfully, with a perineal approach, preserving sphincter function. More than 40 months after the fourth operation, neither local recurrence nor distant metastasis was detected. Our strategy of treatment with imatinib allows not only complete excision of the tumor but it also reduces postoperative impediments in patients with recurrent rectal GIST.

Key words GIST · Rectum · Imatinib mesylate · Sphincter preservation

Introduction

Gastrointestinal stromal tumors (GISTs) account for fewer than 1% of large bowel malignancies. Approximately 10% of all cases of GIST affect the rectum.[1] As most of these tumors spread locally without lymph-node metastases, local excision is generally adopted, regardless of tumor size, in patients without distant metastases. The goal in surgery for rectal tumors is not only curability but also sphincter preservation. Most of the reported rectal GISTs in Japan–before the use of imatinib mesylate was approved were located in the lower rectum, and they were too large to remove completely by local excision.

Imatinib mesylate (Gleevec, Glivec; Novartis, Basel, Switzerland) is a selective inhibitor of transmembrane receptor KIT protein tyrosine kinases and it inhibits the proliferation of GIST tumor cells that are stimulated by the activated KIT receptor.[2–3] Demetri et al.[4] reported that treatment with imatinib mesylate resulted in antitumor responses in more than 80% of recurrent GISTs, but there were no complete remissions. It is true this novel antitumor drug cannot completely remove the tumor cells, but it may provide a chance for the complete resection of the tumor with minimally invasive surgery. We present a case of recurrent GIST that was resected completely, preserving the patient's anal sphincter function, after preoperative chemotherapy with imatinib mesylate.

Case report

On December 6, 2000, a 60-year-old man underwent surgical resection of a rectal-wall tumor by a transanal approach. Immunohistochemistry revealed that the tumor was KIT (+), CD34 (+), and had a low risk of aggressive behavior. Recurrent lesions were excised by the same procedure at another hospital on September 26, 2001, and July 19, 2002. At the third operation, pathological examination of the second recurrent tumor revealed over 20 mitoses per 50 high-power fields (×400). In June 2003, the patient presented at another hospital with complaints of anal pain and dysuria. He was then referred to our hospital.

Two-dimensional fluoro-deoxyglucose (FDG)-positron emission tomography (PET) scanning of the body revealed

M. Hamada (✉) · K. Ozaki · T. Horimi
Department of Digestive Surgery, Kochi Health Sciences Center, 2125-1 Ike, Kochi 781-8555, Japan
Tel. +81-88-837-3000; Fax +81-88-837-6775
e-mail: KGH03145@nifty.com

A. Tsuji
Department of Medicine, Kochi Health Sciences Center, Kochi, Japan

Y. Nasu
Department of Urology, Kochi Health Sciences Center, Kochi, Japan

J. Iwata
Department of Pathology, Kochi Health Sciences Center, Kochi, Japan

Y. Nagata
Department of Surgery, Izumino Hospital, Kochi, Japan

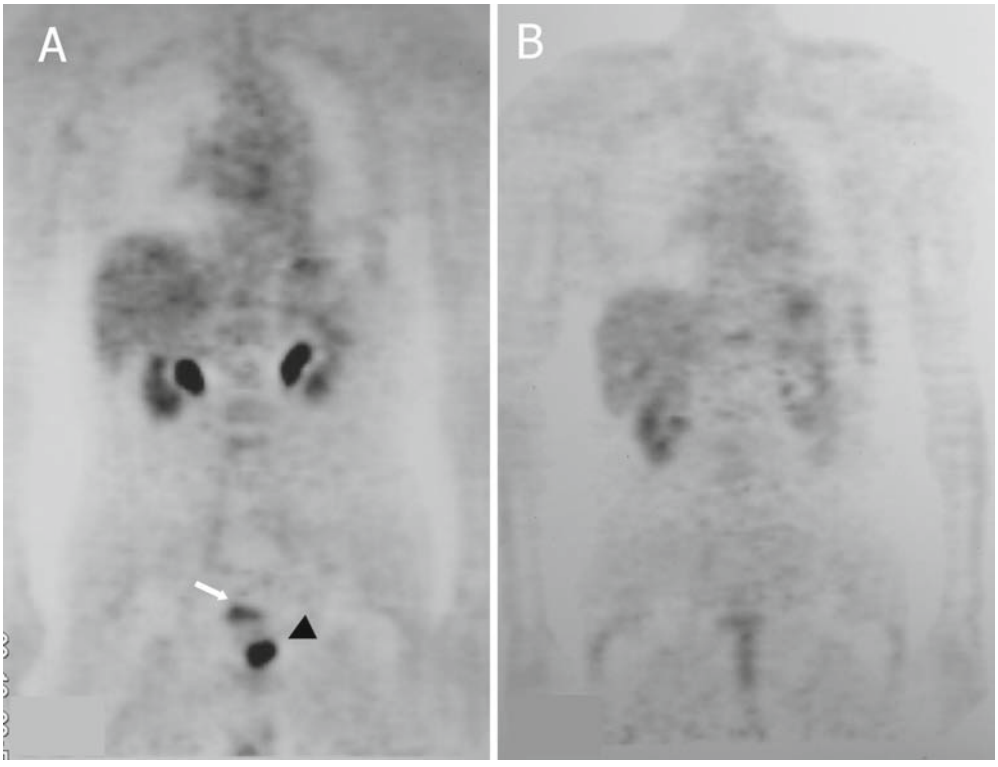

Fig. 1. A Fluoro-deoxyglucose (FDG)-positron emission tomography (PET) scan of the body before operation shows that FDG uptake was well confined around the rectum, and no other lesions were found. *White arrow*, Bladder; *black arrowhead*, tumor. **B** FDG-PET scanning of the body 8 months postoperatively revealed neither recurrent lesion around the rectum nor metastatic lesion

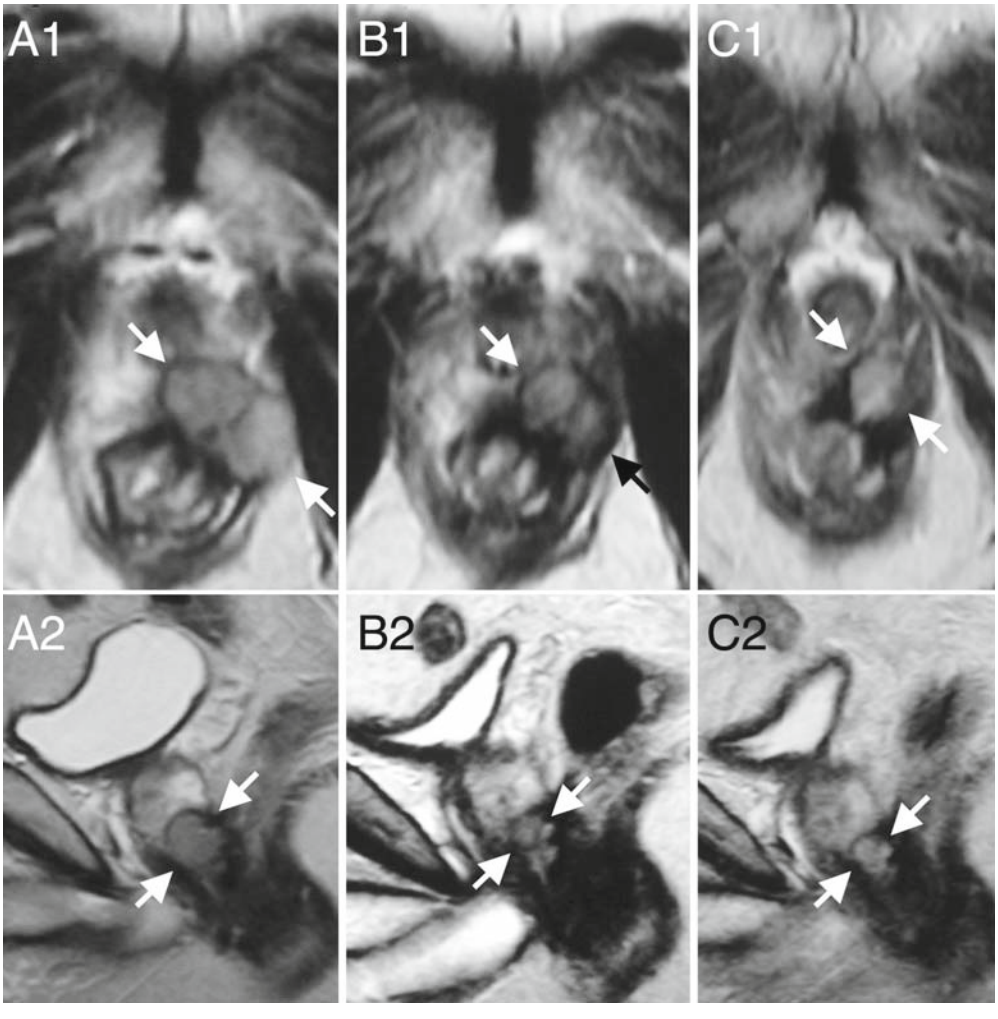

Fig. 2. A1, A2 Preoperative magnetic resonance (MR) T2-weighted images show tumor located just behind the prostate (*arrows*). The tumor size was 3.2×1.8×1.6 cm. **B1, B2** After administration of imatinib mesylate for about 1 month, the tumor size had decreased to 2.0 × 1.4 × 0.9 cm. **C1, C2** After 3 months' administration of imatinib mesylate, the tumor size had decreased to 1.2 × 1.2 × 1.2 cm, and the tumor had separated from the prostate

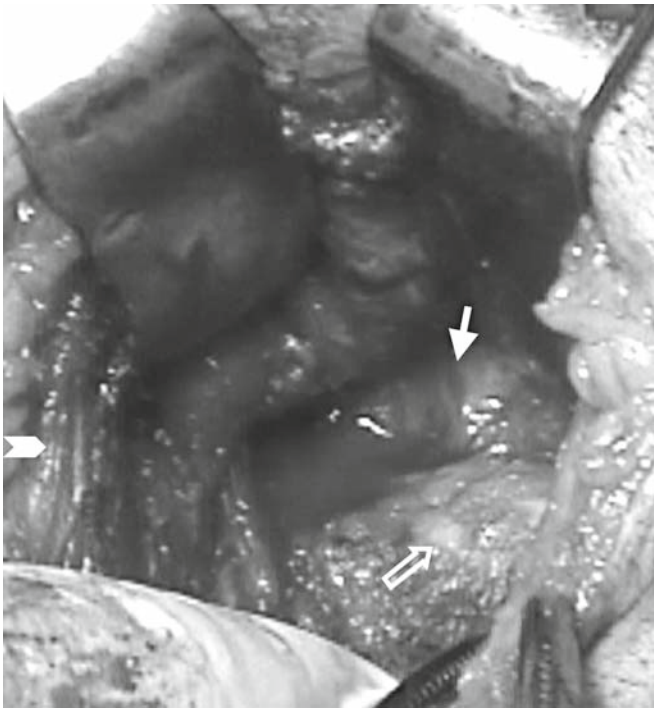

Fig. 3. Intraoperative findings. *Outlined white arrow* shows tumor on the rectal wall. The tumor was well separated from the prostate (*solid white arrow*). The external rectal sphincter muscle was separated from the longitudinal fibers of the ventral wall of the rectum and was elevated with a hook (*large horizontal filled white arrow on left of Fig.*)

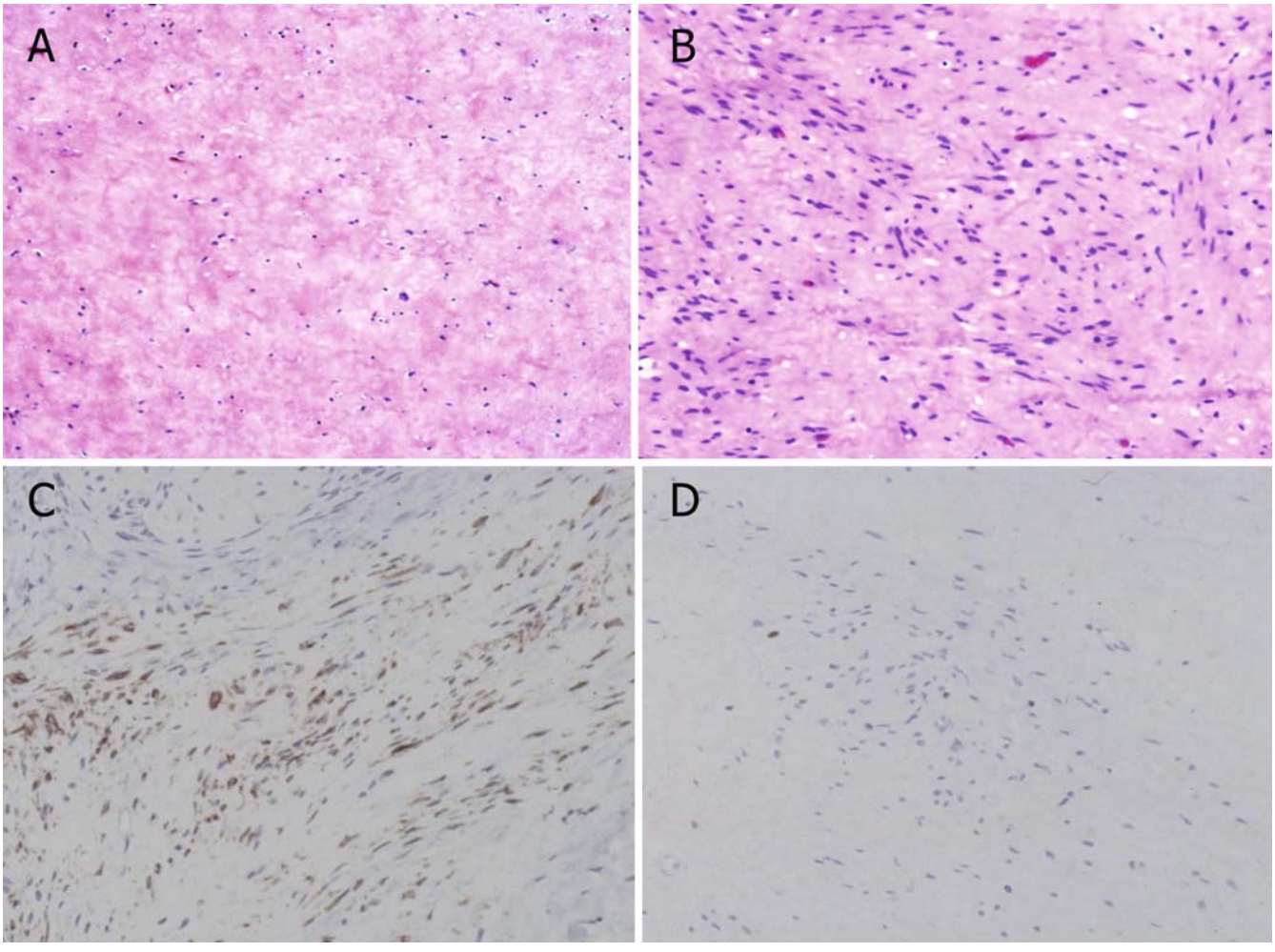

Fig. 4A–D. Microscopic views and immunohistochemistry of the excised tumor. **A** Most of the tumor cells had changed to myxohyaline stroma. **B** A small number of tumor cells survived. **C** Immunohistochemistry revealed that most of the surviving tumor cells were KIT-positive. **D** MIB1-positive cells were extremely rare. **A** ×25; **B, C, D** ×50

uptake only around the rectum (Fig. 1A). Magnetic resonance imaging (MRI)[5] showed a tumor, more than 3.0 cm in maximum diameter, that was located just behind the prostate (Fig. 2A1, A2). Complete resection was strongly anticipated with a fourth operation, but it was considered that injuries of both the urinary and bowel sphincters may not have been avoidable. On July 17, 2003, we started the oral administration of imatinib mesylate (Glivec) at 400 mg per day. MRI after 3 months of this treatment showed that the size of the tumor had decreased to 1.2 cm in diameter (Fig. 2C1, C2). Adverse effects of the drug included edema of the eyelids and periorbital tissues. Desquamation of the face and otorrhea were also observed. On December 12, 2003, a fourth operation was performed (Fig. 3), with a perineal approach, according to the procedure of Hudson and Lilien.[6] Pathological examination of the specimen revealed that most of the tumor cells had changed to myxohyaline stroma (Fig. 4A). A small number of tumor cells survived (Fig. 4B). Immunohistochemistry revealed the surviving tumor cells were KIT-positive (Fig. 4C) and CD34-positive, but few of them were MIB1-positive (Fig. 4D). The patient's postoperative course was uneventful and his continence was preserved. Because of the side effects and the cost of the drug, the administration of imatinib mesylate was not continued postoperatively. On August 4, 2004, F-18 FDG-PET scanning of the body revealed neither a recurrent lesion around the rectum nor a metastatic lesion (Fig. 1B). On June 28, 2005, the patient consulted our hospital complaining of anal discomfort. Though MRI, CT scan, and digital examination did not detect a recurrent lesion, we considered it was better to start administration of imatinib mesylate again at 400 mg/day. However, the patient had disliked the adverse drug reactions of efflorescence with bad desquamation and itching at the time he had taken the drug preoperatively and he did not wish to take the drug again at the normal dose (400 mg/day). However, we managed to start administration of imatinib mesylate again, at 100 mg/day. It was more effective than expected, and his symptoms disappeared after taking the drug. There has been no evidence of tumor recurrence for 42 months since the last operation.

Analysis of reported cases of rectal GISTs in Japan

Before the approval of imatinib mesylate for the treatment of GISTs in Japan, 29 cases of rectal GIST (KIT positive gastrointestinal stromal tumor) had been reported in Japan up to December 2003. The details of reported cases are summarized in Table 1; in addition, we have listed details of four cases from our experience at our hospital. The mean tumor size was 8.2 cm in diameter. The mean distance between the anal verge and the tumor was 4.2 cm. In 19 patients a permanent artificial anus could not be avoided[7] (there were 18 abdominoperineal resections and 1 total pelvic exenteration). Lymph node metastases were not reported.

Discussion

We have presented a case of a third recurrence of a rectal GIST. The patient presented with complaints of dysuria and anal pain, which severely affected his quality of life. In general, the tumor size and the mitotic index of a GIST are considered to reflect a patient's prognosis.[8,9] In our patient, the tumor measured 3.0 cm in diameter, but the mitotic index revealed highly aggressive activity.[10] As the tumor spread just behind the prostate gland and the external urethral sphincter, complete resection of the tumor may have induced incontinence and required an artificial anus. The tumor was well confined to the anterior rectal wall without evidence of distant metastases, and the surgical strategy for complete extirpation of the tumor was very important, in regard to avoiding any mistakes in making the excisional line.

We analyzed 33 cases of rectal GISTs reported in Japan (29 previously reported cases and 4 cases experienced at our hospital; none of these patients, except for the present patient, had been treated with imatinib mesylate. Considering the mean diameter of the tumor and the distance from the anal verge, sphincter-preserving operations were difficult to apply to rectal GISTs. As lymph node metastases are generally not seen in GISTs, downsizing the tumor may enable sphincter preservation.

Imatinib mesylate is a selective inhibitor of transmembrane receptor KIT protein tyrosine kinases. It inhibits the proliferation of GIST tumor cells that are stimulated by the activated KIT receptor. Demetri et al.[4] have reported patients with GIST recurrences that were treated effectively with imatinib mesylate, but there was no case of complete remission. According to the National Comprehensive Cancer Network (NCCN) Clinical Practice Guidelines, surgical strategy is advocated for a residual metastasis, if all viable tumor can be removed once the maximum response to imatinib mesylate has been reached.[11] There was no evidence of an appropriate premedication period for imatinib mesylate for recurrent GIST in July 2003, but no remarkable change was observed in tumor size measured by MRI in December 2003, compared with that in October 2003. As we considered that no further reduction of the tumor could be expected, the fourth operation was done after 5 months' administration of imatinib mesylate. However, the conventional transanal approach was not suitable for visualizing a clear margin, because the tumor had expanded mainly outside the rectal wall. We adopted the perineal approach of Hudson and Lilien[6] which enabled us to preserve the external sphincter muscle, and to visualize the tumor. With this procedure, the circumferential margin in our patient was clearly defined during the operation, especially from the prostate. Kuruma et al.[12] reported a case of GIST of the rectum that was difficult to differentiate from leiomyosarcoma of the prostate.

It is true that neoadjuvant treatment with imatinib has not been recommended outside a clinical trial (NCCN level 2A), but with function-sparing surgery, this strategy can be used as an exceptional situation.[13] Over 40 months after our

Table 1. Analysis of reported cases of rectal GISTs in Japan

Author	Age (years)	Sex	CC	Dist (cm)	Diameter (cm; max)	KIT	CD34	MF	OPE	Outcome	
Takahashi et al.[14]	57	F	Cons	NA	10	NA	(+)	3.6	APR	7 Months	A
Takahashi et al.[14]	33	F	NA	NA	7	NA	(+)	5.3	APR	10 Years 3 months	A
Takahashi et al.[14]	51	F	NA	NA	7.5	NA	(+)	1	LAR	9 Years 6 months	A
Takahashi et al.[14]	47	M	NA	NA	9	NA	(+)	2.5	APR	1 Year 7 months	D
Takahashi et al.[14]	44	M	NA	NA	7.5	NA	(+)	6	APR	6 Years	A
Yokoi et al.[15]	67	F	Cons	3	8	(+)	(+)	NA	APR	3 Years 6 months	A
Yamaguchi et al.[16]	66	F	AB	NA	5	(+)	(+)	1	NA	NA	NA
Imazu et al.[17]	70	M	ABP	3	5	(+)	(+)	NA	APR	10 Months	A
Yamaguchi et al.[18]	57	M	AD, ISU	2	7	(+)	(+)	NA	APR	1 Year	A
Ito et al.[b]	89	M	AB	NA	9	(+)	(+)	NA	APR	NA	A
Hirahara et al.[19]	71	M	AD	4	5	(+)	(+)	NA	APR	1 Year	A
Fukazawa et al.[20]	78	M	CONS	3	10	(+)	(+)	NA	LAR	NA	NA
Nozawa et al.[21]	80	M	AB	2[a]	11	(+)	(+)	4	APR	8 Months	A
Sawada et al.[22]	62	M	Tumor	3	4	(+)	(+)	NA	APR	1 Year	A
Tanaka et al.[b]	46	M	AB	15	12.5	(+)	(+)	NA	LAR	7 Months	D
Ogata et al.[23]	55	F	Tumor	NA	6	(+)	(+)	NA	APR	10 Months	A
Nakazaki et al.[24]	85	F	AB	NA	8	(+)	(+)	NA	APR	10 Months	A
Kuruma et al.[12]	70	M	ISU	NA	5	(+)	(+)	1.4	APR	19 Months	A
Kirizuka et al.[25]	75	F	AB	1	7.5	(+)	(+)	NA	APR	NA	NA
Saito et al.[b]	63	F	Tumor	NA	NA	NA	NA	NA	TPE	NA	NA
Takashima et al.[b]	53	M	AB	3	4.2	(+)	(−)	1	APR	1 Year 8 months	A
Kuratate et al.[b]	84	M	Tumor	3	3	(+)	(+)	NA	LE	NA	NA
Ishikawa et al.[26]	57	F	AP	NA	3.7	(+)	(+)	NA	APR	1 Year 6 months	A
Katsuno et al.[27]	56	M	AD	6	9.5	(+)	(+)	NA	LE	1 Year	A
Terao et al.[28]	51	M	Cons	NA	8	(+)	(+)	15	LE	4 Years	A
Nakayama et al.[29]	65	M	Cons	NA	35	(+)	(+)	NA	(−)	2 Months	D
Sasaki et al.[30]	53	F	AB	NA	6	(+)	(+)	NA	LE	1 Year 6 months	A
Kimura et al.[b]	49	M	AB	NA	8	(+)	(+)	NA	APR	NA	A
Suzuki et al.[31]	51	M	NA	NA	7	(+)	(+)	NA	AR	2 Years 10 months	A
Our patient 1	57	M	AD	5	3.5	(+)	(+)	1.4	APR	7 Years 2 months	D
Our patient 2	53	F	AB	1	6	(+)	(+)	5.6	APR	7 Years 2M	A
Our patient 3	32	M	AD	3	2.5	(+)	(+)	1.2	LE	11 Years 8 months	A
Present patient	60	M	AP	3	3	(+)	(+)	0.8	LE	3 Years 7 months	A
Mean	61.6			4.2	8.2			4.1			

CC, Chief complaint; AB, anal bleeding; ABP, abdominal pain; AP, anal pain; CONS, constipation; ISU, ischuria; AD, anal discomfort; NA, not available; Dist, distance between anal verge and tumor; LE, local excision; AR, anterior resection; APR, abdominoperineal resection; LAR, low anterior resection; A, alive; D, dead; MF, mitotic figure (no. of mitoses/10 hpf)

[a] About 2 cm

[b] Reported in Japanese without English abstract

patient's fourth operation, neither local recurrence nor distant metastasis was detected. To conclude. our strategy of treatment with imatinib allows not only complete excision of the tumor but it also reduces postoperative impediments in patients with recurrent rectal GISTs.

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