

Management of rectal gastrointestinal stromal tumor

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Abstract: Gastrointestinal stromal tumor (GIST) is the most common mesenchymal neoplasm of the gastrointestinal tract. However, rectal GIST is rare, the incident rate of it is approximately 5% of all GISTs. Rectal GIST symptoms generally include bleeding and/or pain and occasionally, urinary symptoms. Immunohistochemical evaluation finds that most rectal GIST tumors are CD117 (KIT) positive, and are sometimes CD34, platelet-derived growth factor receptor alpha (PDGFRA), smooth muscle actin, S-100, or vimentin positive. The National Institutes of Health (NIH) classifies rectal GIST as very-low risk, low risk, intermediate risk, or high risk, and the frequencies have been estimated as 0–23.8% for very-low risk, 0–45% for low risk, 0–34% for intermediate risk, and 21–100% for high risk tumors. The first-line treatment for localized GIST is curative resection, but is difficult in rectal GIST because of anatomical characteristics such as the deep, narrow pelvis and proximity to the sphincter muscle or other organs. Several studies noted the efficacy of the minimally invasive surgery, such as trans-anal, trans-sacral, trans-vaginal resection, or laparoscopic resection. The appropriate surgical procedure should be selected depending on the case. Imatinib mesylate (IM) is indicated as first-line treatment of metastatic or unresectable GIST, and clinical outcomes are correlated with *KIT* mutation genotype. However, the *KIT* mutation genotypes in rectal GIST are not well known. In this review, as in other GISTs, a large proportion (59–100%) of rectal GISTs carry exon 11 mutations. Although curative resection is indicated for localized rectal GIST, a high rate of local recurrence is a problem. Multimodal therapy including perioperative IM may improve postoperative outcomes, contributing to anus-preserving surgery. Moreover, *KIT* mutation analysis before IM treatment is important. This review summarizes current treatment strategies for rectal GIST.

Keywords: Gastrointestinal stromal tumor (GIST); rectal GIST; *KIT* mutation; imatinib mesylate (IM)

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Introduction

Gastrointestinal stromal tumors (GISTs) were first described by Mazur *et al.* in 1983 (1). GISTs are the most common mesenchymal neoplasms of the gastrointestinal tract and can have spindle-cell or epithelioid histology; 80% express the *KIT* protein and 10% express platelet-derived growth factor receptor alpha (PDGFRA) (2,3). Gain-of-function

mutations in the *KIT* proto-oncogene or *PDGFRA* are important in the genesis and classification of these tumors (3–6). These mutations are involved in GIST development, and result in the constitutive activation of *KIT* signaling (4). GISTs account for 0.1–3% of all malignant gastrointestinal neoplasms (7–9), and rectal GIST is rare, with an incidence of approximately 0.1% of all rectal neoplasms (10), and

Table 1 Clinical symptoms of rectal GIST

Authors	Year	No. of patients	Pain	Bleeding	Change of bowel habit	Constipation	Tumor	Urinary symptom	Others
Hamada (22)	2008	33	3.0%	30.3%	–	15.2%	12.1%	3.3%	36.1%
Agaimy (25)	2013	15	–	46.7%	–	–	53.3%	13.3%	–
Pai (23)	2015	13	38.5%	23.0%	–	–	–	–	38.5%
Shen (24)	2015	45	17.8%	28.9%	24.4%	–	–	6.7%	22.2%
Wilkinson (26)	2015	19	21.0%	36.8%	31.6%	–	–	–	31.6%

GIST, gastrointestinal stromal tumor.

comprises approximately 5% of all GISTs (11).

Curative resection is the first-line treatment for localized GISTs in all organs, but is difficult in rectal GIST because of anatomical features including the deep, narrow pelvis and proximity to the sphincter muscle or other organs. Several studies have reported the efficacy of multimodality therapy for rectal GIST, including perioperative imatinib mesylate (IM) treatment. Laparoscopic surgery or anus-preserving surgery for rectal GIST preserves patient quality of life (QOL). This review discusses the current treatment of rectal GIST.

Epidemiology

GIST may occur anywhere in the gastrointestinal tract, but its frequency is mostly in the stomach (60–70%) followed by small intestine (25–30%), rectum (5%), and colon (1%) (12). Furthermore, GIST may also occur as primary tumors outside of the gastrointestinal tract proper as intra-abdominal locations in the mesenteries, omentum, retroperitoneum, or pelvis (12–14). Colorectal GIST was reported to account for 6.3% of cases in western Sweden (15), and other studies reported that rectal GIST accounted for 3.5–5% of all cases (15–17). The annual incidence of GIST is approximately 1.1–1.45 per 100,000 population (15,17) and the overall incidence has been estimated as 10–20 per 100,000 population including incidental, minimal tumors (18). Rectal GIST accounts for 4% of all GISTs, or 800–1,000 new cases in the European Union each year (15,17,19). Hawkins *et al.* found that 333 anorectal GIST patients were registered in the National Cancer Database, that their mean age was 62.3 years, and that the median tumor size was 4.0 cm (20).

Rectal GISTs are also rare in eastern countries, accounting for approximately 0.1% of all rectal neoplasms in South Korea (10). Yasui *et al.* reported that of 737 GIST

patients evaluated between 2003 and 2007 in Japan, 24 (3.3%) were rectal GISTs (21). All were in the lower rectum, within a median of 2.5 cm from the anal verge (21). Hamada *et al.* reported 33 rectal GISTs in Japan before the era of IM. The mean age was 61.6 years, the maximum tumor size was 8.2 cm, and the mean distance from the anal verge was 4.2 cm (22).

Diagnosis

Baik *et al.* reported seven cases of rectal GIST in South Korea with primary symptoms of hematochezia, constipation, and anal pain similar to those of other rectal tumors (10). In a case series in India, the main primary symptoms were pain (38.5%), bleeding (23.0%), and others (38.5%) (23). Shen *et al.* described bleeding (28.9%), pain (17.8%), difficulty with defecation (11.1%), urinary complaints (6.7%), and other symptoms (11.1%) in 45 cases of rectal GIST (24). In a patient series in Japan the chief complaints were anal bleeding (30.3%), constipation (15.2%), anal discomfort (12.1%), palpitation of tumor (12.1%), abdominal pain (3.0%), and ischuria (3.0%) (22). *Table 1* summarizes the most common symptoms of rectal GIST, which are primarily bleeding and/or pain; urinary symptoms may occur more frequently than in GISTs at other sites (22–26).

GISTs of the stomach, colon or rectum generally appear as a submucosal mass in endoscopy (27), and are diagnosed in biopsy tissue. In rectal GISTs, immunohistochemical analysis can be CD117 (KIT) positive dominantly, CD34, PDGFRA, smooth muscle actin, S-100, and vimentin positive occasionally (28). Rectal GISTs are classified as very-low risk, low risk, intermediate risk, or high risk tumors by National Institutes of Health (NIH) criteria (29), and the frequency of recurrence has been estimated as 21–100% for high risk, 0–34% for intermediate risk,

Table 2 The recurrent risk in rectal GIST by NIH criteria

Authors	Year	No. of patients	Very-low risk	Low risk	Intermediate risk	High risk
Farid (30)	2013	9	0%	0%	22.0%	78.0%
Liu (31)	2014	21	23.8%	23.8%	28.6%	23.8%
Zhou (28)	2014	67	0%	45.0%	34.0%	21.0%
Shen (24)	2015	45	8.9%	22.2%	2.2%	66.7%
Wilkinson (26)	2015	19	0%	0%	0%	100%
Yasui (21)	2017	24	20.8%	33.8%	0%	45.8%

GIST, gastrointestinal stromal tumor; NIH, National Institutes of Health.

0–45% for low risk, and 0–23.8% for very-low risk tumors (21,24,26,28,30,31) (Table 2). A diagnosis of GIST in the rectum was also considered to correlate with poor overall prognosis. However, Fletcher *et al.* reported that tumor site was not a reliable predictor of outcome (29). One reason for the poor prognosis of rectal GISTs is that the tumor rupture rate is more than four-fold higher than that of non-rectal GISTs (30).

GISTs are usually seen as an exophytic mass that heterogeneously enhances with intravenous contrast because of its high vascularization (32), and contrast enhanced computed tomography (CT) is the standard method of GIST imaging (33). Magnetic resonance imaging (MRI) is useful for liver-specific lesions or patients contraindicated for CT (33). Fluorodeoxyglucose positron emission tomography (FDG-PET) also has good specificity and sensitivity for evaluation of tumor response after IM treatment (32). However, FDG-PET cannot be used to evaluate treatment response if pretreatment FDG-PET was negative. Approximately 20% of lesions shown on CT do not display appreciable glucose uptake on pretreatment FDG-PET images (32). The imaging characteristics of rectal GISTs have been described by Jiang *et al.* (34). Enhanced MRI with direct multiplanar capability is useful in determining the exact origin tumor of pelvic tumors, which is often difficult to confirm. The imaging technology using MRI can detect invasion of adjacent organs in greater detail than possible with CT (34).

Treatment

Surgery

Surgical resection with curative intent is the standard treatment for localized GIST (35). Complete excision of the tumor is the most significant factor related to outcome, and

can be accomplished in 40–60% of all GIST patients (36). The benefit of histologically negative margins in the surgical treatment of non-metastatic rectal GIST has been confirmed (19). Since GIST may occur anywhere in gastrointestinal tract, the surgical approach varies, with local excision by trans-anal, trans-sacral, or trans-vaginal procedures as the preferred treatments for early, lower rectal GISTs (37). On the other hand, the treatment of advanced rectal GISTs is controversial. Complete curative resection of rectal GISTs is difficult because of its anatomical features (35), and choice of the surgical procedure may be difficult in patients with large tumors close to the anal verge. Rectal GISTs have a high rate of local recurrence regardless of the surgical procedure (21). Surgical treatment is yet to be standardized (20), but local resection, low anterior resection, abdominoperineal resection (APR), and pelvic exenteration are performed. In each procedure, the objective is complete gross resection with negative microscopic margins and without bleeding or rupture of the pseudo capsule (38).

Trans-anal resection is one of the most minimally invasive approaches, but is limited by the distance from the dentate line (39). Trans-coccygeal excision is effective for the lower rectal GISTs, but has high postoperative morbidity, with fistulae occurring in 21% of patients (40). Matsushima *et al.* described a trans-coccygeal/trans-sacral approach that is relatively less invasive and recommended it as the treatment of choice for rectal GISTs because proper bowel preparation, prophylactic antibiotics, and adequate drainage reduce postoperative complications such as fistulae (41). Kinoshita *et al.* recommended a perineal approach as an option to preserve the anal function in patients with GISTs involving the anterior wall of the lower rectum (42). For small rectal GISTs, local resection may be safe (20). In a series of seven rectal GIST patients with curative

resection before the IM era (10), two (28.6%) experienced local recurrence. One patient had undergone Hartmann's procedure for a 12-cm tumor with local recurrence in the rectum. The second, with APR for a 6 cm tumor experienced local recurrence in the presacral area. Positive resection margins are associated with poorer survival (31), and margins free of tumor cells are most important regardless of the surgical procedure. The need for wide margins is controversial (36). McCarter *et al.* reported that there was no difference in recurrence-free survival between R0 and R1 margin surgery in GIST (43). Therefore, we should select appropriate surgical procedure from the anus preserving point of view, especially for rectal GIST's patients.

Laparoscopic surgery has been successful for resection of rectal GISTs (35,44-47), including anus-preserving surgery (46). Laparoscopic colorectal surgery is beneficial because of its minimal access trauma (35). Adequate visualization of deep pelvic lesions is possible. Although the data on laparoscopic surgery for rectal GISTs are limited, this approach seems feasible, especially for small tumors (48).

Prognostic factors of rectal GISTs have been identified. In a series of 21 patients, Xiao *et al.* reported a 5-year overall survival (OS) of 46%, with NIH high risk and hematochezia as independently associated with disease-free survival (DFS) (49). In another series, tumor size >5 cm was identified as the most important determinant of survival after surgery; age [hazard ratio (HR), 2.40; 95% confidence interval (CI), 1.77-3.25], tumor size (HR, 2.24; 95% CI, 1.35-3.73) were associated with increased mortality (20). Tumor size and mitotic index have also been identified as prognostic factors (50). Gold *et al.* developed a nomogram to predict 2- and 5-year recurrence-free survival after curative surgical resection of localized GISTs (48,50). Lymph node dissection is not considered necessary because lymph node metastasis of GISTs is very rare (10).

IM therapy for advanced/metastatic GIST

IM is a selective inhibitor of transmembrane receptor KIT protein tyrosine kinases. It acts by inhibiting the proliferation of GIST cells that are stimulated by activated KIT receptors (51,52). IM is indicated for the first-line treatment of metastatic or unresectable GIST. An international, large-scale phase II study (B2222) (6) demonstrated that IM was safe and highly effective for

advanced GIST. Moreover, a phase II study (STI571B1202) in Japan also found that IM was generally safe for advanced GIST (53). Kanda *et al.* reported a 5-year OS of 60.9% and median survival of 70 months with a median follow-up of 68 months after IM therapy for advanced GIST, and IM treatment was also well tolerated in Japan (54). Several studies have assessed patients with rectal GIST and have reported that IM therapy showed antitumor effects for advanced rectal GIST and common-site GISTs (19-23).

GISTs share many phenotypic features associated with various *KIT* and *PDGFRA* mutations (55). Heinrich *et al.* described the correlations of kinase genotype and clinical outcome of IM treatment of GIST (CALGB 150105) (56). The objective response rate reported as complete response (CR)/partial response (PR) was 71.7% with tumors carrying exon 11 mutations, 44.4% with exon 9 mutations, and 44.6% with wild-type tumors (56). *KIT* mutations involving codons 557-558 were reported to have a poor prognosis (57). Andersson *et al.* found that 57% of GIST patients had *KIT* mutations of exon 11, and that approximately 60% were deletion and 40% were missense or duplication mutations (55).

The *KIT* mutation genotypes in rectal GIST are not well known, but have been described in several studies, which are listed in *Figure 1* (23-26,58). As seen in GISTs developing at other sites, a large proportion (59-100%) of rectal GISTs carried exon 11 mutations. We previously characterized the *KIT* mutations in nine of 12 rectal GIST patients (unpublished data), all of whom were found to have exon 11 mutations. Okamura *et al.* have confirmed that the exon 11 mutations in colonic GIST are like those present in stomach and small intestinal GIST (59). As exon 11 *KIT* mutations are the most frequent mutation genotype in rectal GIST, IM can be considered as a first-line treatment of advanced or metastatic rectal GISTs.

Figure 2 shows an enhanced CT image of our patient with rectal GIST. The patient was a 41-year-old woman with a locally advanced rectal GIST. Laparotomy revealed that the tumor was unresectable owing to tumor rupture. The patient underwent IM therapy as primary chemotherapy. The tumor markedly shrank with 18 months of treatment; the maximum diameter changed from 14 to 5 cm, which is a 64.3% reduction. The patient then underwent secondary surgery and finally achieved complete tumor resection. Histopathological examination of the resected tumor revealed viable tumor cells that accounted for only 20% of the residual tumor.

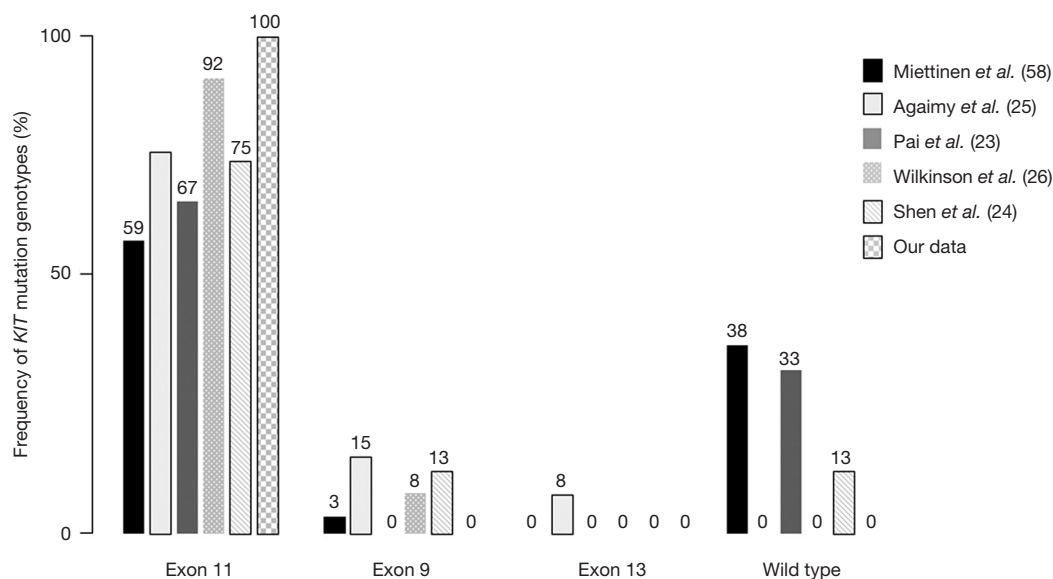


Figure 1 *KIT* mutation genotypes in rectal GISTs. A large proportion of patients have rectal GISTs with exon 11 mutations. GIST, gastrointestinal stromal tumor.

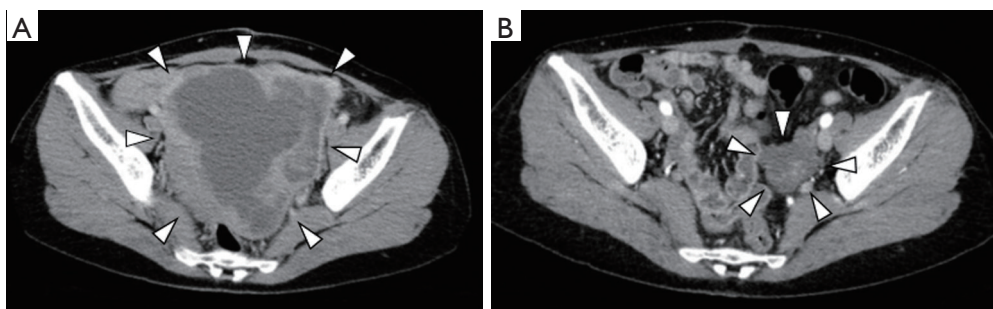


Figure 2 Enhanced pelvic CT scan of a large rectal GIST (A) with maximum diameter of 14 cm imatinib therapy and (B) 5.0 cm 18 months after initiation of the treatment (arrowheads). GIST, gastrointestinal stromal tumor; CT, computed tomography.

Combined modality therapy for rectal GIST

Curative resection is an appropriate treatment for rectal GIST, but the recurrent rate is 25% even in patients with low risk tumor (21). Perioperative treatment with IM may improve outcomes (19-23) and anus-preserving treatment is an important concern because a postoperative stoma decreases a patient’s QOL. Tielen *et al.* reported that preoperative IM led to a decrease in the size of rectal GISTs, but did not lead to less extensive surgery (60). None in a series of seven rectal GIST patients with curative resection before the era of IM experienced anus-preserving surgery (10), and in another series, the anus-preserving rate was 33% in despite preoperative IM treatment (23). In

Table 3, the anus-preserving rate with rectal GIST is summarized. Before IM treatment, the anus-preserving rate was 14.2%; after IM treatment, the rate was 33.0–94.9%. Perioperative IM treatment may be promising, but its benefit in anus-preserving surgery in rectal GIST is controversial, and requires further study.

Fujimoto *et al.* demonstrated the safety and successful use of laparoscopic intersphincteric resection of rectal GIST following IM treatment in a series of five patients (45). The benefits of laparoscopic surgery include an excellent, magnified view in the deep, confined space of the pelvic cavity that enables sphincter and continence conserving surgery (35,44). As there are few reports of the effectiveness

Table 3 Anus-preserving rate of the surgery for rectal GIST

Authors	Year	No. of patients	M/F	Age	Size (cm)	Distance from the anus (cm)	Neoadjuvant IM	Anus-preserving rate
Baik (10)	2007	7	2/5	54	6.6	4.1	0%	14.2%
Jakob (19)	2013	39	29/10	53	5.0	N/A	41.0%	94.9%
Tielen (60)	2013	32	22/10	60	9.3 [†] , 6.0 [‡]	5.9 [†] , 5.3 [‡]	68.8%	37.5%
Agaimy (25)	2013	15	8/7	55	4.8 [§]	N/A	25.0%	75.0%
Shen (24)	2015	45	33/12	55	5.0	N/A	6.7%	71.1%
Pai (23)	2015	13	11/2	53	N/A	2.0	100%	33.0%
Wilkinson (26)	2015	19	11/8	57	7.6	N/A	78.9%	84.2%
Yasui (21)	2017	24	14/10	67	N/A	2.5	16.7%	50.0%

[†], data in patients with imatinib treatment; [‡], data in patients without imatinib treatment; [§], mean. GIST, gastrointestinal stromal tumor; IM, imatinib mesylate; N/A, not applicable.

of laparoscopic resection of rectal GIST following IM treatment, further studies are necessary.

Surgical resection combined with adjuvant IM is expected to improve not only surgical outcome but also survival one. The evidence from randomized trials supports 36 months of adjuvant IM in high risk GIST (61-63). It is important to evaluate the risk of recurrence because rectal GISTs, especially large tumors, have a high risk of recurrence, because of difficulty of curative resection. Tang *et al.* reported that IM treatment facilitated surgery for very large GISTs, avoided tumor rupture, and was associated with low surgical morbidity (64). In patients with tumors >5 cm, 5-year mortality in chemotherapy patients (79.2%) was better than that in patients without chemotherapy (51.2%, $P=0.03$). Hawkins *et al.* reported that preoperative IM treatment resulted in improved survival of patients with tumors >5 cm, treated with radical resection (20), but further study is necessary.

The resection with negative margins of rectal GISTs is most important; wide margins are not generally necessary if a non-residual tumor resection is obtained (36). Preoperative IM has been shown to significantly increase the achievement of negative margins and curative resection and to improve local DFS (19). In a series of 36 rectal GIST patients treated with surgery (19), five (13.9%) developed a local recurrence within a median of 12 months. The patients with local recurrence had not undergone curative resection, and had not received perioperative IM therapy. In another series of 45 patients, Shen *et al.* reported that DFS of patients with NIH high risk tumors was significantly improved by IM treatment (24), and

found that risk category was the only prognostic factor independently associated with DFS (HR, 1.62; 95% CI, 1.034–2.551). Preoperative IM treatment has also been associated with an increased rate of curative resection, and may facilitate surgical procedures at critical anatomic sites, which have been associated with improved DFS (60) and improved prognosis in rectal GIST (19). The DFS benefit of perioperative IM treatment in patients with intermediate risk and high risk rectal GIST ($P=0.030$) was demonstrated by Liu *et al.* (31). On the other hand, when the preoperative treatment is done, there is a possibility that the preoperative treatment may affect the pathological evaluation of the tumor. In that case, we cannot make the risk evaluation appropriately.

In the era of IM, *KIT* mutation genotype analysis in pretreatment biopsy samples greatly assists the choice of treatment (19). Genotyping to identify likely non-responders is important to ensure that a window of opportunity is not missed by delaying surgery in patients who would not benefit from IM or who would benefit from dose escalation (26).

In general, radiotherapy is restricted to symptomatic palliation patient with GIST (65). However, the efficacy of radiotherapy in combination with tyrosine kinase inhibitors for metastatic or advanced GIST has been reported by some researchers (65,66). Ciresa *et al.* described that the introduction of molecularly targeted therapy combined with radiation therapy could improve the outcomes of patients with GIST (65), but the role of radiotherapy for GIST is controversial. Further studies are warranted to investigate combined modality therapy for rectal GIST patients.

Conclusions

Curative resection should be performed for localized rectal GIST. Combined modality therapy, including perioperative IM treatment, is recommended for advanced rectal GIST to facilitate anus-preserving surgery and improve the prognosis. *KIT* mutation genotype analysis before treatment is important. Further studies of perioperative treatment of patients with rectal GISTs are required to establish an appropriate treatment strategy.

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Footnote

Conflicts of Interest: The authors have no conflicts of interest to declare.

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