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REVIEW ARTICLE

Neoadjuvant imatinib therapy in rectal gastrointestinal stromal tumors

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Abstract
Rectal gastrointestinal stromal tumor (GIST) is a rare entity. Thus, its clinical features have not been well documented, and optimal treatment strategies have not been established. Surgery for rectal GISTs may be difficult because they are often large in size. In addition, rectal GISTs were found to be associated with high rates of local recurrence, regardless of the surgical procedure, before imatinib was introduced in the early 2000s. Since the introduction of imatinib therapy, accumulating evidence suggests that neoadjuvant imatinib therapy may improve the outcomes of rectal GIST treatment. Neoadjuvant imatinib therapy for rectal GISTs offers a number of potential benefits, including tumor downsizing, reduction in mitotic activity, reduced morbidity, and a reduced risk of recurrence. Less radical procedures may allow for the preservation of the anal sphincter and avoidance of a permanent colostomy. This review summarizes the current status and future perspectives of neoadjuvant imatinib therapy for the treatment of rectal GISTs.

Keywords Neoadjuvant therapy · Imatinib · Gastrointestinal stromal tumor · Rectum

Introduction

Gastrointestinal stromal tumors (GISTs) are the most common mesenchymal tumors of the gastrointestinal tract, commonly arising in the stomach (50%) and the proximal small intestine (35%) but rarely in the rectum (5%) [1, 2]. Surgery is the mainstay of therapy for GISTs, and the main goals of surgical treatment of rectal GISTs are to achieve negative resection margins and to preserve the anal sphincter. However, this can be challenging because rectal GISTs are often large in size, and the procedure is performed in the anatomically narrow pelvic space [3, 4]. Thus, there are no established standard treatment strategies for rectal GISTs at present because of their rarity.

Negative surgical margins are desirable because recurrence following surgical resection of rectal GISTs predominantly develops in a locoregional pattern; the rate of local recurrence was reportedly 71% for tumors of > 5 cm with a mitotic index (MI) of ≤ 5/50 high-power field (HPF), and 55% for tumors regardless of size, with an MI of > 5/50 HPF according to Miettinen's investigation [5, 6]. These recurrence patterns are very different from those of GISTs in other anatomic sites, which are mainly intra-abdominal dissemination and liver metastasis [7]. There are three different classifications of recurrence risk: the National Institutes of Health (NIH) consensus criteria, Miettinen's criteria, and the modified NIH consensus criteria (Table 1) [6, 8, 9]. The risk is different for each organ with Miettinen's criteria and the modified NIH consensus criteria [6, 8]. However, Miettinen's criteria, which have been used most frequently in recent studies of rectal GISTs [3, 10–13], were established based on insufficient data. In contrast, in the newest modified NIH criteria, GISTs of the small intestine and rectum are not differentiated. Therefore, these classifications seem to be incomplete. It is important to carefully determine which risk classification was used when referring to the literature.

Imatinib mesylate, an adenosine triphosphate analog, is a specific tyrosine kinase receptor inhibitor. For GISTs, the effectiveness of imatinib was first described in 2001; an impressive regression of multiple metastatic lesions was observed in a patient with GIST [14]. In February 2002, its use at a dose of 400–600 mg/day was approved by the US

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Table 1 Risk stratification of rectal gastrointestinal stromal tumor

Tumor parameter			NIH criteria[a]	Miettinen criteria[b]	Modified NIH criteria[c]
Mitotic count	Tumor size	Tumor rupture		Large intestine	Non-gastric
≤5/50 HPF	≤2 cm	No	Very low	None	Very low
	>2, ≤5 cm	No	Low	Low	Low
	>5, ≤10 cm	No	Intermediate	Insufficient data	High
	>10 cm	No	High	High	High
6–10/50 HPF	≤2 cm	No	Intermediate	High	Intermediate
	>2, ≤5 cm	No	Intermediate	High	High
	>5, ≤10 cm	No	High	Insufficient data	High
	>10 cm	No	High	High	High
>10/50 HPF	Any	No	High	–	High
Any	Any	Yes	–	–	High

NIH National Institutes of Health, *HPF* high-power fields

[a]Fletcher et al. [9]; [b]Miettinen et al. [6]; [c]Joensuu [8]

Food and Drug Administration for the treatment of metastatic and unresectable GISTs. In an open-label, randomized, multicenter study conducted in the United States and Finland, 53.7% of patients with advanced GISTs exhibited a partial response (PR) and 27.9% had stable disease (SD), while a European Organization for Research and Treatment of Cancer Phase I study reported a PR rate of 52.7% [15–18]. During the last decade, imatinib has been investigated in an attempt to increase surgical complete resection rates and achieve sphincter preservation and has provided a new approach for the treatment of rectal GISTs in neoadjuvant settings [3, 10–13, 19–38].

We herein review the current knowledge regarding neoadjuvant imatinib therapy for rectal GISTs.

Neoadjuvant imatinib therapy for rectal GISTs

The role of neoadjuvant imatinib therapy is an evolving area of research. Tumor downsizing with imatinib may be a promising strategy to create safe surgical margins that reduce the risk of local recurrence, allow less invasive surgery, and decrease surgical complications. Furthermore, the risk of tumor rupture during surgical manipulation is reduced after a significant tumor response. Another potential benefit of neoadjuvant imatinib for rectal GISTs is that it may enhance the chance of sphincter-preserving surgery if the response is good. The European Society for Medical Oncology (ESMO) guidelines recommend considering neoadjuvant imatinib treatment if R0 tumor resection is not feasible or if it might be achieved through less-mutilating surgery in the case of cytoreduction [39]. In addition, the National Comprehensive Cancer Network (NCCN) guidelines for soft tissue sarcoma recommend preoperative treatment with imatinib for GIST that is resectable with negative margins but with a risk of significant morbidity [40].

Neoadjuvant imatinib therapy for rectal GISTs was first reported in 2005, with the aim of achieving negative resection margins and anal sphincter preservation [19]. In several small studies and case reports, neoadjuvant imatinib therapy has been shown to reduce the size of large rectal GISTs, improving the chances of successful radical surgery, decreasing surgical morbidity, and successfully downsizing tumors to allow for local excision [3, 10–13, 19–38]. The most recently reported surgical techniques for low rectal GISTs to preserve the anal sphincter are intersphincteric resection (ISR) and transanal minimally invasive surgery following neoadjuvant imatinib therapy [24, 36]. Long-term oncologic outcomes of both procedures remain to be fully elucidated.

Given the widespread application of multidisciplinary approaches for rectal GISTs, we should enhance our understanding of neoadjuvant imatinib therapy.

Duration of neoadjuvant imatinib therapy

The optimal duration of neoadjuvant imatinib therapy remains controversial. The main limitation of this therapy is the development of secondary resistance related to additional *KIT* mutations. The general consensus is that imatinib should be continued until the maximal response is noted. The maximal response is defined as no further improvement between two successive computed tomography (CT) scans, which can take as long as 12 months [41, 42]. The NCCN guidelines mention that the maximal response may require treatment for 6 months or more [40].

Previous studies on neoadjuvant imatinib therapy for rectal GISTs have reported that the median treatment duration before surgery ranged from 3 to 19 months [3, 10–13, 24,

30, 34, 35]. Surgical resection should then be performed. However, it is not always necessary to wait for a maximal response to perform surgery. A multidisciplinary team should follow these patients closely and reevaluate the decision for surgery versus continuation of neoadjuvant imatinib after every imaging series.

Response rates and genetic mutations

Two phase II studies have evaluated neoadjuvant imatinib therapy in all-site or gastric GISTs [21, 43]. The RTOG 0132/ACRIN 6665 study was a prospective phase II study evaluating the use of imatinib in the neoadjuvant setting for all-site GISTs, with promising results for its efficacy and safety [21]. In the RTOG 0312/ACRIN 6665 study, the PR rate was 7%, and the SD rate was 83% among patients with primary GISTs of all organs. Kurokawa et al. reported a phase II study evaluating neoadjuvant imatinib for large gastric GISTs, with a PR rate of 62% and an SD rate of 38% [43]. Another phase II study used imatinib preoperatively for all-site GISTs; however, patients in the study only received imatinib within 7 days of surgery [44]. There have been no prospective studies targeting rectal GISTs alone, and only retrospective studies have been performed.

For primary rectal GISTs, neoadjuvant imatinib can induce tumor shrinkage, although a complete response (CR) is rare. In 9 retrospective series assessing 118 patients who had rectal GISTs treated with neoadjuvant imatinib, 5 patients (4.2%) had a CR, 78 patients (66.1%) had a PR, 35 (29.7%) had SD, and 1 (0.8%) had progressive disease according to the Response Evaluation Criteria in Solid Tumors, following preoperative imatinib therapy for 1–62 months [3, 10–13, 24, 30, 34, 35].

Imatinib selectively inhibits c-KIT and platelet-derived growth factor receptor alpha (PDGFRA) tyrosine kinase [45–47]. The presence and type of *KIT* mutations have been found to predict the response to tyrosine kinase inhibitors in recent studies. In GISTs, mutations involving *KIT* exon 11 may benefit most from imatinib [45]. Other mutations, such as *KIT* exon 9, may require a higher dose of imatinib. Patients with exon 11 mutations have a better CR/PR rate (63–83.5%) than those with exon 9 mutations (25–47.8%) or no detectable mutations (wild-type) (0–37%) [46, 48–50]. Furthermore, exon 11 *KIT* mutations were associated with a longer overall survival than those whose tumor expressed either exon 9 KIT mutations or had no detectable mutation [46]. In contrast, a common subset of patients with *PDGFRA* mutations (D842V) does not respond to imatinib [51].

The *KIT* mutation genotypes in rectal GISTs are not well described but have been investigated in several studies on neoadjuvant imatinib for rectal GISTs. Exon 11 of *KIT* was the most frequent site of KIT mutations (57–100%), followed by exon 9 (0–29%) (Table 2) [3, 10–13, 34, 35]. A molecular analysis should be performed if neoadjuvant imatinib therapy is being considered. For patients with wild-type or *PDGFRA* D842V mutant GISTs, we should not prescribe neoadjuvant imatinib [46]. The Gastrointestinal Stromal Tumor Meta-Analysis Group analyzed data from a meta-analysis of 1640 patients and found that, for patients whose tumor harbors an exon 9 *KIT* mutation, which confers relative resistance to adjuvant imatinib, an initial dose of 800 mg per day may be preferred, if tolerated [52]. For other patients, the usual dose of imatinib for neoadjuvant therapy is 400 mg daily. In seven studies in which the mutational status was available, all except 1 included non-responders with wild-type or *PDGFRA* mutations. Thus, response rates may be higher in select patients than previously reported data indicate (CR 4.2%, PR 66.1%, SD 29.7%, PD 0.8%) when their mutation status is determined.

R0 resection rates

Surgical resection is the treatment of choice for potentially resectable GISTs. Local recurrence of rectal GIST has been reported in 33–77% and 29–31% of cases after wide local excision and radical resection, respectively [53, 54]. Furthermore, 38% of patients with rectal GISTs are at risk of incomplete resection despite extensive procedures [55]. Therefore, neoadjuvant imatinib has recently been used when a tumor is locally advanced or for a potentially resectable primary tumor if a reduction in tumor size would decrease the morbidity of surgical resection and increase the chance of R0 resection. In 9 previous studies of neoadjuvant imatinib for rectal GISTs, 106 of 118 patients (89.8%) underwent surgery after neoadjuvant imatinib therapy. Among these, the R0 resection rates ranged from 77.3 to 100% [3, 10–12, 24, 30, 35]. These results are considerably better than those of the pre-imatinib era [3, 13, 53]. Negative resection margins have been reported to be associated with an improved local disease-free survival [10, 35]. Thus, neoadjuvant imatinib therapy may contribute to good local control.

Anal sphincter-preserving surgery rates

Tumor downsizing with imatinib might be crucial for achieving less-invasive surgery with a decreased risk of functional morbidity and neurologic impairments (e.g., sexual and urological dysfunctions). Even patients with smaller perianal lesions may benefit from neoadjuvant therapy if sphincter-preserving surgery instead of abdominoperineal resection can be performed afterward. Previous studies in the pre-imatinib era reported that the sphincter-preserving surgery rates were 28.5–54.8% [4, 55]. Among

Table 2 Clinical outcomes of neoadjuvant imatinib therapy for rectal gastrointestinal stromal tumor

References	Patients who received neoadjuvant imatinib (*n*)	High risk (*n*)	Mutation site (KIT exon11/KIT exon 9/KIT exon13/PDGFRA/wild-type) (%)	Duration of imatinib therapy (months), median (range)	Response rates (%) (CR/PR/SD/PD)	Patients who underwent surgery (*n*)	Sphincter-preserving surgery rates (%)	Surgical margin (R0/R1/R2) (*n*)	Follow-up period (months), median (range)	Survival outcome
Machlenkin [30]	9	5[a]	NA	3 (1−8)	11/67/22/0	7	85.7	6/1/0	32 (9−78)	2: local recurrence (after 6 and 36 months). 1: liver metastases (after 18 months). One patient died from GIST after 78 months
Tielen [3]	22	22[b]	57/29/0/0/14	9 (2−53)	0/73/27/0	22	41	17/4/1	39 (4−238)	1: local recurrence (after 38 months). 2: distant metastases (after 21 and 30 month). Two patients died from GIST after 10 and 32 months
Jakob [10]	16	14[b]	70/26/0/4/0	14 (6−60)	0/75/25/0	16	NA	14/2/0	NA	No recurrence or death
Huynh [34]	12	NA	83/8/0/0/8	7 (2−12)	8/67/25/0	12	83.3	NA	NA	NA
Fujimoto [24]	5	NA	NA	10 (4−12)	0/60/40/0	5	100	5/0/0	36 (13−51)	No recurrence or death
Liu [35]	5	2[c]	100/0/0/0/0	6 (6−8)	0/100/0/0	5	100	5/0/0	48 (38−68)	1: local recurrence (after 28 months)
Wilkinson [11]	15	15[b]	75/13/0/0/13	19 (10−45)	20/80/0/0	9	77.8	9/0/0	NA	No recurrence. Two patients died from GIST
Pai [12]	13	NA	67/0/0/0/33	12 (5−43)	0/54/38/8	9	33.3	7/2/0	34 (8−62)	1: distant metastases (after 6 months). Estimated 5-year OS: 90%
Cavnar [13]	21	13[b]	68/3/3/0/26	7.7 (3−62)	0/42/58/0	21	NA	NA	NA	NA

GIST gastrointestinal stromal tumor; *CR* complete response; *PR* partial response; *SD* stable disease; *PD* progressive disease; *NA* not available; *OS* overall survival

[a]Classified by National Institutes of Health (NIH) criteria; [b]Classified by Miettinen criteria; [c]Classified by modified NIH criteria

the seven previous studies on neoadjuvant imatinib for rectal GISTs, five reported high sphincter-preserving surgery rates (77.8–100%), whereas two studies reported low sphincter-preserving surgery rates (33.3–36.4%) (Table 2) [3, 11, 12, 24, 30, 34, 35].

Surgical procedures differ among institutes. A recent study on treatment with laparoscopic ISR following imatinib treatment for low rectal GISTs reported that laparoscopic ISR was safe and feasible for downsized low rectal GISTs [24]. This method may be a promising alternative to achieve sphincter preservation for low rectal GISTs.

Postoperative complications

A phase II trial of neoadjuvant imatinib therapy followed by surgery for all-site GISTs suggested that neoadjuvant imatinib therapy does not affect the rate of postoperative complications [21]. In four previous studies of neoadjuvant imatinib for rectal GISTs, the postoperative morbidity rates were reported to be 0–33% [12, 24, 30, 34]. Two studies reported that there were no postoperative complications, while Pai et al. reported post-operative morbidity in 3 of 9 patients (33%), with 2 wound complications requiring debridement and secondary suturing under general anesthesia and 1 hemoperitoneum requiring surgical exploration. No study has compared the postoperative morbidity rates between patients with and without neoadjuvant imatinib therapy for rectal GISTs.

Conclusion

Neoadjuvant imatinib therapy may show a good response rate in patients with rectal GISTs selected according to their mutational status. For patients with wild-type or a *PDGFRA* D842V mutant GISTs, we should not prescribe neoadjuvant imatinib. A reduction in tumor size after neoadjuvant imatinib therapy improved the feasibility of surgery and enabled the performance of a less radical procedure. The combination of neoadjuvant imatinib therapy and surgery for rectal GISTs is a challenging but promising method of achieving a complete resection margin and preserving the anal sphincter function. Further studies are warranted to ascertain the efficacy of this strategy.

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Compliance with ethical standards

Conflict of interest Manabu Kaneko and the other co-authors have no conflicts of interest.

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