Impact of neoadjuvant treatment on rectal gastrointestinal stromal tumors

Chinock Cheong1,2, Jeonghyun Kang3, Byung Soh Min4, Nam Kyu Kim5, Joong Bae Ahn6, Kang Young Lee4,*

1 Department of Surgery, Korea University Guro Hospital, Korea University College of Medicine, Seoul, Korea, 2 Graduate School, Yonsei University College of Medicine, Seoul, Korea, 3 Division of Colorectal Surgery, Department of Surgery, Gangnam Severance Hospital, Yonsei University College of Medicine, Seoul, Korea, 4 Division of Colorectal Surgery, Department of Surgery, Colorectal Cancer Clinic, Severance Hospital, Yonsei University College of Medicine, Seoul, Korea, 5 Division of Colorectal Surgery, Department of Surgery, Yongin Severance Hospital, Yonsei University College of Medicine, Seoul, Korea, 6 Division of Medical Oncology, Department of Internal Medicine, Yonsei Cancer Center, Yonsei University College of Medicine, Seoul, Korea

* kylee117@yuhs.ac

Abstract

Although gastrointestinal stromal tumors (GISTs) are rare disease and rectal GISTs is only 5% of total GISTs, they have the worst prognosis. Due to narrow pelvis, tumor rupture or positive resection margin are common in the management of rectal GISTs. The impact of neoadjuvant treatment on the clinical outcomes of rectal gastrointestinal stromal tumors (GISTs) remains unclear. Thus, we conducted a retrospective study to investigate the impact of neoadjuvant imatinib on rectal GIST. The cohort comprised 33 patients; of them, 10 and 23 belonged to the neoadjuvant (i.e., those who underwent neoadjuvant imatinib treatment) and the control group (i.e., those who underwent surgery without prior imatinib treatment), respectively. Neoadjuvant group was associated with more common levator ani muscle displacement (P = 0.002), and showed significantly larger radiologic tumor size (P = 0.036) than the control group. The mean tumor size was significantly decreased after imatinib treatment (6.8 cm to 4.7cm, P = 0.006). There was no significant difference in resection margin involvement (P >0.999), and sphincter preservation rates (P = 0.627) between the two groups. No difference was observed with respect to morbidities, hospital stay, local recurrence and disease-free survival. Neoadjuvant imatinib treated group had similar propensity with control group after treatment. We thought reduced tumor sized could enhance resectability and provide more chance to preserve sphincter for rectal GIST patients. Considering large tumor size and higher rate of sphincter invasion in the neoadjuvant group, imatinib treatment could be helpful as a conversion strategy to make huge and low-lying rectal GIST operable and achieve better surgical outcomes.

Introduction

Gastrointestinal stromal tumors (GISTs) are rare, with an annual incidence of 1/100,000, but they can occur at any site in the gastrointestinal tract [1]. Several prognostic factors, including
tumor size, mitotic count, and tumor location, have been used to stratify the risk of recurrence after complete tumor resection [2]. Among GISTs, rectal GISTs have the worst prognosis, with a reported high recurrence rate as local recurrence 87.5%, systemic recurrence 58% after curative resection [3–6]. Complete tumor excision is the most effective treatment modality for curative intent for rectal GISTs. Regional lymph node dissection is not a mandatory procedure because GISTs do not metastasize to regional lymph nodes [2].

Imatinib (imatinib mesylate, Gleevec, Novartis, Basel, Switzerland) has been proven to be effective for the management of metastatic GISTs, including as adjuvant therapy after complete tumor excision [7, 8]. Furthermore, Imatinib showed clinical efficacy in converting unresectable GISTs [9, 10].

For the surgical management of rectal GISTs, several specific factors should be considered. Tumor rupture or unsuccessful excision of tumor are highly aggressive prognostic factors and well-known risk factors for local recurrence in the management of GIST) [11, 12]. Due to the anatomical limitations such as narrow pelvis, tumor rupture or positive resection margin are more common in the perioperative management of rectal GISTs than others. This is translated into higher rate of sphincter-ablation treatment such as abdominoperineal resection. Thus, preservation of sphincter and functional outcome after complete tumor excision is also another considering factor. In this context, the effect of imatinib on downsizing huge rectal GISTs to resectable ones have clinical relevance. Although, various studies reported the conversional impact of imatinib treatments, few studies focused on the role of preoperative imatinib treatment for rectal GISTs with respect to oncologic and functional outcomes. We focused on the conversion strategy of imatinib for rectal GIST. Therefore, this study aimed to investigate the impact of neoadjuvant imatinib treatment in the management of rectal GISTs as a conversion strategy.

Materials and methods

Patients and ethical concerns

We evaluated patients who underwent surgical resection and were pathologically diagnosed with rectal GIST located within 15 cm of the anal verge between 2002 and 2014. Data were extracted from a maintained database. Two patients were excluded because of incomplete pathologic results. Finally, 33 patients were included in the analysis. Patients who underwent neoadjuvant imatinib treatment and those who underwent surgery without prior imatinib treatment were classified into the neoadjuvant group and the control group, respectively. This study was approved by the Institutional Review Board of Severance Hospital (IRB No.2019-0682-001) with a waiver of informed consent. This study was also followed to the ethical principles included in Declaration of Helsinki in 1964.

Patient selection for preoperative imatinib treatment

All patients were preoperatively staged using abdominopelvic computed tomography (APCT) or pelvic magnetic resonance imaging (MRI). Tumor size was defined as the longest distance of the tumor as measured via APCT or pelvic MRI. We repeated APCT or MRI based on the 3–4 months schedule. The surgical treatment was recommended in case the treatment response was anticipated as maximum. Operative methods were decided according to tumor location and size, which were transanal excision with grossly negative margins or radical resection as a low anterior resection or abdominoperineal resection. Complete resection was defined as the removal of the entire tumor, with a negative resection margin. Lymph node resection was not necessary. Although surgical resection was regarded as the treatment of choice, imatinib treatment before resection was selected at the surgeon’s discretion, according
to the tumor size or invasiveness to the adjacent organs or anal sphincter by preoperative APCT or MRI. In the neoadjuvant group, preoperative Imatinib was continued until the tumor no longer decreased in size on imaging studies. Surgical resection was planned if the tumor size failed to decrease further or when progression was observed during a regular follow-up.

**Postoperative management and follow-up**

Postoperative tumor size and mitotic count were evaluated by pathologists. Risk classification was performed according to the National Institutes of Health consensus criteria (Table 1) [13]. After resection, adjuvant imatinib treatment was used in cases of margin involvement in the pathologic results or GIST recurrence. Recurrence or metastasis was assessed using an APCT scan after surgical resection. Local recurrence (LR) was defined as any pelvic or perineal tumor recurrence, which was radiologically or clinically diagnosed. Systemic recurrence was defined as any recurrence located away from the rectum or adjacent organs in the pelvis. When recurrence was found during follow-up, adjuvant imatinib was administered at 400 mg per day. Dose escalation to 600 or 800 mg per day was applied, according to treatment response. Sunitinib malate (Sutent, Pfizer, New York, USA) was selectively used as second-line chemotherapy.

**Statistical analysis**

Continuous and categorical variables were analyzed using Student’s t test and $\chi^2$ test, respectively. Fisher’s exact test was used for between-group comparisons. Paired t-test was used to compare tumor sizes before and after neoadjuvant treatment. Disease-free survival (DFS) was calculated from the date of first diagnosis to the date of recurrence or the last follow-up date. LR and DFS were assessed using the Kaplan-Meier method. Multivariate analyses for LR and DFS were performed using the Cox proportional hazard model. All statistical analyses were performed using SPSS statistical software (version 20.0, IBM Corp., Armonk, NY, USA). Differences with $P$ values of $<0.05$ were considered statistically significant.

**Results**

**Patient characteristics**

The cohort comprised 33 patients; of them, 10 and 23 were classified into the neoadjuvant group and the control group, respectively. All ten patients who underwent neoadjuvant imatinib treatment were confirmed to have rectal GIST via transanal biopsy before imatinib treatment.

**Table 1. The risk classification for gastrointestinal stromal tumor in the National Institutes of health consensus criteria.**

| Risk category | Tumor size | Mitotic count |
|---------------|-----------|---------------|
| Very low      | <2cm      | <5/50 HPF     |
| Low           | 2-5cm     | <5/50 HPF     |
| Intermediate  | <5cm      | 6-10/50 HPF   |
|               | 5-10cm    | <5/50 HPF     |
| High          | >5cm      | >5/50 HPF     |
|               | >10cm     | Any mitotic rate |
|               | Any size  | >10/50 HPF    |

HPF; high-power field

https://doi.org/10.1371/journal.pone.0270887.t001
There were no significant differences in age, sex, body mass index, American Society of Anesthesiologists (ASA) grade, or tumor location from the anal verge between the two groups. Most of the tumors (31 (93.9%)) were located less than 5 cm from the anal verge. At the time of diagnosis, the rate of levator ani muscle displacement by the tumor on APCT or pelvic MRI was significantly higher in the neoadjuvant group than that in the control group (9 (90%) vs. 7 (31.8%), \( P = 0.002 \)). The mean tumor size was significantly larger in the neoadjuvant group (6.8 ± 2.5 cm in the neoadjuvant group vs. 4.6 ± 2.6 cm in the control group, \( P = 0.036 \)). After neoadjuvant treatment, the mean tumor size decreased significantly from 6.8 cm to 4.7 cm in the neoadjuvant group (\( P = 0.033 \)) (Fig 1). The mean duration of neoadjuvant treatment with imatinib was 9 months in the neoadjuvant group (9.7±5.0 months) (Table 2).

**Postoperative outcomes in the neoadjuvant and control groups**

The sphincter preservation rates did not differ between the two groups (neoadjuvant vs. control: 8 (80%) vs. 20 (87%), \( P = 0.627 \)). There was also no difference in resection margin involvement between the two groups (neoadjuvant vs. control: 9 (90.0%) vs. 19 (82.6%), \( P > 0.999 \)). With respect to difficulty of surgery, there was no difference in the rate of operation time (more than 4 hours) between the two groups. However, intraoperative blood loss >500 ml was more common in the neoadjuvant group than that in the control group (6 (60%) vs. 4 (17.4%), \( P = 0.035 \)). Postoperative complications and hospital length of stay did not differ between the two groups. Most patients showed c-KIT mutations, and there was no difference in mutation frequencies between the two groups (10 (100%) in the neoadjuvant group vs. 22 (95.7%) in the control group, \( P = 0.351 \)). Both groups showed a similar rate of risk stratification (\( P = 0.291 \)) (Table 3).

---

**Fig 1. Changes in tumor size after neoadjuvant treatment and comparison of oncologic outcomes between the neoadjuvant and the control groups.**

https://doi.org/10.1371/journal.pone.0270887.g001
After resection, 20% (n = 2) of patients in the neoadjuvant group and 26.1% (n = 6) of patients in the control group underwent adjuvant treatment with imatinib (P > 0.999). Although there was no significance between the groups, patients underwent adjuvant treatment because of margin involvement (n = 4) and high risk (n = 2) in control group (P > 0.999).

In the neoadjuvant group, two patients underwent adjuvant treatment based on the physician’s decision, even though they had low risk after surgery (Table 3).

**Oncologic outcomes**

The 5-year LR rates did not differ between the neoadjuvant and the control groups (neoadjuvant vs. control: 33.3% vs. 17.5%; P = 0.76) (Fig 2A). In the multivariate analysis, the prognostic factors of LR were pathologic tumor size (<5 vs. ≥ 5 cm) (OR 25.69; 95% CI:2.09–315.32; P = 0.011) and exon 11 mutations (OR 10.41; 95% CI: 1.19–91.16; P = 0.034). In addition, the 5-year DFS was similar between the groups (neoadjuvant vs. control: 66.7% vs. 77.8%; P = 0.99) (Fig 2B). In the multivariate analysis, the prognostic factor of DFS was initial tumor size (<5 vs. ≥ 5 cm) (HR 9.501; 95% CI: 1.141–79.13; P = 0.037) (Table 4).

**Discussion**

This study demonstrated that neoadjuvant imatinib treatment for large rectal GISTs could reduce tumor size and thus increase the resectability. In addition, it seems not to increase postoperative morbidity and seem not to deteriorate the oncologic outcomes such as resection margin positivity or long term oncologic outcomes.

The National Comprehensive Cancer Network guideline recommends preoperative imatinib for metastatic disease or unresectable cases for which surgery would induce significant
Table 3. Postoperative outcomes of the neoadjuvant and the control groups.

|                                      | Neoadjuvant group, n (%) (n = 10) | Control group, n (%) (n = 23) | P value |
|--------------------------------------|----------------------------------|-------------------------------|---------|
| Type of operation                    |                                  |                               |         |
| Transanal excision                   | 1 (10)                           | 6 (26.1)                      | 0.786   |
| Transabdominal excision              | 0                                | 1 (4.3)                       |         |
| LAR                                  | 7 (70)                           | 12 (52.2)                     |         |
| APR                                  | 2 (20)                           | 3 (13.0)                      |         |
| Hartmann operation                   | 0                                | 1 (4.3)                       |         |
| Sphincter preserving surgery         |                                  |                               | 0.627   |
| Yes                                  | 8 (80)                           | 20 (87)                       |         |
| No                                   | 2 (20)                           | 3 (13)                        |         |
| Stoma formation                      |                                  |                               | 0.619   |
| No                                   | 3 (30%)                          | 11 (47.8%)                    |         |
| Temporary stoma                      | 5 (50%)                          | 8 (34.8%)                     |         |
| Permanent stoma                      | 2 (20%)                          | 4 (17.4%)                     |         |
| Pathologic tumor size (cm ± SD)      | 5.0 ± 2.4                        | 4.6 ± 2.6                     | 0.713   |
| Mitosis after operation              |                                  |                               | >0.999  |
| Mitosis ≤ 5/HPF                      | 7 (70)                           | 15 (65.2)                     |         |
| Mitosis > 5/HPF                      | 3 (30)                           | 8 (34.8)                      |         |
| Margin involvement                   |                                  |                               | >0.999  |
| Yes                                  | 1 (10)                           | 4 (17.4)                      |         |
| No                                   | 9 (90)                           | 19 (82.6)                     |         |
| Hospitalization (days), (mean ± SD)  | 7.3 ± 7.9                        | 5.7 ± 3.9                     | 0.253   |
| Clavien-Dindo classification         |                                  |                               | 0.491   |
| I                                    | 1 (50)                           | 2 (22.2)                      |         |
| III                                  | 1 (50)                           | 8 (77.8)                      |         |
| C-kit positive                       |                                  |                               | 0.351   |
| Yes                                  | 10 (100)                         | 22 (95.7)                     |         |
| No                                   | 0                                | 1 (4.3)                       |         |
| Exon mutation                        |                                  |                               | 0.134   |
| Exon 11 mutation                     | 7 (70)                           | 9 (39.1)                      |         |
| Exon 13 mutation                     | 1 (10)                           | 1 (4.3)                       |         |
| Unknown                              | 2 (20)                           | 13 (56.5)                     |         |
| Risk classification                  |                                  |                               | 0.219   |
| Very low                             | 0                                | 5 (21.7)                      |         |
| Low                                  | 5 (50)                           | 4 (17.4)                      |         |
| Intermediate                         | 2 (20)                           | 6 (26.1)                      |         |
| High                                 | 3 (30)                           | 8 (34.8)                      |         |
| Recurrence                           |                                  |                               | 0.789   |
| No                                   | 7 (70)                           | 16 (69.6)                     |         |
| Local                                | 3 (30)                           | 6 (26.1)                      |         |
| Systemic                             | 0                                | 1 (4.3)                       |         |
| Adjuvant treatment                   | 2 (20%)                          | 6 (26.1%)                     | 0.999   |
| Reason for adjuvant treatment        |                                  |                               | >0.999  |
| Margin involvement                   | 0                                | 4 (17.4%)                     |         |
| High risk                            | 0                                | 2 (8.7%)                      |         |
| Unknown                              | 2 (20%)                          | 0                              |         |
| Duration of adjuvant Treatment (months), (mean ± SD) | 26.6±3.5 | 11.0±8.6 | 0.056   |
| Imatinib for relapsed tumor          | 2 (20%)                          | 6 (26.1%)                     | >0.999  |

(Continued)
Nevertheless, there is no consensus on the proper dose or duration of neoadjuvant imatinib especially for the treatment of rectal GISTs. Previous studies have reported the effects of preoperative imatinib for patients with multi-organ or metastatic GISTs [12, 14, 15].

In this study, the duration of neoadjuvant imatinib treatment differed between patients, with a mean duration of 9.7 months. Although changes in tumor density detected on CT scans are known to predict tumor responses after imatinib treatment [16, 17], this prediction modality was not applied to our patients. Maximal responses based on tumor sizes were evaluated by radiologists.

Previously, it has been recommended to use imatinib whenever possible until the effect is insignificant [14, 18, 19]. Nevertheless, it is still unclear how we could decide to stop treatment and proceed to surgery. The adequate duration and dosage of imatinib treatment and imaging parameters that maximize patient response to neoadjuvant imatinib treatment should be evaluated in further studies for rectal GIST.

Another advantage of neoadjuvant treatment is achieving a negative resection margin through a conversion strategy. For rectal GISTs, the rate of positive resection margins is as high as 40% [6], and a positive resection margin is a known independent factor for poor survival [12, 20]. Acquiring a negative resection margin sometimes counters sphincter preservation due to the deep and narrow pelvic cavity. Increasing resectability after neoadjuvant treatment clarifies the resection margin. Cavnar et al. compared neoadjuvant imatinib and control groups of patients who underwent surgical resection for rectal GISTs [21]. Although the ratio of APR in the neoadjuvant group was significantly lower, R1 resection was reported in 30% patients in the neoadjuvant group.

Table 3. (Continued)

|                         | Neoadjuvant group, n (%) (n = 10) | Control group, n (%) (n = 23) | P value |
|-------------------------|----------------------------------|-------------------------------|---------|
| Death                   |                                   |                               | > 0.999 |
| No                      | 9 (90%)                           | 21 (91.3%)                    |         |
| Yes                     | 1 (10%)                           | 2 (8.7%)                      |         |

LAR, low anterior resection; APR, abdominoperineal resection; SD: standard deviation; HPF, high-power field; ASA: American Society of Anesthesiologists

https://doi.org/10.1371/journal.pone.0270887.t003

Fig 2. Oncologic outcomes between neoadjuvant and control groups. (a) Local recurrence rates in the neoadjuvant and the control groups. (b) Disease-free survival rates in the neoadjuvant and the control groups.

https://doi.org/10.1371/journal.pone.0270887.g002
In this study, there was one patient with a positive resection margin in the neoadjuvant group (10%), compared with four patients in the control group (17.4%). We demonstrated the comparison focused on rectal GIST patients and achieved a 90% rate of R0 resection in the neoadjuvant group. The similar resection margin involvement rate and the long-term LR rate indicate that neoadjuvant imatinib treatment can reduce the tumor size and increase its resectability. Therefore, if neoadjuvant imatinib can reduce the size of the tumor and limit its invasion to adjacent organs, it would facilitate complete surgical resection.

In addition to tumor size, mitotic count is also an important risk factor and can determine the malignancy potential. Because mitotic count can be influenced by neoadjuvant imatinib, risk classification might be more accurate when it is evaluated using samples obtained before neoadjuvant treatment. Therefore, if neoadjuvant imatinib can reduce the size of the tumor and limit its invasion to adjacent organs, it would facilitate complete surgical resection.

In addition to tumor size, mitotic count is also an important risk factor and can determine the malignancy potential. Because mitotic count can be influenced by neoadjuvant imatinib, risk classification might be more accurate when it is evaluated using samples obtained before neoadjuvant treatment. Therefore, if neoadjuvant imatinib can reduce the size of the tumor and limit its invasion to adjacent organs, it would facilitate complete surgical resection.

Table 4. Univariate and multivariate analysis for local recurrence and disease-free survival between neoadjuvant and control groups.

| Variables                     | Local Recurrence | Disease Free Survival |
|-------------------------------|-------------------|-----------------------|
|                               | Univariate        | Multivariate          | Univariate        | Multivariate |
|                               | Univariate (OR 95% CI) | P | OR (95% CI) | P | HR (95% CI) | P | HR (95% CI) | P |
| Sex (male vs. female)         | 1.48 (0.32–6.89)  | 0.620 | 0.628 (0.152–2.59) | 0.52 |
| Age (<60 vs. ≥60) (year)      | 1.12 (0.24–5.25)  | 0.886 | 1.554 (0.445–5.422) | 0.49 |
| Sphincter preserving (No vs. Yes) | 0.18 (0.02–1.35) | 0.096 | 0.443 (0.117–1.68) | 0.231 |
| Tumor location (AV <5 vs. ≥5 cm) | 2.87 (0.165–1.53) | 0.473 | 8.904 (0.797–99.55) | 0.0759 | 2.941 (0.254–34.04) | 0.388 |
| Initial tumor size (<5 vs. ≥5 cm) | 11.20 (1.20–104.33) | 0.034 | 9.065 (1.124–73.13) | 0.0385 | 9.501 (1.141–79.13) | 0.037 |
| Pathologic tumor Size (<5 vs. ≥5 cm) | 16.00 (1.69–151.11) | 0.016 | 25.69 (2.09–315.32) | 0.011 | 3.776 (0.773–18.44) | 0.101 |
| Mitosis (<5 vs. ≥5/HPF)       | 6.00 (1.13–31.73) | 0.035 | 2.756 (0.657–11.56) | 0.166 |
| Margin positive               | 2.00 (0.28–14.53) | 0.493 | 1.351 (0.279–6.538) | 0.709 |
| Exon 11 mutation              | 5.83 (0.99–34.44) | 0.052 | 10.41 (1.19–91.16) | 0.034 | 4.67 (0.987–22.1) | 0.052 | 4.829 (0.983–23.71) | 0.052 |
| Neoadjuvant imatinib (No vs. Yes) | 1.21 (0.24–6.27) | 0.817 | 1.009 (0.255–3.993) | 0.99 |

OR, odds ratio; HR, hazard ratio; CI, confidence interval; AV, anal verge; HPF, high-power field; CTx., chemotherapy

In this study, there was one patient with a positive resection margin in the neoadjuvant group (10%), compared with four patients in the control group (17.4%). We demonstrated the comparison focused on rectal GIST patients and achieved a 90% rate of R0 resection in the neoadjuvant group. The similar resection margin involvement rate and the long-term LR rate indicate that neoadjuvant imatinib treatment can reduce the tumor size and increase its resectability. Therefore, if neoadjuvant imatinib can reduce the size of the tumor and limit its invasion to adjacent organs, it would facilitate complete surgical resection.

In addition to tumor size, mitotic count is also an important risk factor and can determine the malignancy potential. Because mitotic count can be influenced by neoadjuvant imatinib, risk classification might be more accurate when it is evaluated using samples obtained before neoadjuvant treatment. Mutational analysis has recently been found to be essential because it helps exclude less sensitive or resistant tumors to imatinib treatment and allows proper dosing for patients with c-kit exon mutations [22, 23]. Four different regions of kit have been found to be mutated in GIST: exons 9, 11, 13, and 17 [24, 25]. Although most kit mutations are sensitive to imatinib, exon 11 mutations are more sensitive than exon 9 mutations, and exon 17 mutations are resistant to imatinib [26]. Thus, surgical resection should not be delayed in patients who do not show a response. In our analysis, 70% of the patients had exon 11 mutations in the neoadjuvant group, compared with 39.1% in the control group. However, the mitotic count results and exon mutational statuses from preoperative biopsy were not reported. Thus, the impact of imatinib on these parameters could not be analyzed. The selective application of neoadjuvant imatinib treatment according to exon mutation and mitotic count results derived from preoperative biopsy samples is an area of clinical interest and should be evaluated in further studies.

There are several potential limitations in this study. Because of the retrospective study design, we could not ignore selection bias on clinical outcomes. In addition, due to the rarity of rectal GISTs, the number of enrolled patients was relatively small. However, we demonstrated the effect of neoadjuvant imatinib focused on rectal GIST, whereas other studies did not. In our study, the application of neoadjuvant imatinib treatment was left to the surgeon’s decision and/or clinical applicability of imatinib. The use of imatinib in the neoadjuvant setting is not fully reimbursed by the National Health Insurance Corporation in Korea, and there is no standardized indication for performing curative resection. Different follow-up and
imaging studies were applied to each patient during imatinib neoadjuvant treatment. Besides there were not enough patients’ functional outcome data or stoma reversal. Because of retrospective study, we could not also evaluate it additionally.

In conclusion, the present study is a comparative analysis of preoperative imatinib treatment between those who underwent neoadjuvant imatinib treatment followed by radical resection and those who underwent surgery without prior imatinib treatment. Our findings showed that neoadjuvant imatinib treatment effected to reduce initial tumor size. Reduced tumor size might increase resectability and thus enhance chance of sphincter preservation for low-lying rectal GISTs. Therefore, neoadjuvant imatinib treatment was worthy of consideration as conversion strategy for huge and low-lying rectal GIST without deterioration long-term outcomes.

Supporting information
S1 Data. (CSV)

Author Contributions
Conceptualization: Byung Soh Min, Nam Kyu Kim, Kang Young Lee.
Investigation: Chinock Cheong.
Methodology: Kang Young Lee.
Software: Chinock Cheong.
Supervision: Jeonghyun Kang.
Validation: Joong Bae Ahn.
Writing – original draft: Chinock Cheong.
Writing – review & editing: Chinock Cheong, Jeonghyun Kang, Kang Young Lee.

References
1. Nilsson B, Bümming P, Meis-Kindblom JM, Odén A, Dortok A, Gustavsson B, et al. Gastrointestinal stromal tumors: the incidence, prevalence, clinical course, and prognostication in the preimatinib mesylate era—a population-based study in western Sweden. Cancer. 2005; 103:821–829. https://doi.org/10.1002/cncr.20862 PMID: 15648083
2. Miettinen M, Lasota J. Gastrointestinal stromal tumors: review on morphology, molecular pathology, prognosis, and differential diagnosis. Arch Pathol Lab Med. 2006; 130:1466–1478. https://doi.org/10.5858/2006-130-1466-GSTROM PMID: 17090188
3. Peralta EA. Rare anorectal neoplasms: gastrointestinal stromal tumor, carcinoid, and lymphoma. Clin Colon Rectal Surg. 2009; 22:107–114. https://doi.org/10.1055/s-0029-1223842 PMID: 20436835
4. Yasui M, Tsujinaka T, Mori M, Takahashi T, Nakashima Y, Nishida T. Characteristics and prognosis of rectal gastrointestinal stromal tumors: an analysis of registry data. Surg Today. 2017; 47:1188–1194. https://doi.org/10.1007/s00595-017-1524-8 PMID: 28421351
5. Changchien CR, Wu MC, Tasi WS, Tang R, Chiang JM, Chen JS, et al. Evaluation of prognosis for malignant rectal gastrointestinal stromal tumor by clinical parameters and immunohistochemical staining. Dis Colon Rectum. 2004; 47:1922–1929. https://doi.org/10.1007/s10350-004-0687-8 PMID: 15622586
6. Frankel TL, Chang AE, Wong SL. Surgical options for localized and advanced gastrointestinal stromal tumors. J Surg Oncol. 2011; 104:882–887. https://doi.org/10.1002/jso.21892 PMID: 21381037
7. Druker BJ, Talpaz M, Resta DJ, Peng B, Buchdunger E, Ford JM, et al. Efficacy and safety of a specific inhibitor of the BCR-ABL tyrosine kinase in chronic myeloid leukemia. N Engl J Med. 2001; 344:1031–1037. https://doi.org/10.1056/NEJM200104053441401 PMID: 11287972
8. Dematteo RP, Ballman KV, Antonescu CR, Maki RG, Pisters PW, Demetri GD, et al. Adjuvant imatinib mesylate after resection of localized, primary gastrointestinal stromal tumour: a randomized, double-blind, placebo-controlled trial. Lancet. 2009; 373:1097–1104. https://doi.org/10.1016/S0140-6736(09)60500-6 PMID: 19303137

9. Blanke CD, Demetri GD, von Mehren M, Heinrich MC, Eisenberg B, Fletcher JA, et al. Long-term results from a randomized phase II trial of standard- versus higher-dose imatinib mesylate for patients with unresectable or metastatic gastrointestinal stromal tumors expressing KIT. J Clin Oncol. 2008; 26:620–625. https://doi.org/10.1200/JCO.2007.13.4403 PMID: 18235121

10. von Mehren M, Randall RL, Benjamin RS, Boles S, Bui MM, Casper ES, et al. Gastrointestinal stromal tumors, version 2.2014. J Natl Compr Canc Netw. 2014; 12:853–862. https://doi.org/10.6004/jnccn.2014.0080 PMID: 24925196

11. Joensuu H, Vehtri A, Rihimäki J, Nishida T, Steigen SE, Brabec P, et al. Risk of recurrence of gastrointestinal stromal tumour after surgery: an analysis of pooled population-based cohorts. Lancet Oncol. 2012; 13:265–274. https://doi.org/10.1016/S1470-2045(11)70299-6 PMID: 22153992

12. Jakob J, Mussi C, Ronellenfitsch U, Wardelmann E, Negri T, Gronchi A, et al. Gastrointestinal stromal tumor of the rectum: results of surgical and multimodality therapy in the era of imatinib. Ann Surg Oncol. 2013; 20:586–592. https://doi.org/10.1245/s10434-012-2647-1 PMID: 22965573

13. Joensuu H. Risk stratification of patients diagnosed with gastrointestinal stromal tumor. Hum Pathol. 2008; 39:1411–1419. https://doi.org/10.1016/j.humpath.2008.06.025 PMID: 18774375

14. Rutkowski P, Gronchi A, Hohenberger P, Bonvalot S, Schöffski P, Bauer S, et al. Neoadjuvant imatinib in locally advanced gastrointestinal stromal tumors (GIST): the EORTC STBSG experience. Ann Surg Oncol. 2013; 20:2397–2493. https://doi.org/10.1245/s10434-013-3013-7 PMID: 23760587

15. Bednarski BK, Araujo DM, Yi M, Torres KE, Lazar A, Trent JC, et al. Analysis of prognostic factors impacting oncologic outcomes after neoadjuvant tyrosine kinase inhibitor therapy for gastrointestinal stromal tumors. Ann Surg Oncol. 2014; 21:2499–2505. https://doi.org/10.1245/s10434-014-3632-7 PMID: 24639192

16. Schramm N, Enghart E, Schlemmer M, Hittinger M, Übles C, Becker CR, et al. Tumor response and clinical outcome in metastatic gastrointestinal stromal tumors under sunitinib therapy: comparison of RECIST, Choi and volumetric criteria. Eur J Radiol. 2013; 82:351–958. https://doi.org/10.1016/j.ejrad.2013.02.034 PMID: 23518148

17. Tirumani SH, Shiniagare AB, Jagannathan JP, Krajewski KM, Raut CP. Radiologic assessment of earliest, best, and plateau response of gastrointestinal stromal tumors to neoadjuvant imatinib prior to successful surgical resection. Eur J Surg Oncol. 2014; 40:420–428. https://doi.org/10.1016/j.ejso.2013.10.021 PMID: 24238762

18. Le Cesne A, Van Glabbeke M, Verweij J, Casali PG, Findlay M, Reichardt P, et al. Absence of progression as assessed by response evaluation criteria in solid tumors predicts survival in advanced G1 stromal tumors treated with imatinib mesylate: the intergroup EORTC-ISG-AGITG phase III trial. J Clin Oncol. 2009; 27:3969–3974. https://doi.org/10.1200/JCO.2008.21.3330 PMID: 19620483

19. Wang D, Zhang Q, Blanke CD, Demetri GD, Heinrich MC, Watson JC, et al. Phase II trial of neoadjuvant/adjuvant imatinib mesylate for advanced primary and metastatic/recurrent operable gastrointestinal stromal tumors: long-term follow-up results of Radiation Therapy Oncology Group 0132. Ann Surg Oncol. 2012; 19:1074–1080. https://doi.org/10.1245/s10434-011-1290-2 PMID: 22203182

20. DeMatteo RP, Lewis JJ, Leung D, Mudan SS, Woodruff JM, Brennan MF. Two hundred gastrointestinal stromal tumors: recurrence patterns and prognostic factors for survival. Ann Surg. 2000; 231:51–58. https://doi.org/10.1097/00000658-200001000-00008 PMID: 10636102

21. Cavoan MJ, Wang L, Balachandran VP, Antonescu CR, Tap WD, Keohan M, et al. Rectal Gastrointestinal Stromal Tumor (GIST) in the Era of Imatinib: Organ Preservation and Improved Oncologic Outcome. Ann Surg Oncol. 2017; 24:3972–3980. https://doi.org/10.1245/s10434-017-6087-9 PMID: 29058144

22. Heinrich MC, Corless CL, Demetri GD, Blanke CD, von Mehren M, Joensuu H, et al. Kinase mutations and imatinib response in patients with metastatic gastrointestinal stromal tumor. J Clin Oncol. 2003; 21:4342–4349. https://doi.org/10.1200/JCO.2003.04.190 PMID: 14654243

23. Debic-Rychter M, Dumez H, Judson I, Wasag B, Verweij J, Brown M, et al. Use of c-KIT/PDGFRα mutational analysis to predict the clinical response to imatinib in patients with advanced gastrointestinal stromal tumours entered on phase I and II studies of the EORTC Soft Tissue and Bone Sarcoma Group. Eur J Cancer. 2004; 40:689–695. https://doi.org/10.1016/j.ejca.2003.11.025 PMID: 15010069

24. Martín J, Poveda A, Llombart-Bosch A, Ramos R, López-Guerrero JA, García del Muro J, et al. Deletions affecting codons 557–558 of the c-KIT gene indicate a poor prognosis in patients with completely resected gastrointestinal stromal tumors: a study by the Spanish Group for Sarcoma Research (GEIS). J Clin Oncol. 2005; 23:6190–6198. https://doi.org/10.1200/JCO.2005.19.554 PMID: 16135486
25. Dematteo RP, Gold JS, Saran L, Gönen M, Liau KH, Maki RG, et al. Tumor mitotic rate, size, and location independently predict recurrence after resection of primary gastrointestinal stromal tumor (GIST). Cancer. 2008; 112:608–615. https://doi.org/10.1002/cncr.23199 PMID: 18076015

26. Heinrich MC, Owzar K, Corless CL, Hollis D, Borden EC, Fletcher CD, et al. Correlation of kinase genotype and clinical outcome in the North American Intergroup Phase III Trial of imatinib mesylate for treatment of advanced gastrointestinal stromal tumor: CALGB 150105 Study by Cancer and Leukemia Group B and Southwest Oncology Group. J Clin Oncol. 2008; 26:5360–5367. https://doi.org/10.1200/JCO.2008.17.4284 PMID: 18955451