The role of neoadjuvant imatinib in gastrointestinal stromal tumor patients: 20 years of experience from a tertiary referral center

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Abstract
Surgery is the cornerstone of gastrointestinal stromal tumor (GIST) treatment, and adjuvant therapy with imatinib has improved survival for high-risk tumors. The use of imatinib preoperatively has been increasing, but efficacy and impact on patient outcomes have not been formally investigated. This is a retrospective study from a single-center cohort of patients diagnosed with GIST and treated with neoadjuvant imatinib at Karolinska University Hospital in Stockholm, Sweden over a 20-year period. Eighty-four patients diagnosed with GIST and treated with neoadjuvant imatinib were identified and included. Tumors were located throughout the whole gastrointestinal tract but most frequently in the stomach (n = 29; 35%) and the small intestine (n = 30; 36%), followed by the rectum (n = 12; 14%) and the gastroesophageal junction (n = 10; 12%). The tumors were large (mean 10.5 cm) and decreased after treatment (mean 7.6 cm). Main indications for neoadjuvant imatinib were tumor size or anatomical location. None of the patients with stomach tumors and four patients with tumors near the gastroesophageal junction underwent gastrectomy. Three patients with tumors in the small intestine underwent pancreaticoduodenectomy, whereas seven patients with rectal tumors underwent rectal amputation. After surgery, 94% (n = 79) of the tumors had R0-resection. About one-fourth experienced local relapse or distant metastasis. In conclusion, neoadjuvant imatinib can reduce tumor size and prevent high morbidity due to more extensive surgery, or at least reduce the extent of the surgery, especially for tumors in the stomach or small intestine.

KEYWORDS
GIST, imatinib, neoadjuvant, surgery

Abbreviations: ALS, amyotrophic lateral sclerosis; CT, computed tomography; EFS, event-free survival; GIST, gastrointestinal stromal tumor; HPF, high-power field; NIH criteria, National Institute of Health criteria; OS, overall survival; PDGFRA, platelet-derived growth factor-alpha; PET-CT, positron emission tomography-computed tomography.
**1 | INTRODUCTION**

Gastrointestinal stromal tumors (GISTs) originate from the Cajal cells of the gastrointestinal tract and have a yearly incidence of 1/100 000. GISTs are most commonly located in the stomach (50%-60%), followed by the small intestine (30%-40%) and then the colon and rectum (5%) and esophagus (5%), and radical surgery is the cornerstone of treatment. However, about half of the patients experience relapses within a few years after surgery. Since the early 21st century, imatinib has had a significant impact on the management and prognosis of GIST patients. Most GISTs have a mutation in the proto-oncogene c-KIT, which codes for the KIT transmembrane receptor tyrosine kinase. Imatinib inhibits this receptor activation and thereof prevents cell survival and proliferation, that is, tumor growth. The second most common gene mutated in GISTs is platelet-derived growth factor-alpha (PDGFRα), where the exon 18 D842V mutation has demonstrated resistance to imatinib.

Imatinib is an established treatment both in the adjuvant setting for high-risk GISTs and as first-line therapy for the majority of metastatic GISTs. Administration of imatinib in the neoadjuvant setting is also gaining ground and aims to: (a) reduce tumor size and thereof facilitate R0 resection and organ or function preserving surgery and (b) to reduce the risk of tumor rupture. Some studies tried to evaluate the benefits of neoadjuvant imatinib in locally advanced tumors, showing a high rate of R0 resection and the chance of organ-preserving surgery after preoperative treatment with imatinib. Even so, large, randomized studies are lacking, probably due to the difficulty of formalizing criteria related to the surgical assessment of the individual tumors and conducting clinical trials in this context. Identifying the patients most likely to benefit from neoadjuvant imatinib, the optimal duration of such an approach and the impact on survival, remains an unmet need.

Herein we present a long-term retrospective study from a single-tertial referral center investigating the clinical and tumor characteristics and GIST-related outcomes of patients treated with neoadjuvant imatinib.

**2 | MATERIALS AND METHODS**

This retrospective cohort study included all patients diagnosed with GIST and treated with neoadjuvant imatinib at Karolinska University Hospital in Stockholm, Sweden, from January 2000 to December 2019. Patient demographics, tumor characteristics, radiological findings, surgical outcomes and recurrence rates were recorded after reviewing medical records.

Neoadjuvant imatinib was recommended if tumor size, location and patient physical status suggested that preoperative imatinib could lead to more minor or less morbid surgery or in primary localized inoperable tumors. A multidisciplinary team of sarcoma specialists in oncology, surgery, radiology and pathology had previously discussed all patients who received neoadjuvant treatment. Usually, a period of 6 to 9 months of neoadjuvant treatment was preliminary planned, but the patient was always reconsidered at the multidisciplinary conference, and more extended treatment was recommended if clinical benefit and further facilitation of surgery were expected.

Tumor location was categorized as the esophagus, gastroesophageal junction, stomach, small intestine, colon or rectum. Tumor size before and after treatment was defined as the largest transverse diameter in centimeters, and the pretreatment size assessment was based on radiological findings (computed tomography [CT] and/or positron emission tomography-computed tomography [PET-CT]). Time of diagnosis was defined as the date of pathological confirmation of the diagnosis by biopsy or cytology. Time of local relapse or distant metastasis was defined as the time of radiologically confirmed relapse. Classification of surgical margins as R0, R1 and R2 were according to Wittekind et al. According to Joensuu, risk stratification for selecting patients for adjuvant treatment followed the modified National Institute of Health (NIH) criteria, in line with institutional guidelines. Mitotic count is reported as per 50 high-power fields (HPF) based on the risk stratification model being used at the institution and that was employed in this analysis. The stratification was made ad hoc based on the available information to provide more homogeneity in the data.

Continuous variables are presented as medians and ranges, whereas categorical variables are frequencies. Comparisons between patients treated preoperatively and patients with high-risk GISTs are mostly for hypothesis-generating since the groups were formed by retrospective material. Event-free survival (EFS) was defined as time from GIST diagnosis to any relapse, local or metastatic, or death, whatever occurred first and overall survival (OS) as time of diagnosis to death. A Kaplan-Meier curve was utilized to visualize relapse and metastasis data, and a post hoc exploratory analysis compared the two groups. All statistical analyses were performed using Stata software version 14.

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**What’s new?**

Imatinib has had a significant impact on the management and prognosis of patients with gastrointestinal stromal tumors. However, which patients are most likely to benefit from neoadjuvant imatinib, the optimal treatment duration and the impact on survival remains to be clarified. This long-term retrospective study suggests that neoadjuvant imatinib can reduce tumor size and the extent of surgery, potentially preventing high morbidity. The findings support neoadjuvant imatinib as a feasible, low-toxicity approach for increasing the chance of radical and organ-preserving surgery. The study adds important information to ongoing discussions on the optimal management of localized gastrointestinal stromal tumor.
3  |  RESULTS

3.1  |  Cohort characteristics

As shown in Figure 1, a total of 457 patients were identified in the local database, and after reassessment by the pathologist, two were considered leiomyomas and were excluded. Of the remaining 455, 30 had primary metastatic GIST at the time of diagnosis. In total, 84 patients out of the 425 nonmetastatic patients included in the analysis received neoadjuvant imatinib: 35 women and 49 men. A slight overrepresentation of men was observed in this cohort compared to the whole cohort of GIST patients, where the gender distribution was equal (n = 229 females, n = 226 men). The mean age of diagnosis for those who received neoadjuvant treatment was 62.5 years (range 31.4-84.9 years).

3.2  |  Neoadjuvant therapy and outcomes

Patient and tumor characteristics for those who received neoadjuvant treatment are presented in Table 1. Most tumors were large and located in the stomach or small intestine. Tumor locations are presented in Figure 2. Indications for neoadjuvant treatment were mainly tumor location (n = 40) or size (n = 35), based on the surgeon’s operability assessment. In a minority of the cohort, the decision to offer neoadjuvant imatinib was based on tumor-related symptoms (n = 5) or other factors (n = 4). The four patients who received neoadjuvant imatinib due to other factors included: (a) a patient with a second malignancy of more aggressive character where GIST surgery was postponed, (b) a patient with pulmonary embolism, (c) a patient initially evaluated as nonoperable due to amyotrophic lateral sclerosis (ALS) and therefore received imatinib before a reevaluation after which the patient underwent surgery and finally, (d) a patient that was initially misdiagnosed with an abdominal abscess and received a drain prior to GIST diagnosis, thus neoadjuvant imatinib was recommended. All but two patients were prescribed a standard dose of imatinib 400 mg/day, and eight of them required dose reduction due to adverse events. The remaining two patients received neoadjuvant sunitinib due to the physician’s choice.

Tumor location was the most determining factor for tumors in the gastroesophageal junction (n = 10 out of 10) and rectum (n = 11 out of 12), and size for tumors in the stomach (n = 21 out of 29). Both location and size were important for tumors in the small intestine (n = 14 and n = 12, respectively, out of 30).

The mean tumor size at diagnosis, based on radiological findings, was 10.5 cm (range 2.27 cm) and reduced to a mean of 7.6 cm (range 1.3-30 cm) after neoadjuvant treatment. A box plot in Figure 3 demonstrates tumor size before and after neoadjuvant imatinib. The pretreatment size was defined according to the radiological findings, whereas the posttreatment size was based on pathological reports (only 82 patients were reported) since the radiological size preoperatively was not always available. The mean duration of neoadjuvant imatinib was 7.1 months (range 0.9-20.9 months). Mitotic count from surgery samples is also presented in Table 1 but since the assessment is after neoadjuvant imatinib, risk-stratification is not feasible.

Forty-five patients (54%) had a size reduction of ≥30%, and the remaining 39 patients (46%) had a size reduction of less than 30%. Tumor size reduction was different based on mutational status; among the 51 tumors with a c-KIT exon 11 mutation, two thirds (n = 33; 65%) had a size reduction ≥30% and one-third (n = 18; 35%) had a size reduction <30%. Out of the three tumors with a c-KIT exon
9 mutation, one had a size reduction ≥30% and two had a size reduction <30%. Out of the five tumors with a PDGFRA exon 18 mutation, four had a D842V activating mutation and one had an exon 18 heterozygote deletion. One of the patients with a D842V mutation had a size reduction ≥30%, and the remaining four with a PDGFRA exon 18 mutation had a size reduction <30%. All patients with a PDGFRA mutation that were treated with neoadjuvant imatinib were diagnosed before institutional guidelines regarding management of patients with PDGFRA mutations were updated. In concordance to international guidelines, neoadjuvant imatinib is no longer recommended in patients with PDGFRA D842V mutations.

3.3 | Follow-up

None of the patients with gastric tumors underwent gastrectomy after the neoadjuvant treatment, but 4 out of 10 with tumors in the gastroesophageal junction did. Only 3 out of 30 patients with tumors in the small intestine underwent a pancreaticoduodenectomy (Whipple procedure). However, despite preoperative imatinib administration, 7 out of 12 patients with rectal tumors had to undergo resection amputation. In total, 94% of the patients that received neoadjuvant therapy had an R0 resection (n = 79 patients). Among the patients who were recommended adjuvant imatinib (n = 71), one patient declined and two patients received sunitinib instead; one had

| TABLE 1 Tumor and patient characteristics for the patients treated with neoadjuvant imatinib |
| Neoadjuvant imatinib, n (%) (N = 84) |
| Gender |
| Female | 35 (42) |
| Male | 49 (58) |
| Tumor location |
| Esophagus | 2 (2) |
| Gastroesophageal junction | 10 (12) |
| Stomach | 29 (35) |
| Small intestine | 30 (36) |
| Colon | 1 (1) |
| Rectum | 12 (14) |
| Tumor size at diagnosis (cm) |
| ≤2 | 1 (1) |
| 2.1-5 | 19 (23) |
| 5.1-10 | 32 (38) |
| >10 | 32 (38) |
| Number of mitosis (/50 HPF) |
| ≤5 | 61 (73) |
| 6-10 | 3 (4) |
| >10 | 2 (2) |
| Not available | 18 (21) |
| Mutations |
| c-KIT |
| Exon 9 | 3 (3) |
| Exon 11 | 51 (61) |
| PDGFRA |
| Exon 18 | 5 (6) |
| Unknown | 1 (1) |
| No c-KIT/PDGFRA mutation identified | 10 (12) |
| Not available | 14 (17) |
| Indication neoadjuvant imatinib |
| Location | 40 (47) |
| Size | 35 (42) |
| Tumor symptoms | 5 (6) |
| Other | 4 (5) |

Abbreviation: HPF, high-power field, evaluated after neoadjuvant imatinib.
also received sunitinib preoperatively and the other one had an allergic reaction to imatinib.

Sixteen (19%) of the patients treated with neoadjuvant imatinib died, six of whom due to GIST. Seven patients (8%) experienced a local relapse, and 16 (19%) developed distant metastasis (three with previous local relapse). Median EFS and OS was 89.23 months (95% confidence intervals [CI]: 78.3-NA) and 166.74 months (95% CI: 166.74-NA), respectively. Two Kaplan-Meier curves, depicted in Figures 4 and 5 respectively, were used to describe EFS and OS for the neoadjuvant treated group.

A logistic regression analysis including gender, tumor location, tumor size and resection margin in terms of R0, R1 and R2 identified positive resection margin R1 to negatively impact risk of relapse despite small numbers (Table 2).

### 3.4 Comparison with high-risk tumors not treated with neoadjuvant imatinib

As shown in Figure 1, 98 patients were classified as high-risk tumors and had not received neoadjuvant imatinib. Median age was 66.7 years and n = 42 were women. Tumor and patient characteristics of this cohort are presented in Table S1. Sixty-seven high-risk patients received adjuvant imatinib and all but one was prescribed a standard dose of imatinib 400 mg daily. One patient was prescribed 800 mg imatinib daily, despite a lack of identifiable mutation and the dose was reduced shortly after, due to toxicity. Dose reduction or

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**TABLE 2** Logistic regression analysis of clinical characteristics and relapse for the 84 patients treated neoadjuvant

|                  | Overall population, N = 84 (%) | Relapse population, N = 20 (%) | Nonrelapse population, N = 64 (%) | P-value |
|------------------|--------------------------------|--------------------------------|-----------------------------------|---------|
| **Gender**       |                                |                                |                                   |         |
| Female           | 8 (40%)                        | 27 (42%)                       | Ref.                              |         |
| Male             | 12 (60%)                       | 37 (58%)                       | .86                               |         |
| **Tumor location** |                               |                                |                                   |         |
| Esophagus        | 2 (2)                          | 0                              | 2 (3)                             | 1       |
| Gastroesophageal junction | 10 (12)                   | 4 (20)                         | 6 (9)                             | .99     |
| Stomach          | 29 (35)                        | 2 (10)                         | 27 (42)                           | .99     |
| Small intestine  | 30 (36)                        | 12 (60)                        | 18 (28)                           | .99     |
| Colon            | 1 (1)                          | 0                              | 1 (2)                             | Ref.    |
| Rectum           | 12 (14)                        | 2 (10)                         | 10 (16)                           | .99     |
| **Tumor margin** |                                |                                |                                   |         |
| R0               | 79 (94)                        | 17 (85)                        | 62 (97)                           | Ref.    |
| R1               | 4 (5)                          | 3 (15)                         | 1 (1.5)                           | .044    |
| R2               | 1 (1)                          | 0                              | 1 (1.5)                           | .99     |
| **Tumor size at diagnosis (cm)** |                         |                                |                                   |         |
| ≤2               | 1 (1)                          | 0                              | 1 (2)                             | Ref.    |
| 2.1-5            | 19 (23)                        | 3 (15)                         | 16 (25)                           | .99     |
| 5.1-10           | 32 (38)                        | 7 (35)                         | 25 (39)                           | .99     |
| >10              | 32 (38)                        | 10 (50)                        | 22 (34)                           | .99     |
premature treatment discontinuation due to toxicity was observed in \( n = 15 \).

High-risk patients who did not receive neoadjuvant treatment had numerically R1- and R2-resection to a greater extent, 12% compared to 6% of the patients treated neoadjuvant. An exploratory comparison between the two groups with Fisher’s exact test did not reveal statistical significance \( (P = .294) \). However, the numbers are small, and the data heterogeneous, hence this comparison should be interpreted with caution and serve primarily as hypothesis-generating.

The surgical methods employed in the two groups did not differ significantly. There were only five patients who had a Whipple procedure; three had received neoadjuvant treatment and two were classified as high-risk tumors but had not received neoadjuvant treatment. Among patients with stomach or gastroesophageal junction tumors, four out of the 39 neoadjuvant treated patients and two out of the 47 high-risk tumors underwent gastrectomy. All patients who underwent rectum amputation had received neoadjuvant treatment.

Median EFS was 87.6 months \( (95\% \text{ CI}: 67.84-146.43 \text{ months}) \) and OS at 108 months was 70.7% \( (95\% \text{ CI}: 60.1\%-83\%) \) whereas median OS was not reached in the high-risk group. An exploratory analysis did not demonstrate statistically significant differences between patients with high-risk GIST vs neoadjuvant treated patients regarding EFS (hazard ratio \( [HR] 0.79; 95\% \text{ CI}: 0.49-1.26, P = .32 \)) or OS \( (HR 0.84; 95\% \text{ CI}: 0.44-1.61, P = .61) \). Figure S1A,B demonstrate EFS and OS, respectively, comparing the neoadjuvant treated group with the group with high-risk tumors that did not receive neoadjuvant treatment.

4 | DISCUSSION

In this retrospective study, 84 out of 425 GIST patients received neoadjuvant treatment with imatinib. Large tumors near vulnerable anatomical structures with increased risk of high morbidity with surgery, became candidates for neoadjuvant treatment. In general, tumors reduced in size after neoadjuvant treatment and therefore extensive surgery such as gastrectomy, pancreaticoduodenectomy or rectum amputation was most likely prevented for several patients, even though it was not achieved to the same extent for the rectal tumors as for the tumors in the stomach and small intestine. A control arm is lacking, and therefore a formal comparison of the utility of neoadjuvant imatinib is not possible. Even though an effort was made to compare the outcomes of neoadjuvant treatment and high-risk patients operated upfront, this comparison should be regarded only as hypothesis-generating. Our cohort goes back 20 years, thus some patients received adjuvant imatinib only for 1 year, a duration known to be inferior to 3 years and that can impact comparisons with preoperatively treated patients.

The decision of whom to operate or not is usually considered subjective since there is an unquestionable intersurgeon variability and on institutional level. However, even though this is a retrospective nonrandomized cohort, the same surgeons were involved in assessing the cases providing some level of homogeneity. Interestingly, the observed outcomes between the patients with high-risk tumors operated upfront and those that received neoadjuvant imatinib are similar.

Our data support the use of neoadjuvant imatinib as a downstaging treatment and provide evidence that delaying surgery with neoadjuvant imatinib does not have a negative impact on clinical outcomes. On the other hand, it is unclear whether neoadjuvant imatinib could also benefit high-risk patients considered for upfront surgery. Designing a randomized control trial of neoadjuvant vs no neoadjuvant imatinib would be troublesome, given the potential good effect of neoadjuvant imatinib. Also, selecting and randomizing patients in a standardized fashion would be almost impossible due to the multifactorial nature of whether to offer neoadjuvant imatinib or not, and the intraoperative assessments about the extent of the surgery.

Several factors should be considered before deciding on neoadjuvant treatment. Since different mutational status indicates sensitivity for imatinib or not, it is essential to do mutation analysis before determining if neoadjuvant imatinib treatment is eligible.\(^1\) Whereas a mutation in \( c\)-KIT implies a response to imatinib treatment, a PDGFR\(\text{A} \) D842V mutation indicates resistance and imatinib should therefore not be used in the neoadjuvant or in the adjuvant setting. Other more uncommon PDGFR\(\text{A} \) mutations do not show the same resistance to imatinib,\(^15\) and in those cases imatinib could be indicated. In our retrospective study, five tumors with PDGFR\(\text{A} \) mutation were treated with neoadjuvant imatinib and describe size reduction. This could possibly be affected due to different modalities employed to measure tumor size pre- and posttreatment. Pretreatment tumor size was based on the radiological findings, a method less rigid than pathological assessment of the specimen. The tumor with PDGFR\(\text{A} \) mutation that responded with a \( \geq 30\% \) size reduction after neoadjuvant imatinib measured in fact the same size radiologically pre and post neoadjuvant treatment, whereas it in the pathological report was reported a smaller tumor size, hence can have led to possible size reduction overestimation. This should be taken into consideration when interpreting the results.

With neoadjuvant treatment, there is a slight risk of preoperative complications such as bleeding or intraabdominal tumor rupture,\(^16\) which in some cases may lead to an acute operation in a worse physical state than an elective surgery.\(^17\) There is also a risk of missing out on a potential curative situation when the patient does not get operated upfront if the surgeon considers it possible. Therefore, a close follow-up during initiation of neoadjuvant imatinib is crucial to provide supportive measures and, not least, to ensure the response to imatinib.

Our study demonstrated that patients treated with neoadjuvant imatinib reached R0 resection to a very high extent, which has been the case in previous studies.\(^11,18-20\) but it is not certain whether that affects the risk of relapse and long-time survival. Some studies have shown that R0-resection enhances the chance of local disease-free survival\(^20\) and tumor progression\(^21\) as well as overall survival,\(^22\) whereas others have shown that the risk of relapse is not reduced despite radical surgery.\(^23\) Our results suggest that R1 resection after NA imatinib led to increased risk for relapse, although there were very few patients with R1 in this group and therefore results should be interpreted with caution. Maybe the ambiguity regarding the value of R0 resection is due to the fact that it includes marginal as well as wide
surgical margin. A previous study from our center has shown a lower rate of local relapse with a wide surgical margin compared to marginal margin, but this type of analysis was not possible in the current material. Out of our 84 patients, n = 20 (24%) experienced local relapse or distant metastasis after the primary operation, which is fewer than usually described for the total GIST population. This could be explained by the fact that also small tumors had been included due to their anatomical location, but it might also indicate that neoadjuvant treatment could influence the risk of recurrence and/or long-time survival.

Despite the lack of formal evidence, imatinib demonstrates benefit in the neoadjuvant setting, but there is an unmet need to adopt methods to identify the patients who will benefit the most. In our study, we identified patients where a primary operation was not feasible or was combined with a high risk for morbidity; in other words, patients with large tumors and/or tumors located near the gastrointestinal junction, ligament of Treitz or the lower part of the rectum. The connection was most apparent for tumors in the stomach or small intestine. Our findings are concordant with previous studies and suggest that neoadjuvant treatment with imatinib reduces the risk for more extensive surgery. For example, a multicenter phase II study by Kurokawa et al demonstrated that among 53 neoadjuvant treated gastric GISTs, only three had to undergo total gastrectomy and, additionally, 48 achieved R0 resection, with the vast majority (n = 42) keeping at least 50% of their stomach after surgery. In our study, we did not grade the extent of gastric surgery more than total gastrectomy or not, but the results are consistent given that none of the 29 patients with gastric GIST had to undergo total gastrectomy.

In conclusion, although the benefit of neoadjuvant imatinib on the risk of relapse or long-time survival for patients with high-risk GISTs remains to be established, it seems clear that this approach is feasible, with low toxicity and increases the chance of radical and organ preserving surgery. Future studies should be investigating the potential role of neoadjuvant imatinib in large, high-risk GISTs in terms of local or distant recurrence risk reduction and in the longer term, also increase the chance of survival.

**AUTHOR CONTRIBUTIONS**
The work reported in the article has been performed by the authors, unless clearly specified in the text. Conceptualization: Andri Papakonstantinou, Sara Renberg, Felix Haglund de Flon. Formal Analysis: Andri Papakonstantinou. Investigation: Sara Renberg, Yifan Zhang, Fredrik Karlsson, Jan Åhlen, Li Jalmell, Christina Linder-Stragliotto, Andri Papakonstantinou. Methodology: Andri Papakonstantinou, Sara Renberg. Resources: Andri Papakonstantinou, Robert Bräström, Felix Haglund de Flon. Supervision: Andri Papakonstantinou, Robert Bräström. Writing - original draft: Sara Renberg, Andri Papakonstantinou. Writing - review and editing: all authors.

**ACKNOWLEDGEMENTS**
The authors would like to acknowledge statistician Víctor Navarro Garcés for his valuable assistance.

**CONFLICT OF INTEREST**
The authors declare no conflicts of interest.

**DATA AVAILABILITY STATEMENT**
The dataset used and analyzed during the current study is available from the corresponding author on reasonable request.

**ETHICS STATEMENT**
The study protocol was approved by the Swedish Ethical Review Authority and all study-related activities have been in line with current Swedish legislation. No dedicated informed consent was pursued given the retrospective nature of the study.

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**REFERENCES**
1. Casali PG, Abecassis N, Aro HT, et al. Gastrointestinal stromal tumours: ESMO-EURACAN clinical practice guidelines for diagnosis, treatment and follow-up. Ann Oncol. 2018;29:68-78.
2. Katz SC, DeMatteo RP. Gastrointestinal stromal tumors and leiomyosarcomas. J Surg Oncol. 2008;97:350-359.
3. Eisenberg BL, Judson I. Surgery and imatinib in the management of GIST: emerging approaches to adjuvant and neoadjuvant therapy. Ann Surg Oncol. 2004;11:465-475.
4. 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.
5. Hirota S, Isozaki K, Moriyama Y, et al. Gain-of-function mutations of c-kit in human gastrointestinal stromal tumors. Science. 1998;279:577-580.
6. Joensuu H, Roberts PJ, Sarlomo-Rikala M, et al. Effect of the tyrosine kinase inhibitor STI571 in a patient with a metastatic gastrointestinal stromal tumor. N Engl J Med. 2001;344:1052-1056.
7. Heinrich MC, Corless CL, Duensing A, et al. PDGFRA activating mutations in gastrointestinal stromal tumors. Science. 2003;299:708-710.
8. Joensuu H, Eriksson M, Sundby Hall K, et al. One vs three years of adjuvant imatinib for operable gastrointestinal stromal tumor: a randomized trial. JAMA. 2012;307:1265-1272.
9. Nishida T, Doi T, Naito Y. Tyrosine kinase inhibitors in the treatment of unresectable or metastatic gastrointestinal stromal tumors. Expert Opin Pharmacother. 2014;15:1979-89.
10. Rutkowski P, Gronchi A, Hohenberger P, et al. Neoadjuvant imatinib in locally advanced gastrointestinal stromal tumors (GIST): the EORTC STBSG experience. Ann Surg Oncol. 2013;20:2937-2943.
11. Kurokawa Y, Yang HK, Cho H, et al. Phase II study of neoadjuvant imatinib in large gastrointestinal stromal tumours of the stomach. Br J Cancer. 2017;117:25-32.
12. Ramaswamy A, Jain D, Sahu A, et al. Neoadjuvant imatinib: longer the better, need to modify risk stratification for adjuvant imatinib. J Gastrointest Oncol. 2016;7:624-631.
13. Wittekind C, Compton CC, Greene FL, Sobin LH. TNM residual tumor classification revisited. Cancer. 2002;94:2511-2516.
14. Joensuu H. Risk stratification of patients diagnosed with gastrointestinal stromal tumor. Hum Pathol. 2008;39:1411-1419.
15. Corless CL, Schroeder A, Griffith D, et al. PDGFRA mutations in gastrointestinal stromal tumors: frequency, spectrum and in vitro sensitivity to imatinib. J Clin Oncol. 2005;23:5357-5364.
16. Wang SY, Wu CE, Lai CC, et al. Prospective evaluation of neoadjuvant imatinib use in locally advanced gastrointestinal stromal
tumors: emphasis on the optimal duration of neoadjuvant imatinib use, safety, and oncological outcome. Cancers (Basel). 2019;11(3):42-436.

17. Mullen MG, Michaels AD, Mehaffey JH, et al. Risk associated with complications and mortality after urgent surgery vs elective and emergency surgery: implications for defining “quality” and reporting outcomes for urgent surgery. JAMA Surg. 2017;152:768-774.

18. Vassos N, Jakob J, Kähler G, et al. Preservation of organ function in locally advanced non-metastatic gastrointestinal stromal tumors (GIST) of the stomach by neoadjuvant imatinib therapy. Cancers (Basel). 2021;13:586-599.

19. Tang S, Yin Y, Shen C, et al. Preoperative imatinib mesylate (IM) for huge gastrointestinal stromal tumors (GIST). World J Surg Oncol. 2017;15:79.

20. Jakob J, Mussi C, Ronellenfitsch U, 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.

21. Wang D, Zhang Q, Blanke CD, 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.

22. Cavnar MJ, Seier K, Gönen M, et al. Prognostic factors after neoadjuvant imatinib for newly diagnosed primary gastrointestinal stromal tumor. J Gastrointest Surg. 2021;25:1828-1836.

23. Hølmebakk T, Bjerkehagen B, Hompland I, Stoldt S, Boye K. Relationship between R1 resection, tumour rupture and recurrence in resected gastrointestinal stromal tumour. Br J Surg. 2019;106:419-426.

24. Åhlén J, Karlsson F, Wejde J, Nilsson IL, Larsson C, Bränström R. Wide surgical margin improves the outcome for patients with gastrointestinal stromal tumors (GISTs). World J Surg. 2018;42:2512-2521.

25. Jakob J, Hohenberger P. Neoadjuvant therapy to downstage the extent of resection of gastrointestinal stromal tumors. Visc Med. 2018;34:359-365.

26. Shrikhande SV, Marda SS, Suradkar K, et al. Gastrointestinal stromal tumors: case series of 29 patients defining the role of imatinib prior to surgery. World J Surg. 2012;36:864-871.

27. Fiore M, Palassini E, Fumagalli E, et al. Preoperative imatinib mesylate for unresectable or locally advanced primary gastrointestinal stromal tumors (GIST). Eur J Surg Oncol. 2009;35:739-745.

28. Wilkinson MJ, Fitzgerald JE, Strauss DC, et al. Surgical treatment of gastrointestinal stromal tumour of the rectum in the era of imatinib. Br J Surg. 2015;102:965-971.

29. Kaneko M, Emoto S, Murono K, et al. Neoadjuvant imatinib therapy in rectal gastrointestinal stromal tumors. Surg Today. 2019;49:460-466.

SUPPORTING INFORMATION

Additional supporting information may be found in the online version of the article at the publisher’s website.

How to cite this article: Renberg S, Zhang Y, Karlsson F, et al. The role of neoadjuvant imatinib in gastrointestinal stromal tumor patients: 20 years of experience from a tertial referral center. Int J Cancer. 2022;151(6):906-913. doi:10.1002/ijc.34052