Neoadjuvant imatinib in locally advanced gastrointestinal stromal tumors (GIST) is effective and safe: results from a prospective single center study with 108 patients

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Neoadjuvant Imatinib in Locally Advanced Gastrointestinal Stromal Tumors (GISTs) is Effective and Safe: Results from a Prospective Single-Center Study with 108 Patients

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ABSTRACT

Background. Neoadjuvant imatinib is considered for gastrointestinal stromal tumors (GISTs) when decreased tumor size provides less extensive surgery and higher R0 resection rates. This study evaluates the effectivity and safety of neoadjuvant imatinib for large or locally advanced GIST.

Patients and Methods. From the prospective database of the Dutch GIST Consortium, all patients who underwent surgery after neoadjuvant imatinib at our center between 2009 and 2022 were selected. Independent and blinded assessment of surgical strategy was performed by two surgeons, based on anonymized computed tomography (CT) scans before and after neoadjuvant imatinib.

Results. Of 113 patients that received neoadjuvant imatinib, 108 (95%) [mean age 61.6, standard deviation (SD) 11.5, 54% male] underwent a GIST resection. Of all GISTs, 67% was localized in the stomach and 25% in the duodenum or small intestine. In 74% of the patients with GIST, a KIT exon 11 mutation was found. Decreased tumor size was seen in 95 (88%) patients. Having a KIT exon 11 mutation [odds ratio (OR) 5.64, 95% confidence interval (CI) 1.67–19.1, $p < 0.01$] or not having a mutation (OR 0.19, 95% CI 0.04–0.89, $p = 0.04$) were positive and negative predictive values for partial response, respectively. In 55 (51%) patients, there was deescalation of surgical strategy after neoadjuvant imatinib. Surgical complications were documented in 16 (15%) patients ($n = 8$, grade II; $n = 5$, grade IIIa; $n = 3$, grade IIIb) and R0 resection was accomplished in 95 (89%) patients. The 5-year disease-free and overall survival were 80% and 91%, respectively.

Conclusion. This study shows that neoadjuvant imatinib is effective and safe for patients with large or locally advanced GIST.

A gastrointestinal stromal tumor (GIST) is a rare type of mesenchymal cancer arising from the gastrointestinal tract, with an incidence of 1–1.5 per 100,000 persons per year.[1,2] Despite the low incidence, it is the most common type of soft tissue sarcoma.[3,4] It arises predominantly in the stomach (60%) and small intestine (35%), and 5% are located in the colon, rectum, or oesophagus.[5] The mainstay of treatment for localized and locally advanced disease is surgery and varies from small wedge excisions to extensive multivisceral resections.[6–8] Nowadays, 3-year adjuvant treatment with imatinib is considered standard of care for high risk GISTs with imatinib-sensitive mutations in c-KIT exon 11, c-KIT exon 9, or PDGFR exon 18 (non-D842V mutations) have been shown to improve disease-free survival (DFS) and overall survival (OS).[7,9,10] The definition of high risk GISTs is based on mitotic rate, tumor size, and origin according to the Miettinen criteria.[5]

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The role of neoadjuvant imatinib has not been well defined to date, although it is frequently applied in GIST expertise centers.[11] Neoadjuvant imatinib can reduce the size of the GIST by 10–50% before surgery.[12–19] This reduction in size potentially leads to less extensive surgery, i.e., a wedge excision of the duodenum instead of a pancreaticoduodenectomy.[13,20] Several studies have shown that neoadjuvant imatinib has significantly improved OS.[20–22] However, this was not compared with adjuvant imatinib. Because of the potential positive effect of neoadjuvant imatinib on the surgical strategy, many patients with GIST in our center are treated with neoadjuvant imatinib. It is considered for large, often locally advanced GISTs of any origin when downsizing of the tumor might lead to a less extensive surgical procedure or higher R0 rate. Also, it is taken into consideration if a patient would be eligible for adjuvant imatinib anyway.

In this study, we aim to evaluate the effectivity and safety of neoadjuvant imatinib in our patient cohort. Also, we aim to identify predictive factors for downsizing the primary tumor and to analyze oncological outcomes in terms of DFS and OS.

PATIENTS AND METHODS

For this study, we used the prospective Dutch GIST consortium database to select all patients who received imatinib as neoadjuvant treatment for a primary GIST at the Netherlands Cancer Center (NKI). Patients were excluded if aged < 18 years or if metastasized disease was seen at the start of treatment with neoadjuvant imatinib. For further analysis, patients that did not undergo surgery were excluded.

Before starting neoadjuvant imatinib, all patients were discussed in a dedicated multidisciplinary tumor board (MDT) to determine the indication for neoadjuvant imatinib. As mentioned in the introduction, neoadjuvant imatinib was considered if a primary resection of tumors would result in extensive or morbid surgery or low anticipated R0 rates and/or if it was already known that there was an indication for adjuvant imatinib anyway. The timing of the resection was determined during the MDT based on follow-up with a computed tomography (CT) scan or magnetic resonance imaging (MRI). Surgery was usually performed when the plateau phase of tumor shrinkage was achieved. Adjuvant imatinib was given to patients who had a 5-year recurrence risk of > 50% according to the Miettinen criteria over a period of 3 years in total.[5] The mitotic rate for risk assessment was determined on material obtained from biopsy before the start of imatinib.

Treatment with neoadjuvant imatinib was considered safe if no patients developed metastasis during treatment, if no patients had to stop treatment due to toxicity, and if the complication rate and R0 rate were comparable with other studies. The effectiveness of neoadjuvant imatinib was evaluated on the basis of a decrease in size of the tumor and the anticipation of less extensive surgery. The change in size was categorized by decreased size, no change in size (visible on imaging), or an increased size. To assess if neoadjuvant imatinib resulted in less extensive surgery, two surgeons blindly assessed all CT and MRI scans independently, before and after neoadjuvant imatinib. They both completed a questionnaire to determine: (1) which organs were involved with the GIST, (2) if a R0 resection was feasible, (3) if a laparoscopic resection was possible, and (4) what surgical procedure was necessary (e.g., gastric wedge excision or partial gastrectomy). All scans were anonymized and assessed in randomized order. Less extensive surgery after neoadjuvant imatinib was determined as monovisceral resection instead of a multivisceral resection or a deescalation of surgery based on the completed questionnaire (e.g., from partial gastrectomy to gastric wedge excision). Furthermore, the results of the questionnaires were used to analyze whether neoadjuvant imatinib would increase the number of anticipated R0 resections and the number of anticipated laparoscopic resections. Performed surgical strategies were compared with the anticipated strategies.

With approval of the local institutional review board, clinical data such as age, sex, size of the tumor before neoadjuvant imatinib, mutational status, duration and dosage of Imatinib, complications after surgery, R0 resections, and long-term outcomes (recurrence, metastasis, and death) were retrieved from the prospectively kept database. Race/ethnicity was not a variable in the database and therefore not included. Additional data, such as body mass index (BMI), American Society of Anesthesiologists (ASA) classification,[23] size of the tumor after neoadjuvant imatinib, and date of last contact were retrospectively extracted from the electronic patients files. Furthermore, patients were classified according to the Miettinen risk score in the categories very low to low, or intermediate to high. These two classifications were chosen because the mitotic rate is necessary to differentiate between very low and low, and between intermediate and high, but the mitotic rate was missing or unreliable because of the effect of imatinib on the resected material. Rupture was defined as either a rupture described at the operation report, or a capsular tear in the pathology report.

Statistical Analysis

SPSS version 27 was used to analyze the data. To describe normally distributed data, a mean was used, and not normally distributed data was described with a median. The Shapiro–Wilk normality test and interpretation of histogram were used to determine the normality of distribution. Means were compared with the paired *t*-test, and paired nominal data was compared with McNemar's test. Multivariate

regression analyses were done to search for predictors of decreasing tumor size and for positive perioperative outcomes. Variables with $p < 0.2$ in a univariate regression analysis were used for the multivariate regression analyses. In the case of insufficient number of events, backward selection was done to select the maximum number of variables. To analyze OS and DFS, Kaplan–Meier curves were made. OS was measured from the start of treatment and DFS from the moment of surgery. A $p < 0.05$ was considered statistically significant.

RESULTS

From 2009 to 2022, 113 patients with GIST were treated with neoadjuvant imatinib in our center. Of these patients, 5 (5%) did not undergo resection and were excluded from further analyses. Three patients refused surgery because of their high age (average 82 years) and expected morbidity of the procedure, which would be two abdominal perineal resections (APR) and a Whipple procedure, and they continued imatinib treatment. One patient had to stop neoadjuvant imatinib because of toxicity and metastasized disease was found shortly after, before an operation could take place. The fifth patient was 52 years old and had a GIST with a KIT exon 11 mutation in the esophagus and showed progression of disease with new metastases within 2 months after start of neoadjuvant imatinib.

Of the 108 patients with GIST who underwent operation, the tumors originated in the stomach in 72 patients (67%) and in the small bowel in 18 patients (17%). The other GISTs originated in the duodenum, rectum, and esophagus. Pathological examination showed a KIT exon 11 mutation in 80 (74%) patients. The mitotic rate after biopsy was ≤ 5/5 mm^2 in 42 patients (39%), while 17 patients (16%) had a mitotic rate of > 5/5 mm^2. For the rest of the patients, the mitotic rate was missing because the amount of biopsy material was limited. Neoadjuvant imatinib was given for a median duration of 31 weeks [interquartile range (IQR) 24–43]. Of all the patients, 62% received the standard dosage of 400 mg once a day, the other 38% received either a (temporary) lower dosage due to toxicity, or a higher dosage if the standard dosage did not have the desirable effect. Toxicity with a Common Terminology Criteria for Adverse Events (CTCAE) grade > 2 was seen in 12 patients (11.2%). All patient characteristics are shown in Table 1.

Tumor Size Reduction

The median size of a GIST before starting neoadjuvant imatinib was 10 cm (IQR 64–149) and this was reduced to 6.4 cm (IQR 44–102) after treatment, a statistically significant decrease of 36% ($p < 0.001$) (Fig. 1). Decreased tumor size was seen in 95 (88%) patients, while 4 (4%) patients had

TABLE 1 Patient characteristics

	N = 108	
Age (mean; SD)	61.6	(11.5)
Sex (male; %)	58	(53.7)
BMI (median; IQR)	25.8	(24.0 – 29.5)
Missing (%)	2	(1.8)
ASA score (%)		
1	41	(38.0)
2	53	(49.1)
3	8	(7.4)
4	1	(0.9)
Missing	5	(4.6)
Mutation		
KIT exon 9	6	(5.6)
KIT exon 11	80	(74.1)
KIT exon 13	2	(1.9)
PDGFR 18 (D842V)	5	(4.7)
PDGFR 18 (other)	5	(4.7)
No mutation	7	(6.5)
Missing	3	(2.8)
Tumor location (%)		
Stomach	72	(66.7)
Small bowel	18	(16.7)
Duodenum	9	(8.3)
Rectum	7	(6.5)
Esophagus	2	(1.9)
Tumor size before imatinib		
< 5 cm	9	(8.3)
5–10 cm	46	(42.6)
> 10 cm	53	(49.1)
Tumor size after imatinib		
< 5 cm	35	(32.4)
5–10 cm	45	(41.7)
> 10 cm	28	(25.9)
Mitotic rate after biopsy ≤ 5/5 mm^2 (%)	42	(38.8)
Mitotic rate after biopsy > 5/5 mm^2 (%)	17	(15.7)
Missing	49	(45.4)
Miettinen		
Very low–low	11	(10.2)
Intermediate–high	71	(65.7)
Missing	26	(24.1)
Number of weeks of imatinib (median; IQR) (temporary) dosage of imatinib	31.0	(24.0–42.0)
< 400 mg	8	(7.4)
400 mg	67	(62.0)
> 400 mg	33	(30.6)
Toxicity (CTCTAE grade > 2)		
3	11	(10.2)
4	1	(0.9)

BMI body mass index, ASA American society of anesthesiology, CTCAE Common Terminology Criteria for Adverse Events

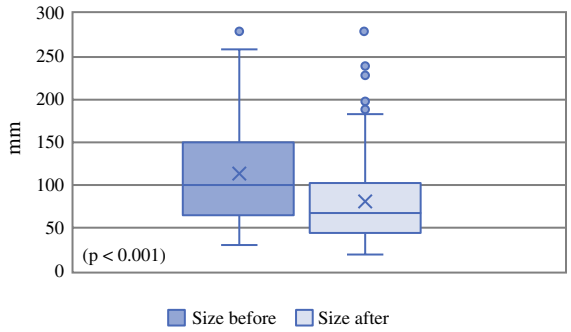

FIG. 1 Median tumor size in mm before and after neoadjuvant imatinib

no change in size, and 9 (8%) patients showed an increase in tumor size. The 13 tumors without decreased tumor size originated in the stomach, small bowel, and duodenum in seven, three, and three patients, respectively. Two of these patients had a KIT exon 9 mutation, one patient a KIT exon 13 mutation, five patients a KIT exon 11 mutation, two patients a PDGFR 18 mutation (of which one was a D842V mutation), and in three patients no mutation was found (Fig. 2). Univariate regression analyses showed that having a KIT exon 11 mutation was a statistically significant positive predictive value [odds ratio (OR) 5.64 95% confidence interval (CI), 1.67–19.1, $p < 0.01$] for size reduction and not having a mutation had a statistically significant negative predictive value (OR 0.19, 95% CI 0.04–0.89, $p = 0.04$). The other mutational types did not have a significant predictive value for tumor size reduction. Tumor location, size before neoadjuvant imatinib, age, and sex did not have a $p < 0.2$ after univariate regression analyses.

Change in Surgical Strategy after Neoadjuvant Imatinib

Analysis of the surgical strategy of both surgeons based on the CT scans showed they anticipated 41 (38%) less multivisceral resections after neoadjuvant imatinib. Also, when analyzing the strategies on open versus minimally invasive surgery (MIS) and the chance of a R0 resection, more minimally invasive surgery and more R0 resections after neoadjuvant imatinib were anticipated compared with before the start of neoadjuvant imatinib. The decrease in anticipated multivisceral resections and open surgery was statistically significant for both surgeons, while the increase of anticipated R0 resection was statistically significant for only one surgeon. The anticipated number of multivisceral resection was comparable with the actual number of multivisceral resections, while more open surgery and less R0 resections were seen than anticipated (Fig. 3A–C). Further analyses showed that in nine patients (8%), less extensive surgery on a single organ was anticipated, for example a wedge resection instead of a partial gastrectomy. Thus, less extensive surgery was anticipated in a total of 55 patients (51%). An interesting extra finding was that the seven patients with a rectal GIST all responded well in terms of tumor size reduction, but there was no decrease in extensiveness of surgery since the tumor did not reach the threshold of a transanal endoscopic microsurgery/transanal minimally invasive surgery (TEM/TAMIS) procedure. Six APRs and one low anterior resection were performed.

Perioperative and Postoperative Results

The surgical characteristics are shown in Table 2. Successful R0 resections were achieved in 96 patients (89%) and univariate regression analyses showed that a smaller size after neoadjuvant imatinib (OR 1.02, 95% CI 1.005–1.015, $p < 0.01$) and no multivisceral resection (OR 3.8, 95% CI 1.1–13.1, $p = 0.03$) was significantly correlated with a higher chance of R0 resection. Complications [Clavien–Dindo (CD) with grade ≥ 2] were seen in 16 patients (15%; $n = 8$, grade II; $n = 5$, grade IIIA; $n = 3$, grade IIIb). Reoperation was necessary for the CD IIIb complications because

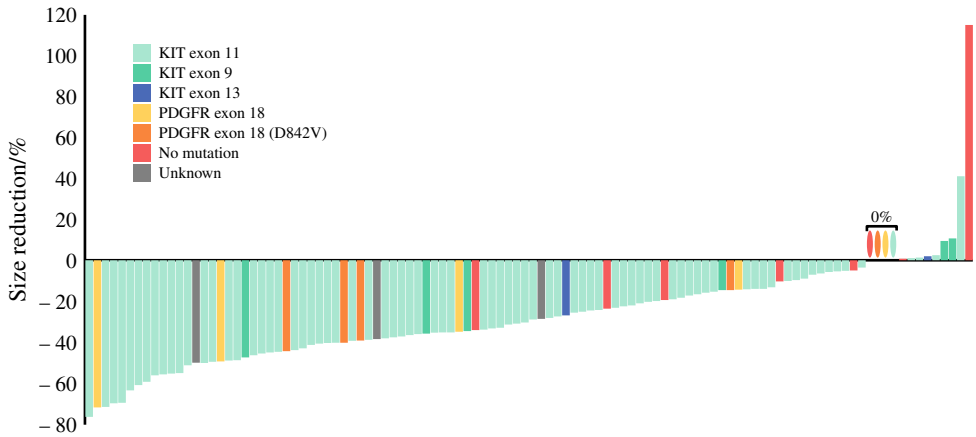

FIG. 2 A waterfall plot showing the mutation of all patients together with the percentage of size reduction of the tumor

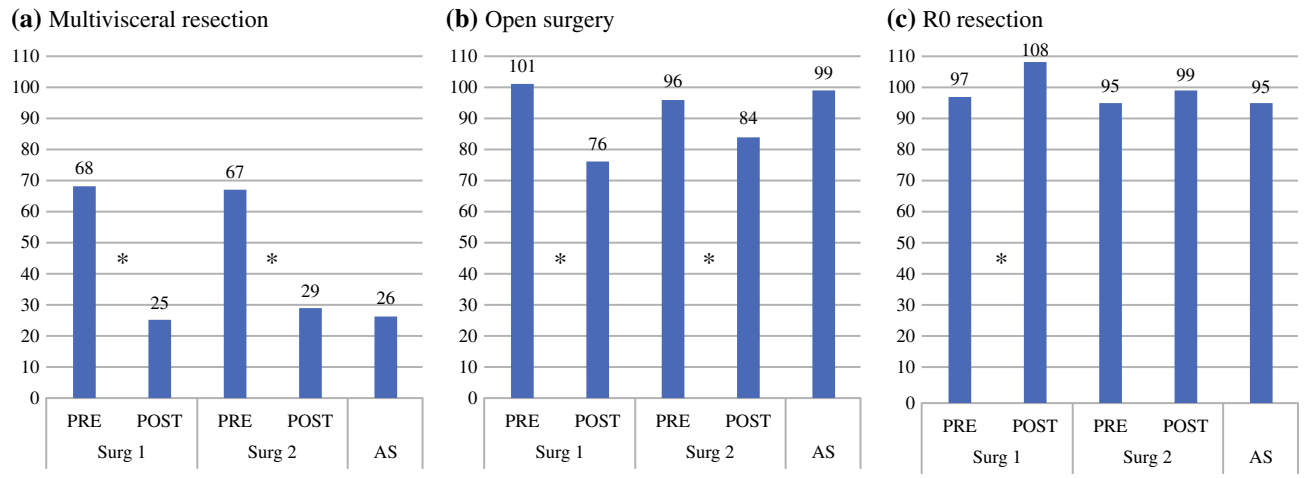

FIG. 3 Anticipated surgery before and after neoadjuvant imatinib per surgeon compared with the actual performed surgery. **A** shows the number of patients with anticipated multivisceral resections before and after neoadjuvant imatinib per surgeon and the actual number of multivisceral resections. **B** shows the number of patients with anticipated open surgical resections before and after neoadjuvant imatinib per surgeon and the actual number of open resections. **C** shows the number of patients with anticipated R0 resections before and after neoadjuvant imatinib per surgeon and the actual number of R0 resections. *Statistical significant difference according to McNemar's test. *Surg* surgeon, *AS* actual surgery

TABLE 2 Surgical characteristics

	$N = 108$	
Type of surgery (%)		
Gastric wedge resection	53	(49.1)
Partial gastrectomy	18	(16.7)
Small bowel segment resection	18	(16.7)
Duodenal segment resection	7	(6.5)
Abdominal perineal resection	6	(5.6)
Other	6	(5.6)
Multivisceral resection (%)	26	(24.1)
Surgical technique:		
Open surgery (%)	97	(89.8)
Laparoscopic surgery:	11	(10.2)
Margins:		
R0 (%)	96	(88.9)
R1 (%)	12	(11.1)
Intraoperative rupture (%)	5	(4.6)
Duration in surgery in minutes (median; IQR)	111	(82–150)
Missing (%)	5	(4.6)
Blood loss in ml (median; IQR)	200	(50–631)
Missing (%)	26	(24.1)
Complications ≥ CD grade 2 (%)	16	(15.0)
Grade 2 (%)	8	(7.5)
Grade 3a (%)	5	(4.6)
Grade 3b (%)	3	(2.8)
Missing (%)	1	(0.9)
Mitotic rate after surgery ≤ 5/5 mm^2 (%)	75	(69.4)
Mitotic rate after surgery > 5/5 mm^2 (%)	9	(8.3)
Missing (%)	24	(22.2)

CD Clavien–Dindo

of a bleeding, anastomotic leakage, and bile leakage after a Whipple procedure.

Follow-up

After surgery, 60 patients (56%) received adjuvant imatinib based on the Miettinen risk profile of their resected GIST. Median follow-up time of the patients was 54.5 months. The OS after 3 and 5 years was 94% and 91%, respectively. For the DFS this was 86% and 80% at 3 and 5 years, respectively. Kaplan–Meier for OS and DFS showed that patients without a decrease in tumor size during neoadjuvant imatinib had a statistically significant worse outcome ($p = 0.037$ and 0.006, respectively) (Fig. 4).

DISCUSSION

This study aimed to evaluate the effectivity and safety of neoadjuvant imatinib in a prospective single-center cohort. To the best of our knowledge, this is the largest single-center study to date evaluating neoadjuvant imatinib in patients with large and mostly locally advanced primary GISTs. Our results demonstrate that neoadjuvant imatinib is effective given the significant reduction in tumor size in 88% of the patients, which led to less extensive surgery in 51% of all patients. Furthermore, due to the fact that only one patient metastasized during neoadjuvant imatinib, only one patient stopped imatinib because of toxicity, the relatively high R0 rates, and acceptable complication rates observed after surgery, neoadjuvant imatinib can be considered to be safe.

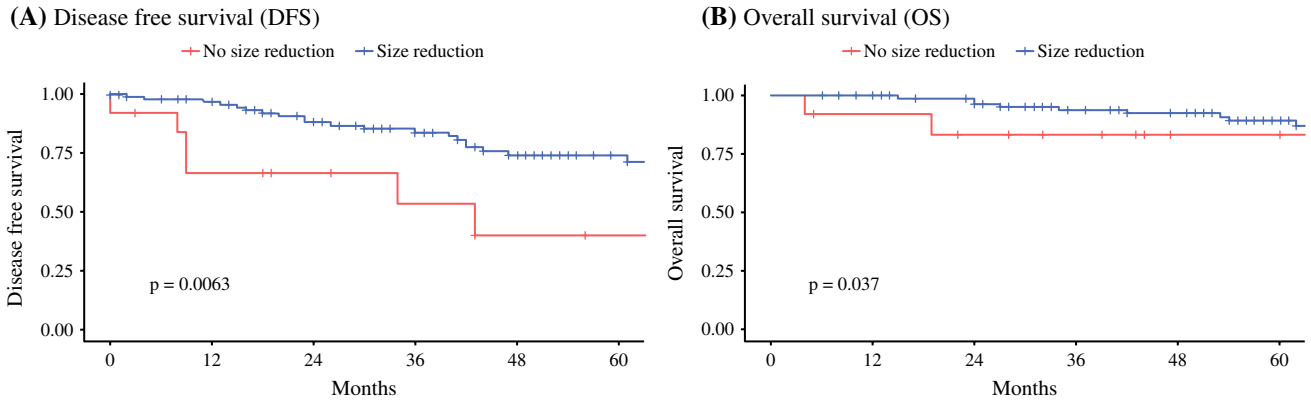

FIG. 4 Kaplan–Meier for DFS **A** and OS **B** where the blue line displays the patients without a decrease in tumor size

The high percentage of patient with a decreased tumor size (88%) and the median reduction in tumor size (36%) is comparable with other neoadjuvant imatinib studies, with a tumor size reduction varying from 10 to 50% before surgery.[12–16,18,24] Of the 108 patients, only 13 patients did not show a reduction in size of the tumor. Having a KIT exon 11 mutation was a positive predictor for reduction in size, which is in line with a previous study.[25] Not having a imatinib sensitive mutation was an indicator for not having a decrease in tumor size, which confirms that performing mutational analysis before starting neoadjuvant imatinib is essential. Surprisingly, 4 of 5 (80.0%) PDGFR (D842V) mutated GISTs responded well to imatinib, while this type of mutation is known for its resistance to imatinib treatment. In contrast, two other studies showed response to neoadjuvant imatinib in 0/5 (0%) and 2/16 (12.5%) of GISTs with similar mutations.[10,26] This suggests that treating PDGFR (D842V) mutated GIST with neoadjuvant imatinib could still be attempted if primary surgery would cause large morbidity and avapritinib cannot be considered for any reason.

This study illustrates that neoadjuvant imatinib frequently (51%) leads to less extensive surgical procedures. The studies of Shrikhande et al. and Fiore et al. also described the effect of neoadjuvant imatinib on the surgical strategy in patients with a primary inoperable or locally advanced GIST at different locations in the gastrointestinal tract.[13,16] They found an improvement of the planned surgical procedure in 15 out of 15 (100%) patients and 24 out of 26 (92.3%), respectively. They considered it an improvement when an anticipated unresectable tumor became resectable after neoadjuvant imatinib or when less extensive surgery was necessary after neoadjuvant imatinib. Ang et al. showed that 9 (90%) of the 10 patients with a locally advanced GIST in the duodenum for whom a pancreaticoduodenectomy was planned, were operated after neoadjuvant imatinib with organ preserving surgery.[27] The percentages in these three studies are higher compared with our study (51%), which can be explained by the fact that in our study less tumors were inoperable before start of treatment, and not all tumors were locally advanced. However, the combination of tumor size reduction in 88% of patients, low percentages of ≥ grade III toxicity and disease progression, and less extensive surgery in more than half of the patients is compelling evidence to consider neoadjuvant imatinib, especially for patients for whom adjuvant imatinib is indicated anyway. We suggest that eligible patients should always be discussed in specialized MDTs to give personalized advice.

GISTs are well known for their risk of rupture since they are often very fragile, and especially in locally advanced tumors this risk might be even higher.[28] In our study population, five patients (4.6%) had intraoperative ruptures. Other studies with populations varying from 13 to 46 patients treated with neoadjuvant imatinib mentioned ruptures in 0–2.2% of their patients.[21,29,30] However, the relatively small number of patients in these studies might underrepresent the percentage of ruptures, and also the definition of rupture in these studies is unclear while our definition is very strict. Nishida et al.[28] showed in a review of 12 studies, with 71–1198 patients, that tumors without neoadjuvant imatinib ruptured in 3–22% of patients. However, the rupture definition again was not clearly defined in these studies. We hypothesize that neoadjuvant imatinib results in less GIST ruptures because of hyalinization. The 4.6% in our cohort compared with the study of Nishida et al. supports that theory.

Because of the high risk of rupture of a GIST, open resections were the standard of care in our center until 2018. This explains the difference between the anticipated MIS of both surgeons and the actual number of MIS. Multiple publications demonstrated that MIS did not lead to a difference in long term outcomes for gastric GIST,[31–33] or higher rupture rates.[34,35] Therefore, more MIS is also performed in our center since then.

The R0 resection rate after a GIST resection in our cohort was 88%, which is comparable with studies including 27–161 patients demonstrating R0 resection rates of 81.5–94.0% after neoadjuvant imatinib for locally advanced GISTs.[14,20–22,36,37] Rutkowski et al.[35] demonstrated R0 rates 75.5% in a population operated without neoadjuvant imatinib. Therefore, it appears that neoadjuvant imatinib improves R0 rates, which correlates with higher DFS.[1,7,9]

Complications with CD ≥ 2 were observed in only 15% of the patients, no grade IV or V complications occurred, and only three (2.3%) patients needed a reoperation (CD IIIB). Since many surgeries in this cohort were quite extensive, the percentage of complications is considered relatively low. Other studies demonstrated similar complication rates of 7.8–15.0% and reoperations in 3.0–3.9%.[13,17,20,37]

We compared our survival rates with other studies about neoadjuvant imatinib. In our population, a 3-year DFS of 86% was seen, while two single-center studies with populations of 15 and 22 patients reported a 3-year progression-free survival (PFS) of 77% and 94%, respectively,[16,29] and one single-center study with 13 patients reported a DFS of 76%.[22] Our 5-year DFS was 80%, while two other single-center studies with 25 and 57 patients and a multicenter study with 31 patients showed PFS of 57–77%.[14,21,24] A DFS of 65% was demonstrated by only one multicenter study with 161 patients.[20] Our study demonstrated a 3- and 5-years OS of 93 and 90%, respectively. A 3-year OS of 94% was reported in a single-center study with 51 patients and 5-year OS of 77% and 88% were demonstrated in the earlier mentioned multicenter study with 31 patients and the single-center study with 57 patients, respectively.[14,17,21] Overall, our 3-year survival rates were similar compared with the other studies and the 5-year survival rates were even slightly better. In the pre-imatinib era, 5-year DFS and OS of 38–45% and 50–65%, respectively, were normal, which illustrates the importance of imatinib treatment.[38–42]

This study has several limitations. First, even though this is the largest single-center study with prospectively collected data, this study did not compare patients with and without neoadjuvant imatinib. Only a randomized controlled trial could answer that question, but this is ethically not feasible because of the already clearly demonstrated benefit judged by common sense. Second, the interpretation of surgical strategies was subjective and thus open for discussion. Last, the number of patients with other mutations than KIT exon 11 was low. A larger cohort could result in more significant predictive values for the other mutations.

CONCLUSIONS

In this single-center cohort study, we demonstrate that neoadjuvant imatinib for large and often locally advanced GIST results in resections in 95% of the patients. Furthermore, it results in reduced tumor size, less extensive surgery and low R1 and complication rates. Thus, it can be concluded that neoadjuvant imatinib for this population is effective and safe and should be considered after determining the mutational status.

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REFERENCES

1. Joensuu H, DeMatteo RP. The management of gastrointestinal stromal tumors: a model for targeted and multidisciplinary therapy of malignancy. *Annu Rev Med*. 2012;63:247–58.
2. van der Graaf WTA, Tielen R, Bonenkamp JJ, Lemmens V, Verhoeven RHA, de Wilt JHW. Nationwide trends in the incidence and outcome of patients with gastrointestinal stromal tumour in the imatinib era. *Br J Surg*. 2018;105(8):1020–7.
3. Sanders L, Silverman M, Rossi R, Braasch J, Munson L. Gastric smooth muscle tumors: diagnostic dilemmas and factors affecting outcome. *World J Surg*. 1996;20(8):992–5.
4. Ducimetière F, Lurkin A, Ranchère-Vince D, Decouvelaere AV, Péoc'h M, Istier L, et al. Incidence of sarcoma histotypes and molecular subtypes in a prospective epidemiological study with central pathology review and molecular testing. *PLoS ONE*. 2011;6(8):e20294.
5. Miettinen M, Lasota J. Gastrointestinal stromal tumors: review on morphology, molecular pathology, prognosis, and differential diagnosis. *Arch Pathol Lab Med*. 2006;130(10):1466–78.
6. Corless CL, Ballman KV, Antonescu CR, Kolesnikova V, Maki RG, Pisters PW, et al. Pathologic and molecular features correlate with long-term outcome after adjuvant therapy of resected primary GI stromal tumor: the ACOSOG Z9001 trial. *J Clin Oncol*. 2014;32(15):1563–70.
7. Casali PG, Abecassis N, Aro HT, Bauer S, Biagini R, Bielack S, et al. Gastrointestinal stromal tumours: ESMO-EURACAN clinical practice guidelines for diagnosis, treatment and follow-up. *Ann Oncol*. 2018;29(Suppl 4):iv68–78.
8. von Mehren M, Randall RL, Benjamin RS, Boles S, Bui MM, Ganjoo KN, et al. Soft tissue sarcoma, version 2. 2018, NCCN clinical practice guidelines in oncology. *J Natl Compr Cancer Netw*. 2018;16(5):536–63.
9. Joensuu H, Eriksson M, Sundby Hall K, Hartmann JT, Pink D, Schütte J, et al. One vs three years of adjuvant imatinib for

operable gastrointestinal stromal tumor: a randomized trial. *JAMA*. 2012;307(12):1265–72.
10. Farag S, Somaiah N, Choi H, Heeres B, Wang WL, van Boven H, et al. Clinical characteristics and treatment outcome in a large multicentre observational cohort of PDGFRA exon 18 mutated gastrointestinal stromal tumour patients. *Eur J Cancer*. 2017;76:76–83.
11. Andtbacka RH, Ng CS, Scaife CL, Cormier JN, Hunt KK, Pisters PW, et al. Surgical resection of gastrointestinal stromal tumors after treatment with imatinib. *Ann Surg Oncol*. 2007;14(1):14–24.
12. Tirumani SH, Shinagare AB, Jagannathan JP, Krajewski KM, Ramaiya NH, 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(4):420–8.
13. Shrikhande SV, Marda SS, Suradkar K, Arya S, Shetty GS, Bal M, et al. Gastrointestinal stromal tumors: case series of 29 patients defining the role of imatinib prior to surgery. *World J Surg*. 2012;36(4):864–71.
14. Tielen R, Verhoef C, van Coevorden F, Gelderblom H, Sleijfer S, Hartgrink HH, et al. Surgical treatment of locally advanced, non-metastatic, gastrointestinal stromal tumours after treatment with imatinib. *Eur J Surg Oncol*. 2013;39(2):150–5.
15. Seshadri RA, Rajendranath R. Neoadjuvant imatinib in locally advanced gastrointestinal stromal tumors. *J Cancer Res Ther*. 2009;5(4):267–71.
16. Fiore M, Palassini E, Fumagalli E, Pilotti S, Tamborini E, Stacchiotti S, et al. Preoperative imatinib mesylate for unresectable or locally advanced primary gastrointestinal stromal tumors (GIST). *Eur J Surg Oncol*. 2009;35(7):739–45.
17. Wang J, Yin Y, Shen C, Yin X, Cai Z, Pu L, et al. Preoperative imatinib treatment in patients with locally advanced and metastatic/recurrent gastrointestinal stromal tumors: a single-center analysis. *Medicine (Baltimore)*. 2020;99(9):e19275.
18. Li GZ, Fairweather M, Raut CP, Wang J. Use of neoadjuvant imatinib to facilitate minimally invasive resection of gastric gastrointestinal stromal tumors. *Ann Surg Oncol*. 2022;29(11):7104–13.
19. de Vos tot Nederveen Cappel RJ, van Hillegersberg R, Rodenhuis S, Peterse JL, van Coevorden F. Downstaging of an advanced gastrointestinal stromal tumor by neoadjuvant imatinib. *Dig Surg*. 2004;21(1):77–9.
20. 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(9):2937–43.
21. Eisenberg BL, Harris J, Blanke CD, Demetri GD, Heinrich MC, Watson JC, et al. Phase II trial of neoadjuvant/adjuvant imatinib mesylate (IM) for advanced primary and metastatic/recurrent operable gastrointestinal stromal tumor (GIST): early results of RTOG 0132/ACRIN 6665. *J Surg Oncol*. 2009;99(1):42–7.
22. Yang W, Yu J, Gao Y, Shen Q, Zhang Q, Liu X, et al. Preoperative imatinib facilitates complete resection of locally advanced primary GIST by a less invasive procedure. *Med Oncol*. 2014;31(9):133.
23. Daabiss M. American society of anaesthesiologists physical status classification. *Indian J Anaesth*. 2011;55(2):111–5.
24. Qi J, Liu HL, Ren F, Liu S, Shi W, Liu WH, et al. Preoperative adjuvant therapy for locally advanced and recurrent/metastatic gastrointestinal stromal tumors: a retrospective study. *World J Surg Oncol*. 2020;18(1):70.
25. Quek R, Farid M, Kanjanapan Y, Lim C, Tan IB, Kesavan S, et al. Prognostic significance of KIT exon 11 deletion mutation in intermediate-risk gastrointestinal stromal tumor. *Asia Pac J Clin Oncol*. 2017;13(3):115–24.
26. Yoo C, Ryu MH, Jo J, Park I, Ryoo BY, Kang YK. Efficacy of imatinib in patients with platelet-derived growth factor receptor alpha-mutated gastrointestinal stromal tumors. *Cancer Res Treat*. 2016;48(2):546–52.
27. Lv A, Qian H, Qiu H, Wu J, Li Y, Li Z, et al. Organ-preserving surgery for locally advanced duodenal gastrointestinal stromal tumor after neoadjuvant treatment. *Biosci Trends*. 2017;11(4):483–9.
28. Nishida T, Hølmebakk T, Raut CP, Rutkowski P. Defining tumor rupture in gastrointestinal stromal tumor. *Ann Surg Oncol*. 2019;26(6):1669–75.
29. Xu J, Ling TL, Wang M, Zhao WY, Cao H. Preoperative imatinib treatment in patients with advanced gastrointestinal stromal tumors: patient experiences and systematic review of 563 patients. *Int Surg*. 2015;100(5):860–9.
30. Kurokawa Y, Yang HK, Cho H, Ryu MH, Masuzawa T, Park SR, et al. Phase II study of neoadjuvant imatinib in large gastrointestinal stromal tumours of the stomach. *Br J Cancer*. 2017;117(1):25–32.
31. Gertsen EC, van Boxel GI, Brosens LAA, Ruurda JP, van Hillegersberg R. Minimally invasive resection of large gastric gastrointestinal stromal tumors. *Dig Surg*. 2020;37(6):441–6.
32. Ortenzi M, Ghiselli R, Cardinali L, Guerrieri M. Surgical treatment of gastric stromal tumors: laparoscopic versus open approach. *Ann Ital Chir*. 2017;88(2):163–9.
33. Iordanou C, Theodoridis CA, Lykoudis PM, Dimitroulis D, Machairas N, Spartalis E, et al. Current evidence on laparoscopic vs. open resection for gastric stromal tumours. *Oncol Lett*. 2021;22(4):734.
34. Bischof DA, Kim Y, Dodson R, Carolina Jimenez M, Behman R, Cocieru A, et al. Open versus minimally invasive resection of gastric GIST: a multi-institutional analysis of short- and long-term outcomes. *Ann Surg Oncol*. 2014;21(9):2941–8.
35. Park SH, Lee HJ, Kim MC, Yook JH, Sohn TS, Hyung WJ, et al. Early experience of laparoscopic resection and comparison with open surgery for gastric gastrointestinal stromal tumor: a multicenter retrospective study. *Sci Rep*. 2022;12(1):2290.
36. Renberg S, Zhang Y, Karlsson F, Bränström R, Åhlen J, Jalmsell L, 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):906–13.
37. Wang SY, Wu CE, Lai CC, Chen JS, Tsai CY, Cheng CT, 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):424.
38. Rutkowski P, Nowecki ZI, Michej W, Debiec-Rychter M, Woźniak A, Limon J, et al. Risk criteria and prognostic factors for predicting recurrences after resection of primary gastrointestinal stromal tumor. *Ann Surg Oncol*. 2007;14(7):2018–27.
39. Wozniak A, Rutkowski P, Schöffski P, Ray-Coquard I, Hostein I, Schildhaus HU, et al. Tumor genotype is an independent prognostic factor in primary gastrointestinal stromal tumors of gastric origin: a european multicenter analysis based on ConticaGIST. *Clin Cancer Res*. 2014;20(23):6105–16.
40. Connolly EM, Gaffney E, Reynolds JV. Gastrointestinal stromal tumours. *Br J Surg*. 2003;90(10):1178–86.
41. Eisenberg BL, Judson I. Surgery and imatinib in the management of GIST: emerging approaches to adjuvant and neoadjuvant therapy. *Ann Surg Oncol*. 2004;11(5):465–75.
42. Valadão M, de Mello EL, Lourenço L, Vilhena B, Romano S, Castro LS. What is the prognostic significance of metastatic lymph nodes in GIST? *Hepatogastroenterology*. 2008;55(82–83):471–4.