Original Article

Neoadjuvant versus adjuvant imatinib in primary localized gastrointestinal stromal tumor

Jiayu Ling[1,2#], Lishuo Shi[2,3#], Xingyu Cheng[1,2], Yang Fu[1,2], Ziqin Lin[1,2], Yandong Zhao[2,4], Zheqing Li[2,5], Jianwei Zhang[1,2], Huabin Hu[1,2], Yue Cai[1,2], Yanhong Deng[1,2]

[1]Department of Medical Oncology, The Sixth Affiliated Hospital of Sun Yat-sen University, Guangzhou, China; [2]Guangdong Provincial Key Laboratory of Colorectal and Pelvic Floor Diseases, The Sixth Affiliated Hospital of Sun Yat-sen University, Guangzhou, China; [3]Center for Clinical Research, The Sixth Affiliated Hospital of Sun Yat-sen University, Guangzhou, China; [4]Department of Pathology, The Sixth Affiliated Hospital of Sun Yat-sen University, Guangzhou, China; [5]Department of Data Management, The Sixth Affiliated Hospital of Sun Yat-sen University, Guangzhou, China

Contributions: (I) Conception and design: Y Deng, J Ling; (II) Administrative support: Y Deng, J Ling; (III) Provision of study materials or patients: Y Deng, J Ling, J Zhang, H Hu, Y Cai; (IV) Collection and assembly of data: J Ling, X Cheng, Y Fu, Z Lin, Y Zhao, Z Li; (V) Data analysis and interpretation: L Shi, J Ling; (VI) Manuscript writing: All authors; (VII) Final approval of manuscript: All authors.

[#]These authors contributed equally to this work and should be considered as co-first authors.

Correspondence to: Yanhong Deng, MD, PhD. Department of Medical Oncology, The Sixth Affiliated Hospital of Sun Yat-sen University, 26 Yuancun Erheng Rd., Guangzhou 510655, China. Email: dengyanh@mail.sysu.edu.cn.

Background: The effect of neoadjuvant therapy (NAT) with imatinib versus upfront resection (UR) followed by adjuvant therapy (AT) with imatinib on the outcomes of gastrointestinal stromal tumors (GIST) is unknown.

Methods: This is a retrospective study at a high-volume center. All the patients with primary localized GIST were identified in a hospital database from 2007 to 2021. The endpoints included local recurrence-free survival (LRFS), distance recurrence-free survival (DRFS), and overall survival (OS). Cox regression was used to perform multivariate survival analyses. The sensitivity analysis was conducted with the inverse probability of treatment weighting (IPTW) method.

Results: A total of 211 patients were included (Group A: UR + AT, n=140; Group B: NAT + resection + AT, n=71). In the entire cohort, 5-year DRFS, LRFS, and OS were 85.6%, 90.7%, and 92.5%, respectively. In the multivariate analysis, better DRFS was linked to NAT, tumor size of 5 cm, and AT. Sixteen patients (11.4%) in Group A and 1 (1.4%) in Group B had distant recurrences after AT discontinuation. The sensitivity analysis by IPTW provided approximately similar results. An interaction effect was observed between NAT and tumor location on DRFS. In non-gastric GISTs, NAT was associated with better DRFS [hazard ratio =0.131, 95% confidence interval (CI): 0.017–0.989, P=0.049], which was not the case in gastric GIST (P=0.08). NAT was not independently associated with LRFS or OS.

Conclusions: When compared to UR + AT, NAT + resection + AT may reduce the risk of distant recurrence in localized GIST and may be especially beneficial for patients with non-gastric GISTs.

Keywords: Gastrointestinal stromal tumors; imatinib mesylate; neoadjuvant therapy; retrospective studies; treatment outcome

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Introduction

Gastrointestinal stromal tumor (GIST) is the most common mesenchymal tumor in the gastrointestinal system. Most studies reported an annual incidence of 10–15 cases per million people (1). The majority of GISTs originate in the stomach (60–70%) and small bowel (20–25%), while colon, rectum, and esophagus (6.7%) are less common sites of origin (1). Most GISTs are caused by gain-of-function mutations of *KIT* and *PDGFRA*, which encode the receptor tyrosine kinase (RTK) (2). The emergence of the RTK inhibitor imatinib has dramatically enhanced the treatment of GIST (3). The foundation of curative treatment for primary localized GIST remains surgery (4). Imatinib-based adjuvant therapy (AT) improved survival results in intermediate—and high-risk patients compared with those of patients undergoing surgery alone (5).

Neoadjuvant therapy with imatinib (NAT) is one of the useful options for the multidisciplinary treatment of localized GISTs, especially for those in complex anatomical regions. Several retrospective studies and single-arm prospective studies indicated that neoadjuvant imatinib allowed a higher R0 resection rate and better oncologic outcomes compared with surgery alone, without compromising surgical safety (6-10). Consequently, the Chinese Society of Clinical Oncology (CSCO), the National Comprehensive Cancer Network (NCCN) in the United States, and the European Society for Medical Oncology (ESMO) have recommended that NAT be considered when R0 surgery is not feasible or implies major sequelae (11-13).

Highlight box

Key findings

- The effect of neoadjuvant therapy (NAT) with imatinib versus upfront resection (UR) on the outcomes of gastrointestinal stromal tumors (GIST) is unknown. Our earlier study showed that imatinib NAT reduced tumor size, metastasis, and tumor-related mortality in localized rectal GIST.

What is known and what is new?

- This larger retrospective study investigates the influence of NAT on prognostic outcomes in GISTs at all sites. Once again, we found that NAT decreases the risk of metastasis when compared to UR, particularly in non-gastric GIST.

What is the implication, and what should change now?

- These findings emphasize the importance of NAT in the integrated treatment of localized GIST. Further prospective validation is needed.

However, the impact of NAT on the oncologic outcomes of this disease compared to upfront resection followed by adjuvant imatinib is uncertain in the absence of randomized control trial (RCT) data. RCTs are the gold standard by which we can determine the efficacy of treatments, but they are not always feasible or ethical (14). Compared to upfront resection (UR) paired with adjuvant therapy (AT) in localized rectal GIST, our earlier study demonstrated that NAT not only reduced tumor size but also decreased the probability of metastasis and tumor-related mortality (15).

This retrospective analysis aimed to investigate the additional effect of NAT in localized GISTs. We compared the oncologic outcomes of patients who got NAT followed by resection and AT to those of patients who received UR followed by AT. We present the following article in accordance with the STROBE reporting checklist (available at https://jgo.amegroups.com/article/view/10.21037/jgo-22-931/rc).

Methods

Study design and patients

This study was a retrospective observational study. A search for "GIST" was conducted in the prospectively archived pathologic database of the Sixth Affiliated of the Sun Yat-sen University between July 2007 and August 2021. The enrollment criteria were as follows: (I) complete clinical information and follow-up; (II) primary localized GIST and pathological diagnosis; and (III) patients undergoing surgical resection of primary lesions. The exclusion criteria were as follows: (I) patients with an initial diagnosis of metastatic disease; or (II) patients with no perioperative administration of imatinib. The study was conducted in accordance with the Declaration of Helsinki (as revised in 2013). The study was approved by the Medical Ethics Committee of the Sixth Affiliated Hospital of Sun Yat-sen University (No. E2021104), and individual consent for this retrospective analysis was waived.

Exposure and outcomes

The patients with localized primary GIST were classified into two groups based on their treatment patterns (Groups A and B). Group A included patients who had received UR and AT for the prescribed period of 1 or 3 years if the tumor characteristics fulfilled the modified National Institutes of Health (NIH) consensus criteria for intermediate or high

risk (12,16). Group B consisted of patients who had received NAT, surgical resection, and AT with the administration of perioperative imatinib for a recommended duration of 3 years (12). The choice of taking neoadjuvant therapy was based on the joint decision of the surgeon and patient, with the concern of finding a balance between R0 resection and function preservation. The outcomes of interest were distance recurrence-free survival (DRFS), local recurrence-free survival (LRFS), and overall survival (OS). LRFS was calculated from the date of surgery untill local tumor recurrence. DRFS was calculated from the date of surgery untill distant tumor recurrence. OS was measured from the date of the first diagnosis to the date of the patient's death from any cause.

Data collection

The patient's characteristics, clinicopathological features, treatment history, and survival data were extracted from the medical records. GIST was diagnosed on the basis of the histology and the immunohistochemical expression of KIT and/or DOG-1. According to the Response Evaluation Criteria in Solid Tumors 1.1 criteria (17), every 3–6 months a physical examination and chest, abdomen, and pelvic computed tomography or magnetic resonance imaging were conducted to assess the tumor's response to NAT. Postoperative recurrence risk was classified as per modified NIH criteria (16). Before administering imatinib, it was proposed that each patient have a mutation analysis. DNA sequencing was carried out for the mutational analyses on *KIT* exons 9, 11, 13, and 17 as well as *PDGFRA* exons 12 and 18 using Sanger sequencing. The results were most recently updated in December 2021.

Statistical analysis

For continuous variables, descriptive statistics were expressed as the median and interquartile range (IQR), and for categorical variables, as numbers and percentages. The continuous variables (size and mitotic index) were converted into categorical variables, with category boundaries mirroring those used within the modified NIH consensus criteria (16). The Mann-Whitney or Fisher's test was used to compare the distribution of baseline variables between groups. The survival curves were generated by the Kaplan-Meier method, and the log-rank tests were used to compare DRFS, LRFS, and OS between groups. Variables with clinical relevance and those heading toward significance ($P<0.10$) in univariate analysis were included in a multivariate Cox proportional-hazards model to investigate the independent effect of NAT administration on DRFS, LRFS, and OS. The propensity score adjustment using inverse probability of treatment weighting (IPTW) (18) was used to conduct a sensitivity analysis to confirm the robustness of the main result of COX regression. The survival analyses were then performed with the inverse probability of treatment weighting model (18).

Subgroup analyses were carried out to determine the benefits of neoadjuvant treatment across different patient cohorts, and interactions were tested. The statistical analysis was performed with SPSS (IBM SPSS 26.0; SPSS Inc.) and R software version 3.4.2 (Vienna, Austria). All tests were two-sided, and a P value of <0.05 indicated that the difference was statistically significant. For data analysis, the R packages IPW survival, survey, and boot were used (Appendix 1).

Results

Demographics and tumor features

A total of 922 patients with GIST were identified (*Figure 1*, Figure S1, and Table S1). Two hundred and eleven patients who met the selection criteria were included in the study. The median age was 58 years, and 59.2% were men. The most common primary tumor sites were the stomach (39.3%), followed by the small intestine (33.2%), rectum (23.7%), colon (0.9%), others (1.9%), and other unspecified sites (0.9%). A total of 140 patients (66.4%) underwent UR + AT (Group A), and 71 (33.6%) underwent NAT + resection + AT (Group B). The patient demographics, tumor characteristics, treatment, and pathological variables are summarized in *Table 1*. Based on the modified NIH consensus criteria (16), tumor size was categorized into the following 3 groups: ≤5 cm, 5–10 cm and >10 cm. Except for adjuvant imatinib (P=0.005), no significant differences were found between the two groups in the majority of parameters.

The risk stratification was based on the modified NIH consensus criteria (16). The grading by mitotic count was not accurate in regular biopsy (19), and NAT had evidence of a pathologic treatment effect that did not yield accurate mitotic information (20). Consequently, in the absence of mitotic count, the NAT group (Group B) consisted of 49 patients (69.0%) with high-risk tumors only based on tumor size and location (21 tumors of size >10 cm, 1 tumor

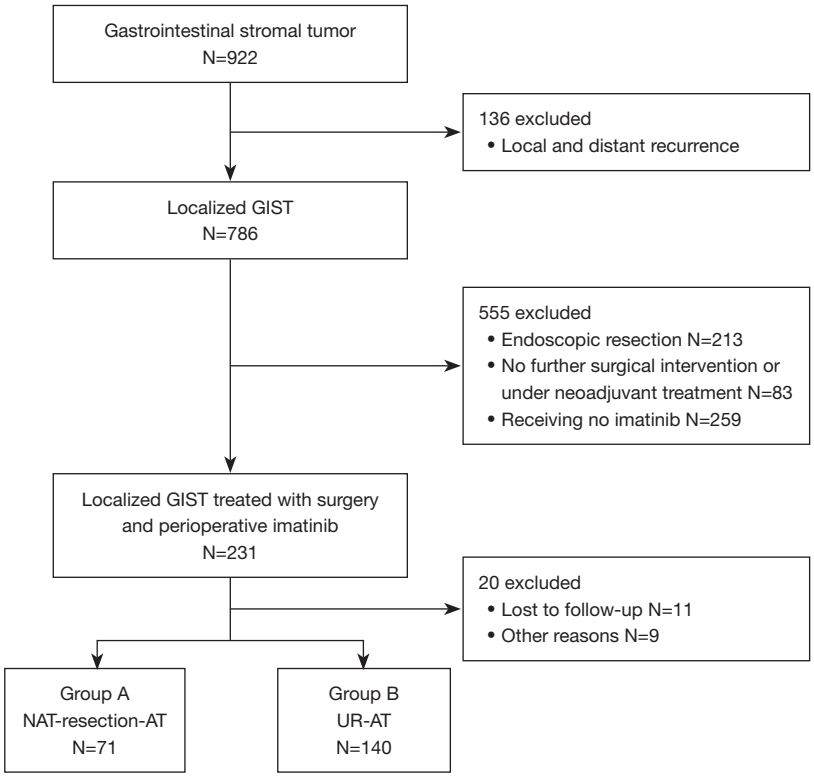

Figure 1 Flowchart of patient selection and grouping. NAT, neoadjuvant therapy of imatinib; AT, adjuvant therapy of imatinib; UR, upfront resection; GIST, gastrointestinal stromal tumor.

of size >10 cm and rupture, and 27 tumors of size >5 cm with nongastic origin) (Tables S2,S3). In the UR group (Group A), the tumors were classified as high risk in 84 (60%) patients based on size, location, and mitotic count. The size and proportion of high-risk tumors did not differ significantly between groups A and B.

Treatments

NAT was given to 71 patients (33.6%), with a median duration of 5.6 months (range, 0.8–29.6 months). Sixty-five patients were evaluable for response. The disease control rate was 96.9%, the partial response rate (PR) was 44.6%, and the stable disease rate was 52.3% (Figure S2). One (1.5%) of the patients with PR disease (66% of the maximum change from baseline) after 13 months of NAT had achieved pathological complete response (pCR) postoperatively. In the entire cohort of 211 patients, all patients underwent surgical resection of the primary lesions.

AT was given to 137 (97.9%) patients in Group A and 62 (87.3%) patients in Group B (P=0.005) (*Table 1*), with the median duration of 21.3 months (range, 1.0–119 months) and 12.0 months (range, 1.0–63.9 months) (P<0.001), respectively. The percentage of patients who discontinued AT due to local or distant recurrence in groups A and B was 4.3% and 2.9%, respectively (P=0.143). In addition, one (1.4%) patient in Group B discontinued AT due to accidental death from a heart attack (Table S4). Sixteen patients (11.4%) in Group A and one (1.4%) in Group B had distant recurrence after AT discontinuation (P=0.043, Table S5).

Survival estimates

In the entire cohort (n=211), the median DRFS, LRFS, and OS were not reached, with a median follow-up time of 40.8 months (range, 4.5–147.1 months). At the last follow-up, 9 (4.3%) patients had died (*Table 2*). A total of 31 patients experienced recurrence, including 16 with distant recurrence, 8 with local recurrence, and 7 with local and distant co-recurrences (*Table 2* and Tables S6,S7). The estimated 5-year DRFS, LRFS, and OS were 85.6%,

Table 1 Baseline demographics and GIST characteristics in groups A and B

Variable	Category	Overall study population, n=211 (n, %)	Group A UR+AT, n=140 (n, %)	Group B NAT+R+AT, n=71 (n, %)	P value[a]
Age, year	Median (IQR)	57.5 (16.7)	58.7 (17.6)	54.8 (14.2)	0.102
	Range	24.8–81.4	24.8–81.4	26.9–72.8	
Gender	Male	125 (59.2)	82 (58.6)	43 (60.6)	0.781
BMI	Median (IQR)	22.9 (4.0)	22.9 (4.5)	23.0 (3.2)	0.917
Symptomatic	Yes, %	169 (80.9)	116 (84.1)	53 (74.6)	0.146
Location	Non-gastric	128 (60.7)	79 (56.4)	49 (69.0)	0.077
	Gastric	83 (39.3)	61 (43.6)	22 (31.0)	
CD117[b]	Positive	202 (95.7)	136 (97.1)	66 (93.0)	0.289
	Weakly positive/negative	9 (4.3)	4 (2.9)	5 (7.0)	
DOG-1[b]	Positive	200 (94.8)	131 (93.6)	69 (97.2)	0.431
	Weakly positive/negative	11 (5.2)	9 (6.4)	2 (2.8)	
Molecular typing	KIT 11	75 (42.6)	43 (42.2)	32 (43.2)	0.263
	KIT 9	10 (5.7)	8 (7.8)	2 (2.7)	
	KIT 13	1 (0.6)	0 (0)	1 (1.4)	
	KIT 17	2 (1.1)	1 (1.0)	1 (1.4)	
	PDGFRA 18 D842V[c]	1 (0.6)	1 (1.0)	0 (0)	
	PDGFRA 18 Non D842V	2 (1.1)	1 (1.0)	1 (1.4)	
	Wild-type SDHB-deficient	1 (0.6)	1 (1.0)	0 (0)	
	Missing	84 (47.7)	47 (46.1)	37 (50.0)	
Size, cm	≤5	60 (28.4)	45 (32.1)	15 (21.1)	0.125
	5–10	108 (51.2)	71 (50.7)	37 (52.1)	
	>10	43 (20.4)	24 (17.1)	19 (26.8)	
Rupture	Yes	4 (1.9)	3 (2.1)	1 (1.4)	0.712
	No	207 (98.1)	137 (97.9)	70 (98.6)	
Risk stratification[d]	High risk	133 (63.0)	84 (60.0)	49 (69.0)	0.226
	Non high risk or unknown	78 (37.0)	56 (40.0)	22 (31.0)	
AT, month	Yes	199 (94.3)	137 (97.9)	62 (87.3)	0.005*
	No	12 (5.7)	3 (2.1)[e]	9 (12.7)	
	Median (IQR)	17.0 (29.6)	21.3 (24.2)	12.0 (23.4)	<0.001*

[a], Statistical comparisons between Group A and Group B cases were performed with a chi-square test for categorical, with a *t*-test for numerical. [b], Based on tissue specimens obtained before taking imatinib. [c], The adjuvant imatinib was administrated for the patient with intermediate risk, in parallel with genotyping. After 4 weeks, imatinib was stopped as soon as a PDGFRA mutation in exon 18 (p.D842V) was detected. [d], Risk stratification based on modified NIH consensus criteria. [e], Taking imatinib no more than 7 days. *, Denotes statistically significant. NAT, neoadjuvant therapy with imatinib; R, resection; AT, adjuvant therapy with imatinib; UR, upfront resection; BMI, body mass index; IQR, interquartile range.

Table 2 Primary endpoints and Kaplan-Meier estimates by treatment groups

Outcomes	Overall study population, n=211	Group A: UR+AT, n=140	Group B: NAT+R+AT, n=71	P value
LRFS-event, n (%)	15 (7.1)	10 (7.1)	5 (7.0)	0.979
DRFS-event, n (%)	23 (10.9)	20 (14.3)	3 (4.2)	0.037
OS-event, n (%)	9 (4.3)	6 (4.3)	3 (4.2)	0.984
5-year LRFS	90.70%	90.30%	92.50%	0.42
5-year DRFS	85.60%	84.10%	89.50%	0.189
5-year OS	92.50%	93.80%	87.50%	0.783

NAT, neoadjuvant therapy with imatinib; R, resection; AT, adjuvant therapy with imatinib; UR, upfront resection; LRFS, local recurrence-free survival; DRFS, distance recurrence-free survival; OS, overall survival.

90.7%, and 92.5%, respectively. A log-rank test was used to compare Kaplan-Meier estimates between the groups. The 5-year DRFS, LRFS, and OS of groups A and B were 84.1% *vs.* 89.5% (P=0.189), 90.3% *vs.* 92.5% (P=0.42), and 93.80% *vs.* 87.50% (P=0.783) (*Table 2* and *Figure 2A*,*2B*, Figure S3A,S3B).

Univariate Cox regression analysis

Univariate Cox regression analyses were performed on factors predicting the DRFS, LRFS, and OS. Size, location, mitotic rate, and rupture predict independently the recurrence of primary GIST after resection (21). As mentioned earlier, the mitotic indexes were inadequate in the NAT group. Also, only four patientss of intraoperative rupture were confirmed. As a result, neither the mitotic index nor the rupture were included in the univariate or multivariate survival analysis. Adjuvant imatinib was associated with improved recurrence-free survival in patients with operable GIST (5). In our recent study, neoadjuvant imatinib was found to decrease the risk of metastasis and tumor-related deaths in patients with rectal GIST (15). Consequently, the tumor size, location, and neoadjuvant and adjuvant treatments were included in the univariate and multivariate survival analyses. *Table 3* shows that tumor size was a predictor for all outcomes in the univariate analysis.

Multivariate Cox regression analysis

In the multivariate analysis, neoadjuvant treatment (HR =0.23, 95% CI: 0.056–0.96, P=0.044), tumor size ≤5 cm (P=0.014), and adjuvant imatinib (P=0.046) were associated with better DRFS, while tumor size ≤5 cm was associated with better LRFS (P=0.072) and OS (P=0.078) with marginal significance (*Table 4*). Notably, an interaction effect was observed between neoadjuvant treatment and tumor location on DRFS estimated from the survival data (interaction test P=0.006) (Table S8). In the subgroup analyses, NAT was associated with better DRFS in patients with non-gastric GISTs (HR =0.131, 95% CI: 0.017–0.989, P=0.049) (Table S4), while DRFS for patients with NAT did not significantly differ from that for patients with UR in patients with gastric GISTs (P=0.08) (Table S9). The Kaplan-Meier curves for DRFS of patients in Group A versus Group B stratified by location subgroups are shown in *Figure 2C*,*2D*. In patients with non-gastric GISTs, the estimated 5-year DRFS was 78.6% in Group A versus 97.3% in Group B (P=0.020).

Sensitivity analyses using inverse treatment probability weighting and stratified analyses

We fitted a logistic model to obtain IPTW for our sensitivity analyses. After adjusting for tumor size, location, and AT, NAT-treated patients demonstrated a better DRFS than UR-treated ones (HR =0.26, 95% CI: 0.076–0.905, P=0.048; Table S10, *Figure 2B*). However, no significant relationship was discovered between treatment groups and LRFS or OS (HR =1.02, 95% CI: 0.314–3.34, P=0.969; Table S10 and Figure S3). The results of the IPTW analyses were similar to the original findings.

Discussion

The effect of NAT versus UR followed by AT on the oncologic outcomes of primary localized GIST is unknown. In this 14-year, single-center observational study, the oncologic endpoints of patients who got NAT followed by

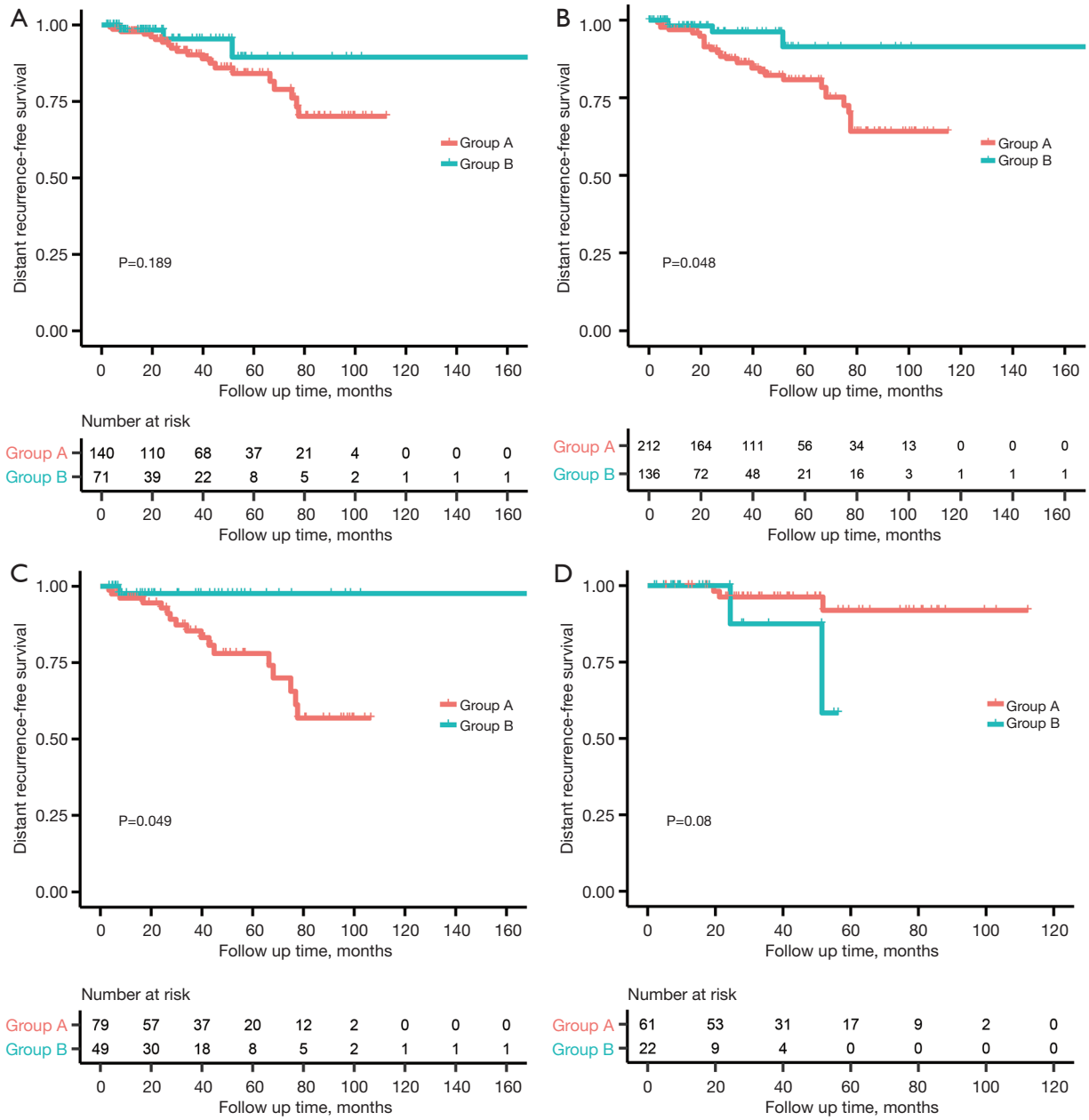

Figure 2 Kaplan-Meier curves for DRFS to treatment groups DRFS in (A) original cohort (n=211), (B) inverse probability of treatment weighting adjusted cohorts (n=347), (C) non-gastric GIST subgroup in original cohort (n=128) and (D) gastric GIST subgroup in original cohort (n=83). DRES, distant recurrence-free survival; GIST, gastrointestinal stromal tumor.

resection and AT were compared to those of patients who received UR followed by AT. The multivariate analysis by the Cox proportional-hazards model and sensitivity analysis by IPTW revealed that NAT was associated with better DRFS (HR =0.232, 95% CI: 0.0166–0.806, P=0.022), especially in patients with non-gastric GISTs (HR =0.131, 95% CI: 0.017–0.989, P=0.049).

Prior studies showed that the advantages of neoadjuvant imatinib included adequate downstaging, organ preservation, and meaningful survival benefits compared with surgery alone (6,10,22,23). Only a few studies investigated the impact of NAT on the outcomes of patients

Table 3 Univariate Cox regression analysis of oncologic outcomes

Variables	Category	DRFS			LRFS			OS		
		HR	95% CI	P value	HR	95% CI	P-value	HR	95% CI	P value
NAT	Yes	1.989	(0.588–6.724)	0.268	1.773	(0.596–5.272)	0.303	1.253	(0.251–6.245)	0.783
Location	Gastric	0.412	(0.153–1.109)	0.079	0.536	(0.171–1.682)	0.285	0.55	(0.11–2.75)	0.467
	Non-gastric	1			1			1		
Size, cm	≤5	0.258	(0.086–0.778)	0.016*	0.192	(0.037–1.001)	0.05	0.138	(0.015–1.233)	0.076
	6–10	0.328	(0.13–0.83)	0.019*	0.536	(0.175–1.645)	0.276	0.278	(0.062–1.243)	0.094
	>10	1			1			1		
AT	Yes	0.435	(0.129–1.47)	0.18	1.061	(0.139–8.085)	0.954	0.553	(0.068–4.51)	0.58

*, Denotes statistically significant. DRFS, distant recurrence-free survival; LRFS, local recurrence-free survival; OS, overall survival; HR, hazard ratio; CI, confidence interval. NAT, neoadjuvant therapy; AT, adjuvant therapy.

Table 4 Multivariate Cox regression analysis of oncologic outcomes

Variables	Category	DRFS			LRFS			OS		
		HR	95% CI	P value	HR	95% CI	P value	HR	95% CI	P value
NAT	Yes	0.232	(0.056–0.96)	0.044*	1.476	(0.477–4.569)	0.5	0.955	(0.171–5.345)	0.958
Location	Gastric	0.48	(0.173–1.332)	0.159	0.638	(0.2–2.035)	0.447	0.669	(0.129–3.461)	0.632
	Non-gastric	1								
Size, cm	≤5	0.237	(0.075–0.746)	0.014*	0.216	(0.041–1.146)	0.072	0.136	(0.015–1.247)	0.078
	6–10	0.396	(0.153–1.024)	0.056	0.564	(0.18–1.769)	0.326	0.316	(0.067–1.48)	0.144
	>10	1			1			1		
AT	Yes	0.216	(0.048–0.97)	0.046*	1.096	(0.128–9.378)	0.933	0.513	(0.05–5.221)	0.573

*, Denotes statistically significant. DRFS, distant recurrence-free survival; LRFS, local recurrence-free survival; OS, overall survival; HR, hazard ratio; CI, confidence interval.

who also received AT. Using the National Cancer Database (2004–2016) for comparative research, Marqueen *et al.* discovered that receiving 3 months of NAT for localized GIST was associated with a slight improvement in OS compared with upfront surgery (7). However, the difference in OS between those in the NAT + R + AT group and those in the UR + AT group was no longer significant. Marqueen pointed out that the insufficient coding of treatment details, such as the length of AT, hampered the analysis's interpretability. In our previous study (15), patients with localized rectal GIST who received NAT exhibited superior DRFS and disease-specific survival compared to those who underwent UR. Also, the correlation of OS with treatment groups was not statistically significant (P=0.07). The present study, including GIST from all sites with careful clinical follow-up and detailed information, revealed that NAT was independently associated with better DRFS (HR =0.23, 95% CI: 0.0166–0.806, P=0.022). Despite a minor numerical advantage for Group A (upfront resection) in 5-year OS, the log rank test revealed no difference in OS between the two groups (see *Table 2*, Figure S3B). This could be due to the small number of events, which made the estimated probability of survival at a given interval less accurate (24). A prolongation of the follow-up time period may be required. Furthermore, a trend for OS in favor of NAT was shown in the multivariate analysis. Although the present study was not an RCT, the sample size was relatively large, and the DRFS benefit of NAT was significant after adjusting for important GIST risk factors, such as tumor size, location, and adjuvant treatment, in both the Cox and IPTW models. Mitotic rate was also identified as an important prognostic factor (12). The proportions of high-

risk patients were similar in the two groups (*Table 1*) in the present study. As in other neoadjuvant studies (20), we did not obtain accurate mitotic information before the preoperative administration of imatinib in Group B. This might lead to an underestimation of the proportion of high-risk patients in Group B (NAT). Even without adjustment for the mitotic count, the results showed that NAT was more beneficial compared with UR+AT in terms of DRFS. Hence, the true effect of NAT on the prognosis of GIST might be close to that estimated in the present study. In other words, NAT combined with surgery and AT might decrease the risk of metastasis compared with UR and AT.

The interaction of NAT with the site of tumor origin is interesting, but not surprising. For non-gastric GISTs in the present study, NAT was associated with better DRFS (HR =0.131, 95% CI: 0.017–0.989, P=0.049). This finding was consistent with our previous study on rectal GIST (15). In the pre-imatinib era, non-gastric GISTs were associated with less favorable outcomes than gastric GIST (16,25). Our data showed that more patients with non-gastric GIST underwent NAT than those with gastric GIST (38.3% *vs.* 26.5%, P=0.077, *Table 1*), particularly those with GISTs in the esophagus, duodenum, and rectum (73.7%). A population-based study by Ulrich Guller, including more than 5000 patients, showed that patients with non-gastric GIST had outcomes similar to those of patients with gastric GIST (26). Previous analyses verified that NAT offered several potential advantages, including preventing tumor rupture during surgery (10), eliminating micrometastases (27,28). Perioperative imatinib could counteract the unfavorable impact of non-gastric origin on the prognosis of GIST. For gastric GIST, only five events were observed in our study. It was difficult to assess the treatment effect in this subset of patients. In addition, a trend in favor of Group A was observed in gastric GIST. A possible reason might be that gastric GIST in Group B was characterized by larger tumor sizes (Table S11) and more high-risk tumors (Table S12) than in Group A. The marked disparate distribution of tumor size and risk classification between two groups in gastric GIST is known as "confounding by indication." Allan *et al.* described "confounding by indication" as a bias in the connection between a treatment and its intended outcome caused by the severity of the underlying condition and its impact on the treatment decision. (29). Our findings were unable to invalidate the association between NAT and DRFS in stomach GIST. The majority of proximal gastric GISTs are *KIT*-mutant tumors (30), which also require function preservation. NAT has a key role in the therapy of proximal gastric GIST and distal gastric GIST with sensitive mutations. In clinical practice, NAT dismissmal in gastric GIST may be misleading. Further exploration of the link between NAT and DRFS in gastric GIST is needed.

The optimal length of NAT is undetermined, and the NCCN guidelines recommend a treatment duration of >6 months (12). In the present study, the median length of neoadjuvant therapy was 5.6 months (range 0.8–29.6 months), with an ORR of 49.4% in the entire cohort. The ORR in a neoadjuvant setting ranged from 60% to 65.9% when the median duration exceeded 6 months (10,15,31). Insufficient NAT probably led to unsatisfactory tumor shrinkage (32). In the univariate analyses, the duration of NAT was not related to DRFS or LRFS, but tumor size after NAT had a negative correlation with both DRFS (P=0.007, HR, 1.038, 1.01–1.067) and LRFS (P=0.022, HR, 1.03, 1.004–1.056). Hence, these results implied that the optimal length of NAT could be the time to the tumor nadir. Also, an imaging review for the tumor should be performed every 2–3 months during NAT so as not to miss the best operating time.

The recommended length of NAT + AT in patients undergoing neoadjuvant treatment is 3 years (12). It has been verified that imatinib should be taken postoperatively for at least 3 years in patients who have a high-risk GIST (5,33,34). Patients with ruptured localized GIST may require adjuvant imatinib treatment for 5 years, or even lifelong, since they have an extremely high chance of recurrence (35). Nishida *et al.* suggested that the micrometastases were not eradicated but remained under control for many years through drug therapy (36). The preclinical data implied that imatinib induced cellular quiescence but not death (37). This hypothesis was supported by the observation that the rates of disease recurrence similarly increased in both the 1-year and 3-year groups within 6–12 months of discontinuing adjuvant imatinib (38). In the present study, more patients in group A experienced distant recurrence after AT discontinuation than those in Group B (P=0.043, Table S5), which further confirmed that NAT might decrease distant recurrence. Also, the result increased the possibility that neoadjuvant therapy might allow for a shorter duration of perioperative imatinib for those with very high-risk GIST.

The local recurrence rate in the present study was 7.1%. No statistically significant association between the NAT and local recurrence was observed. The independent prognostic factors in LRFS were tumor size at diagnosis (P=0.039, HR,

0.196, 0.042–0.919) and adjuvant imatinib (P=0.014, HR, 0.956, 0.922–0.991). This finding was consistent with our previous study on rectal GIST and the published findings (8,15,39). Although NAT led to tumor downsizing, LRFS relied more on R0/R1 resection without rupture and postoperative imatinib.

However, this study had several inherent limitations due to its retrospective design. Given that the data of patients who underwent the resection of localized GIST and received perioperative imatinib was collected from our hospital database, sex, age, tumor size, and location were distributed equally among groups A and B (*Table 1*). Although we corrected for the differences in baseline characteristics, unknown confounders remained, for example, an inadequate baseline pre-NAT mitotic index. In the absence of an accurate mitotic index in Group B, the proportion of high-risk patients was similar for the two groups (*Table 1*). The originally high mitotic index might be masked by neoadjuvant imatinib, resulting in an underestimation of the true proportion of high-risk individuals in the NAT group. Even without mitotic count, when we adjusted the NAT effects for other prognostic key covariates such as tumor size, location, and AT by Cox regression and IPTW, the results showed that neoadjuvant imatinib (NAT) might be more beneficial than classic, postsurgical AT in terms of DRFS. The gold standard to assess the effect of neoadjuvant treatment is an RCT. However, neoadjuvant therapy is sometimes necessary for GIST, particularly when it is located at the esophagogastric junction and in the duodenum and rectum, to achieve complete resection and avoid extensive organ disruption. For ethical reasons, the random assignment of participants is not permitted under this circumstance. Thus, the guideline recommendation for neoadjuvant treatment for GIST is based on phase II single-arm trials or retrospective series (1-6). Moreover, no pertinent surgical data are available to determine the impact of margin and rupture status on the outcome of neoadjuvant GIST therapy.

Conclusions

Overall, this retrospective exploratory study compared the oncologic outcomes of NAT + surgery + AT with those of UR + AT in localized GIST. A multivariate Cox proportional-hazards regression model and the IPTW method were used to minimize the imbalances in key clinical variables and to make a robust estimate of the benefit of NAT over UR + AT in localized GIST. The findings suggested that NAT decreased the risk of metastasis, especially in patients with non-gastric GISTs, compared with UR and AT. Further prospective studies are warranted to verify these preliminary findings.

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Footnote

Reporting Checklist: The authors have completed the STROBE reporting checklist. Available at https://jgo.amegroups.com/article/view/10.21037/jgo-22-931/rc

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Conflicts of Interest: All authors have completed the ICMJE uniform disclosure form (available at https://jgo.amegroups.com/article/view/10.21037/jgo-22-931/coif). The authors have no conflicts of interest to declare.

Ethical Statement: The authors are accountable for all aspects of the work in ensuring that questions related to the accuracy or integrity of any part of the work are appropriately investigated and resolved. The study was conducted in accordance with the Declaration of Helsinki (as revised in 2013). The study was approved by the Medical Ethics Committee of the Sixth Affiliated Hospital of Sun Yat-sen University (No. E2021104), and individual consent for this retrospective analysis was waived.

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Appendix 1 R Code

R package code for inverse probability of treatment weighting (IPTW) adjusted Kaplan-Meier estimator, log-rank test, and Cox proportional hazards regression model

```
library(survminer)
library(survival)
library(tableone)
library(survey)
library(MatchIt)
library(reportReg)
library(foreign)

setwd("C:\\Users\\shilish\\Desktop\\psm")
testdata<-read.csv2("data1.1.csv",header = T,sep = ",")

testdata$DRFS<-as.numeric(testdata$DRFS)
testdata$OS<-as.numeric(testdata$OS)
testdata$RFS<-as.numeric(testdata$RFS)
testdata$DSS<-as.numeric(testdata$DSS)
testdata$LRFS<-as.numeric(testdata$LRFS)

testdata$age<-as.numeric(testdata$age)
testdata$sex<-factor(testdata$sex,labels=c("female","male"))
testdata$group<-factor(testdata$group,labels=c("A","B"))
testdata$SIZE3<-factor(testdata$SIZE3,labels=c("1","2","3"))

testdata$sym<-factor(testdata$sym,labels=c("1","2","3"))
testdata$sizeover3<-factor(testdata$sizeover3,labels=c("small","big"))
str(testdata)

fit <- survfit(Surv(DSS,DSSstatus) ~ group,
                    data = testdata)
summary(fit)
fit

ggsurvplot(fit,
           data = testdata,
           conf.int = FALSE,
           pval = TRUE,
           surv.median.line = "hv",
           risk.table = TRUE,
           xlab = "Follow up time(month)",
           legend = c(0.8,0.75),
           legend.title = "ABC",
           legend.labs = c("A", "B"),
           break.x.by = 10)
```


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```
attach(testdata)

attach(testdata)

vars<-c("sex","SIZE3")

psModel<-glm(group–sex+SIZE3,family=binomial(link="logit"),data=testdata)

testdata$ps=predict(psModel,type="response")

head(testdata$ps)

testdata$IPTW<-ifelse(testdata$group=="B",1/testdata$ps,1/(1-testdata$ps))

fit.IPTW<- survfit(Surv(DSS,DSSstatus) – group,
                   weights=testdata$IPTW,
                   data = testdata)
summary(fit.IPTW)

ggsurvplot(fit.IPTW,
           data = testdata,
           conf.int = FALSE,
           pval = TRUE,
           surv.median.line = "hv",
           risk.table = TRUE,
           xlab = "Follow up time(d)",
           legend = c(0.8,0.75),
           legend.title = "ABC",
           legend.labs = c("A", "B"),
           break.x.by = 10)

testdata1 <- testdata[testdata$Age45== "young",]
testdata2 <- testdata[testdata$Age45== "old",]

model.IPTW=coxph(Surv(DRFS,DRFSstatus)–group,data=testdata1,weights=testdata1$IPTW)
gsum=summary(model.IPTW)
gsum$coefficients
gsum$conf.int
```


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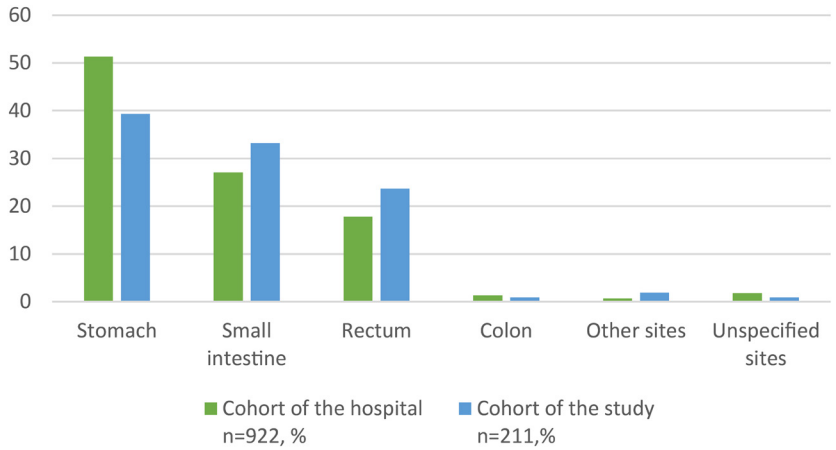

Figure S1 Distribution of anatomical location of GIST tumors in the hospital and study cohorts. GIST, gastrointestinal stromal tumor.

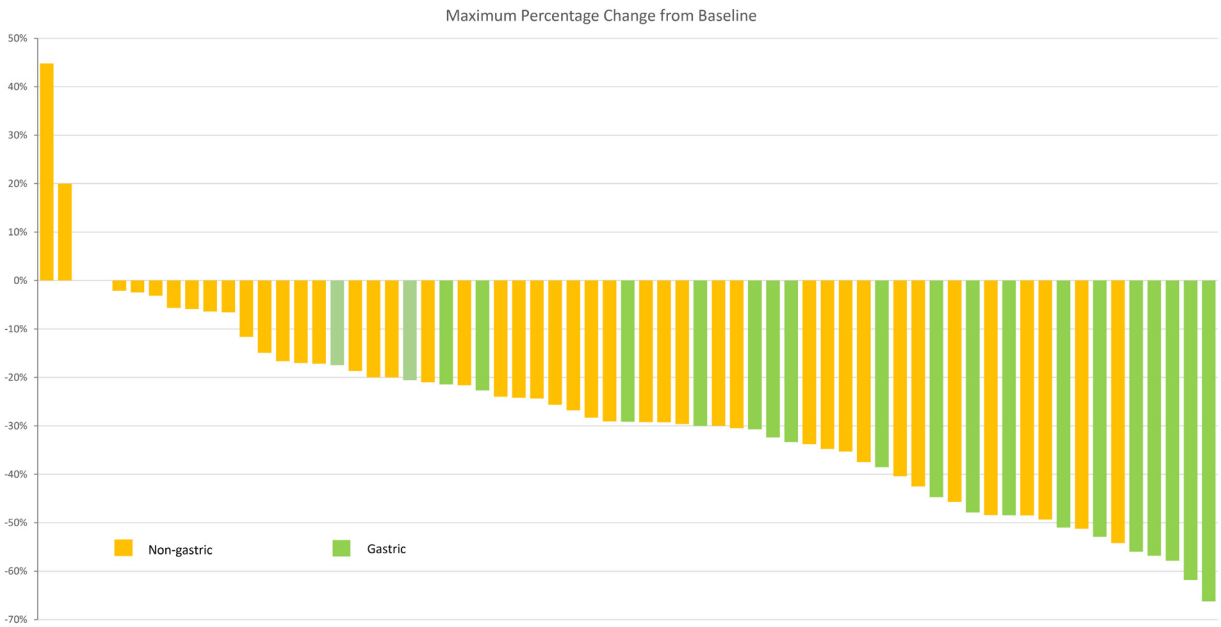

Figure S2 Decrease in the sum of lesion diameter (SLD) prior to surgery, taking as reference the baseline SLD.

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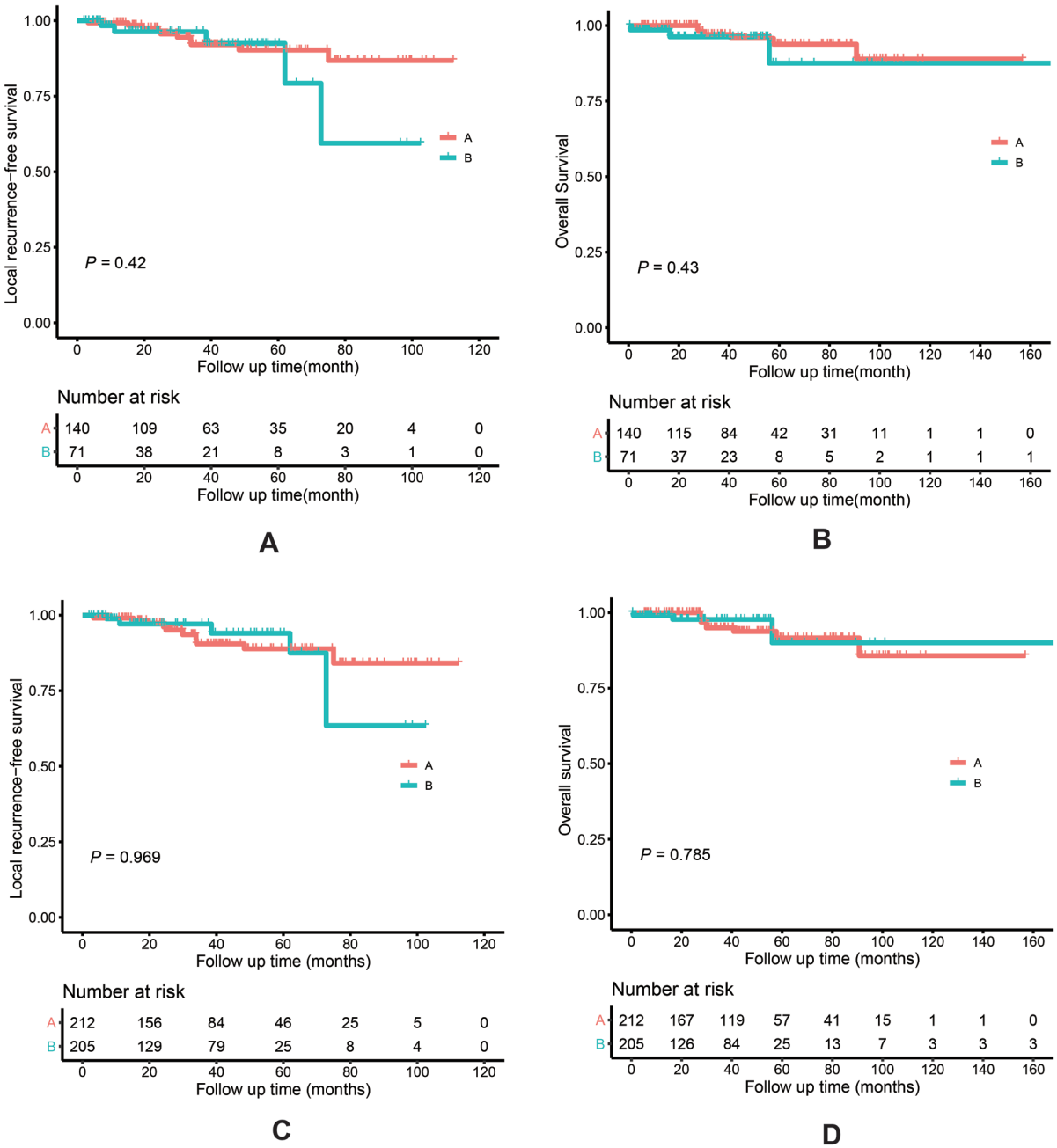

Figure S3 Kaplan-Maier analyses of original cohorts (n=211) for (A) local recurrence-free survival (LRFS), (B) overall survival (OS), and Kaplan-Maier analyses of inverse probability of treatment weighting adjusted cohorts (n=417) for (C) LRFS, and (D) OS.

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Table S1 Distribution of anatomical location of GIST tumors in the cohorts of the hospital and the study

Sites	Cohort of the hospital n=922, %	Cohort of the study n=211, %
Stomach	51.3	39.3
Small intestine	27.1	33.2
Rectum	17.8	23.7
Colon	1.3	0.9
Other sites*	0.7	1.9
Unspecified sites**	1.8	0.9

*, Other sites included esophagus, prostate and the omentum. **, The tumors were found in abdominal or pelvic cavity with unknown anatomical location.

Table S2 Risk stratification in groups A and group B

Risk stratification	Group A: UR N=140		Group B: NAT N=71		Total N=211	
	N	%	N	%	N	%
High risk	84	60	49	69	133	63
Intermediate risk	30	21.4	NA	NA	30	14.2
Low risk	25	17.9	NA	NA	25	11.9
Undetermined	1	0.7	22	31	23	10.9
Summary	140	100	71	100	211	100

UR, upfront resection; NAT, neoadjuvant therapy of imatinib; NA, not available.

Table S3 Modified NIH consensus criteria for defining postsurgical risk of recurrence in localized GIST

Risk category	Tumor longest diameter (cm)	Mitotic index, per 50 HPF	Primary tumor
Very low	<2	≤5	Any
Low	2–5	≤5	Any
Intermediate	2–5	>5	Gastric
	<5	6–10	Any
	5–10	≤5	Gastric
High	Any	Any	Tumor rupture
	>10	Any	Any
	Any	>10	Any
	>5	>5	Any
	2–5	>5	Non-gastric
	5–10	≤5	Non-gastric

HPF, high power field.

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Table S4 Outcomes correlated to adjuvant therapy

Category	Group A UR+AT, n=140 (n, %)	Group B NAT+R+AT, n=70 (n, %)	Overall study population, n=211 (n, %)	P value
DR after AT discontinuation	15 (10.7)	1 (1.4)	16 (7.6)	0.143
LR after AT discontinuation	3 (2.1)	3 (4.3)	6 (2.9)	
LR+DR after AT discontinuation	1 (0.7)	0 (0)	1 (0.5)	
Recurrence free after AT discontinuation	115 (82.1)	63 (90)	178 (84.8)	
Event In AT	6 (4.3)	3 (4.3)*	9 (4.3)	

*The 3 cases in group B discontinued adjuvant treatment due to events including 2 recurrence and 1 accidental death from a heart attack. UR, upfront resection; NAT, neoadjuvant therapy; AT, adjuvant therapy; DR, distant recurrence; LR, local recurrence; Event In AT, events occurred during AT and caused AT discontinuation.

Table S5 Distant recurrence correlated to adjuvant therapy

Category	Group A UR+AT, n=140 (n, %)	Group B NAT+R+AT, n=70 (n, %)	Overall study population, n=211 (n, %)	P value
DR after AT discontinuation	16 (11.4)	1 (1.4)	17 (8.1)	0.043
DR free after AT discontinuation	118 (84.3)	66 (94.3)	184 (87.6)	
Event In AT	6 (4.3)	3 (4.3)*	9 (4.3)	

*The 3 cases in group B discontinued adjuvant treatment due to events including 2 recurrence and 1 accidental death from a heart attack. UR, upfront resection; NAT, neoadjuvant therapy; AT, adjuvant therapy; DR, distant recurrence; Event In AT, events occurred during AT and caused AT discontinuation.

Table S6 DRFS and LRFS status in the cohort (n=211)

LRFS status	DRFS status		Sum
	No DR	DR	
No LR	180	16	196
LR	8	7	15
Sum	188	23	211

DRFS, distant recurrence free survival; LRFS, local recurrence free survival; DR, distant recurrence; LR, local recurrence.

Table S7 DRFS and LRFS status in the cohort by groups (n=211)

			DRFS status		Sum
			No DR	DR	
Group A: UR+AT	LRFS status	No LR	115	15	130
		LR	5	5	10
	Sum		120	20	140
Group B: NAT+R+AT	LRFS status	No LR	65	1	66
		LR	3	2	5
	Sum		68	3	71

DRFS, distant recurrence free survival; LRFS, local recurrence free survival; DR, distant recurrence; LR, local recurrence; UR, upfront resection; NAT, neoadjuvant therapy; AT, adjuvant therapy; R, resection.

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Table S8 P value for interaction between neoadjuvant imatinib and tumor location, calculated with Cox proportional hazards model

Variables	Category	DRFS		
		HR	95% CI	P value
NAT	Yes	0.056	0.006–0.51	0.011*
Size, cm	≤5	0.241	0.069–0.833	0.025*
	6–10	0.435	0.17–1.113	0.083
	>10			
AT	Yes	0.125	0.028–0.566	0.007*
Location	Gastric	0.271	0.078–0.939	0.039*
	Nongastric			
NAT*Location		54.95	3.199–943.785	0.006*

* denotes statistically significant; DRFS: distant recurrence-free survival.

Table S9 DRFS subgroup analysis stratified by tumor location, calculated using Cox proportional-hazards model

Location	Variable	DRFS		
		HR	95% CI	P value
Gastric	NAT	5.013	(0.822–30.556)	0.08
Nongastric	NAT	0.131	(0.017–0.989)	0.049*

* denotes statistically significant; DRFS: distant recurrence-free survival

Table S10 COX regression on treatment groups after IPTW adjustment

Variables	DRFS			LRFS			OS		
	HR	95% CI	P	HR	95% CI	P	HR	95% CI	P
Neoadjuvant imatinib	0.26	(0.076–0.905)	0.048*	1.02	(0.314–3.34)	0.969	2.039	(0.471–8.818)	0.34

*IPTW-adjustment for location, tumor size and adjuvant imatinib. IPTW, inverse probability of treatment weighting; DRFS, distant recurrence-free survival; LRFS, local recurrence-free survival.

Table S11 Size distribution in groups A and B by location

Location	Variable	Category	Group A UR+AT, n=140 n (%)	Group B NAT+R+AT, n=70 n (%)	P
Gastric	Size, cm	≤5	26 (42.6)	1 (4.5)	<0.001
		5–10	30 (49.2)	10 (45.5)	
		>10	5 (8.2)	11 (50)	
Nongastric	Size, cm	≤5	19 (24.1)	14 (29.2)	0.578
		5–10	41 (51.9)	26 (54.2)	
		>10	19 (24.1)	8 (16.7)	

UR, upfront resection; NAT, neoadjuvant therapy; R, resection; AT, adjuvant therapy.

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Table S12 High-risk in groups A and B by location

Location	Risk classification	Group A UR+AT, n=140 n (%)	Group B NAT+R+AT, n=70 n (%)	P
Gastric	High risk	15 (24.6)	14 (63.6)	0.001
	Non high or unknown	46 (75.4)	8 (36.4)	
Non-gastric	High risk	69 (87.3)	34 (70.8)	0.021
	Non high or unknown	10 (12.7)	14 (29.2)	

UR, upfront resection; NAT, neoadjuvant therapy; R, resection; AT, adjuvant therapy.

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