Int Surg 2015;**100:**860–869
DOI: 10.9738/INTSURG-D-14-00178.1

Preoperative Imatinib Treatment in Patients With Advanced Gastrointestinal Stromal Tumors: Patient Experiences and Systematic Review of 563 Patients

Jia Xu, Tian-Long Ling, Ming Wang, Wen-Yi Zhao, Hui Cao

Department of Gastrointestinal Surgery, Ren Ji Hospital, School of Medicine, Shanghai Jiao Tong University, Shanghai, China

Preoperative IM therapy for GIST is now a research focus. Due to the low incidence of the disease, there are few RCTs on the preoperative treatment for advanced GIST, let alone relevant meta-analysis. Efficacy of this therapy and targeting population are still undetermined. Therefore, the first part of this article is composed of a controlled retrospective study and demonstrates that preoperative therapy with IM can significantly improve the outcome of advanced GIST. In the second part of the paper, we further investigated what portion of advanced GIST patients benefit more from the therapy, based on a meta-analysis. As the disease is relatively rare, we involved 563 cases in the meta-analysis, much higher than in the controlled clinical studies (51 cases). The objective of this paper is to investigate effects of surgical resection on imatinib-treated advanced GIST. Twenty-two consecutive advanced GIST patients (Group A) with preoperative IM treatment were compared to 29 patients (Group B) who underwent initial tumor resection during the same period. Subsequently, a systematic review of 563 patients was applied to identify the benefit of the advanced GIST patients receiving imatinib before surgery. Compared with Group B, less patients in Group A underwent multivisceral resection (18.2% versus 48.3%, $P = 0.026$) or suffered tumor rupture at time of surgery (0% versus 17.2%, $P = 0.04$). The 3-year estimated progression-free survival of Group A (94.4%) was also superior to that of Group B (61.4%; $P = 0.045$). Subsequent meta-analysis indicated that primarily unresectable patients had higher complete resection and 2-year PFS rates than recurrent/metastasis patients ($P = 0.005$ and 0.20,

Corresponding author: Hui Cao, MD, PhD, FACS, Department of Gastrointestinal Surgery, Ren Ji Hospital, School of Medicine, Shanghai Jiao Tong University, 1630 DongFang Rd., Shanghai, China 200127.
Tel.: 86 21 68383751; Fax: 86 21 58394262; E-mail: caohuishcn@hotmail.com

respectively); (b) stable disease (SD) patients had better outcome in resection including resectability rate ($P < 0.0001$), PFS ($P < 0.00001$) and OS ($P = 0.0008$) than progressive disease (PD) patients; (c) in recurrent/metastatic PD patients, surgery played a minor role, because they had a higher bulky residual disease rate ($P = 0.0005$) and higher progression risk ($P < 0.00001$) within 2 years after surgery. Preoperative IM treatment improves prognosis of advanced GISTs. Among recurrent/metastatic patients, postimatinib surgery may benefit those who have SD after IM treatment but not those resistant to IM.

Key words: Gastrointestinal stromal tumors – Imatinib – Targeted therapy – Surgical resection

Gastrointestinal stromal tumor (GIST) is the most common mesenchymal neoplasia of the digestive tract, with a worldwide incidence of approximately 15 per 1 million people. Between 15% and 50% of GISTs are advanced at the time of diagnosis.[1] Historically, owing to the low response rate of GISTs to conventional chemotherapy or radiation therapy (overall response rate $< 5\%$),[2] surgery was the only recognized treatment for GIST before the advent of imatinib. However, surgery has historically had poor outcomes, so surgery alone is seldom sufficient for advanced GIST. Even if patients with locally advanced GIST undergo complete resection, tumor recurrence occurs frequently, and the 5-year survival can be as low as 54%. In patients with locally nonresectable, recurrent or metastatic disease, the outcomes are even poorer, with a median survival of 12–19 months and a 5-year survival rate of < 5–10%.[3]

In 2000, imatinib mesylate (IM), a tyrosine kinase inhibitor, was first reported to have been used in one patient with metastatic GIST, and it achieved remarkable success.[4] Currently, IM is the first-line palliative treatment for advanced GIST.[5,6] Nevertheless, although IM confers clinical benefits to more than 80% of patients with advanced disease, complete response to IM therapy is restricted to a few patients. Furthermore, while the majority of patients initially benefit from IM, the development of resistance to the drug still limits long-term IM use. Clinical trials have shown that two-thirds of the patients with metastatic disease who use IM develop progression, with a median progression-free survival (PFS) of approximately 20 to 24 months.[7] These flaws in IM treatment led us to investigate the value of potential multimodal approaches combining surgery and IM therapy. Several multi-institutional trials have described the successful use of postoperative IM treatment,[8,9] which was approved for adjuvant treatment of patients with primary GIST in December 2008 by the US Food and Drug Administration (FDA). In addition, surgery following primary IM treatment is feasible in advanced GIST.[10,11] However, limited by low case numbers, most of these studies have been based on the results of isolated cases or small joint institutions, and they do not include randomized controlled clinical trials. Therefore, little is known about the exact effects of postimatinib surgical resection on outcomes of patients with locally advanced primary, recurrent or metastatic GIST. In the present study, we retrospectively analyzed the outcomes of patients with advanced GISTs who received preoperative IM treatment at our institution and compared their outcomes with the prognostic results of patients with high-risk GIST (according to the NIH risk stratification system[12]) who did not receive preoperative IM. Then, we performed a meta-analysis in which we further divided advanced patients into an unresectable and a metastasis group or a stable disease and a progressive disease group to identify which portion of the advanced patients benefit more from the surgery following IM therapy. By combining our findings with the results of our meta-analysis, we evaluated the role of postimatinib surgical intervention in patients with advanced GISTs.

Methods

Patient characteristics

This retrospective study was approved by the institutional review boards of the Renji Hospital, Shanghai Jiaotong University School of Medicine, Shanghai, China. A consecutive series of 22 patients (Group A) with locally advanced and/or metastatic GIST receiving IM treatment before surgery from May 2008 to January 2012 were reviewed. In addition, 29 patients who had a high risk of recurrence and underwent initial tumor resection

Table 1 Clinical and demographic characteristics of the two study groups

Variable	Group A (n = 22)	Group B (n = 29)	*P* value
Age (y)			0.627
Median	58	58	
IQR	51–64	53–69	
Gender			0.484
Male	15 (68.2)	17 (58.6)	
Female	7 (31.8)	12 (41.4)	
Primary site			0.511
Stomach	11 (50.0)	13 (44.8)	
Small bowel	6 (27.3)	12 (41.4)	
Other	5 (22.7)	4 (13.8)	
Tumor size (cm)			0.661
Median	11.5	10	
IQR	8–15	8–13	
Mitotic index			0.23
<5/50 HPF	6 (27.3)	4 (13.8)	
≥5/50 HPF	16 (72.7)	25 (86.2)	
Genetic mutation			0.451
KIT exon 11	19 (86.4)	23 (79.3)	
KIT exon 9	3 (13.6)	4 (13.8)	
Other	0 (0)	2 (6.9)	
Extent of disease			0.098
Metastasis	20 (90.9)	29 (100)	
No metastasis	2 (9.1)	0 (0)	
Intraoperative tumor spill			0.04*
No	22 (100)	24 (82.8)	
Yes	0 (0)	5 (17.2)	
Curability			0.099
R0	20 (90.9)	21 (72.4)	
R1/R2	2 (9.1)	8 (27.6)	
Multivisceral resection			0.026*
No	18 (81.8)	15 (51.7)	
Yes	4 (18.2)	14 (48.3)	
Postoperative complications			0.987
No	19 (86.4)	25 (86.2)	
Yes	3 (13.6)	4 (13.8)	
Postoperative TKI therapy (mo)			0.976
Median	12	12	
IQR	12–15.5	12–17	
Progression			0.033*
No	21 (95.5)	21 (72.4)	
Yes	1 (4.5)	8 (27.6)	
Survival			0.271
Yes	21 (95.5)	25 (86.2)	
No	1 (4.5)	4 (13.8)	

Data reported as median and IQR or n (%).
*$P < 0.05$.

during the same period constituted the control (Group B). Emergency cases were excluded in the present study. In the former group, the diagnosis of GIST was confirmed histologically through a core needle biopsy, which was obtained endoscopically or transabdominally before the onset of IM treatment. IM treatment started at 400 mg once daily orally. The response to treatment was evaluated according to the Response Evaluation Criteria in Solid Tumors (RECIST)[13] criteria with computed tomography imaging examinations performed every 2 to 3 months. When there was no further reduction or increase in tumor size between 2 consecutive radiographic images or the surgeon deemed that further treatment would play minimal impact to the surgical procedure, the patients underwent surgical resection. The primary goal of the surgery was radical cure, with the aim of a 2-cm clear margin when possible. According to the NCCN guidelines,[5] all patients started and continued adjuvant IM treatment after a median time of 13 postoperative days, except 1 patient in Group B refused to receive continued IM treatment because of cost issues. Patients with localized primary GISTs were generally treated for approximately 1 year. For patients with metastasis, intraoperative tumor rupture, or failed R0 resection, adjuvant therapy continued unless resistance occurred. Sunitinib was applied as an alternative if there was disease progression or side effects with IM.

Clinical and surgical parameters

The clinical parameters that we recorded included sex, age, pathologic classification, extent of disease at initial presentation, dose and duration of tyrosine kinase inhibitor (TKI) treatment, surgical outcome, and disease status at last follow-up. Patient demographic data are listed in Table 1. Preoperative IM efficacy was assessed by dividing the patients into 2 clinical categories. The first category, stable disease (SD), included patients initially presenting with primarily unresectable disease or metastatic GIST who achieved a drug response significant enough to render their disease completely resectable. The second category included patients who, during the treatment with IM, had progressive disease (PD), defined as growth of at least 1 extra tumor by radiologic images.

The primary goal of surgery was to remove all sites of tumors with function-preserving as much as possible. The type of the surgical resection was determined from the operative reports and the

pathology records. If a visible tumor was not completely resected or if the margins were grossly involved, the resection was considered R2. If positive margins were confirmed by the postoperative pathologic examinations, the resection was coded as R1. If all the lesions were completely resected with microscopically tumor-free margins, the resection was considered R0.

The clinical follow-up of the cohort study was updated in August 2012, with a median follow-up of 25 months (range, 8–44 months) after the surgery. PFS was measured from the date of surgery to the initiation of documented progression of residual disease, recurrent disease, or death associated to the tumor. Overall survival (OS) was defined as the length of time from the time of the initial treatment to the associated death. All the times were reported in months.

Pathologic analysis

All the GIST specimens were confirmed immunohistochemically according to the immunohistochemistry examination and CD117, CD34, or PDGFRA positivity. Mutational analyses of KIT exons 9, 11, 13, and 17 and PDGFRA exons 12 and 18 were performed with denaturing high-performance liquid chromatography (dHPLC), and bidirectional direct sequencing in all tumors treated by IM.

Systematic review and data extraction

A systematic literature review was conducted using the EMBASE, Medline, and PubMed databases to detect relevant English-language articles (published up to November 2012). The following search terms were used: "gastrointestinal stromal tumor," "surgery," and "imatinib." All eligible studies were retrieved, and their bibliographies were checked for other relevant publications. Only published studies with full-text articles were included. Two authors independently searched and extracted the data. Any differences were resolved by mutual agreement.

To be included in our analysis, studies had to meet the following criteria: (1) they assessed the efficacy of preoperative IM treatment associated with surgery in patients with advanced GIST, regardless of its status as unresectable, recurrent, or metastatic; (2) they were clinical trials; and (3) they had sufficient data for estimating a risk ratio (RR) with a 95% confidence interval (CI).

A study was excluded if (1) the outcomes of interest were not reported or impossible to calculate; or (2) there was considerable overlap between authors, centers, or patient cohorts evaluated in another published study. If patient or material was reported more than once by the same institution, the most recent article was included in our analysis.

Statistical analysis

Retrospective study:

Summary data are reported as the median and interquartile range (IQR) or percentages. Continuous variables were compared using the Wilcoxon rank-sum test. Categoric variables were compared using Pearson's chi-square test or Fisher's exact test and multiple forward stepwise logistic regression analysis when appropriate. Actuarial survival analysis was conducted using the Kaplan–Meier method. The log-rank test was utilized to compare the survival curves, and the Cox proportional hazards model was employed for multivariate regression analysis. All statistical analyses were carried out with SPSS statistical software (SPSS, Chicago, Illinois). A value of $P < 0.05$ was considered statistically significant.

Meta-analysis.

The meta-analysis was performed based on the recommendations from the Cochrane Collaboration.[14] Dichotomous data were analyzed for relative risk ratios. The absolute effects were measured with the risk differences, and 95% CIs were calculated for these measures of effect. The Mantel-Haenszel method was used for the meta-analysis. The results are presented in forest plot graphs. The chi-square test was used to assess heterogeneity.

Results

Institutional experience

In Group A, the median duration of IM treatment prior to surgery was 6 months (range, 2–14 months). All 22 patients received 400–600 mg IM per day and had partial response, with primary tumors decreasing in mean diameter from 12.0 ± 4.9 cm to 6.9 ± 3.1 cm by the time of surgery. All the patients tolerated the prescribed therapy, with only mild complications in 10 (45.5%) patients. These complications included fatigue, rash, mild edema, and gastrointestinal upset. All the patients had a complete resection without tumor spread, and only 2 (9.1%) of them had a positive resection margin confirmed by pathologic diagnosis after operation. Multi-organ resection was needed in 4 (18.2%)

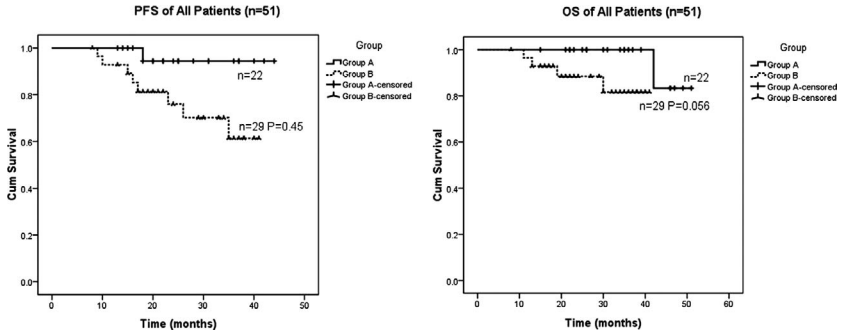

Fig. 1 Kaplan-Meier curves for the PFS and the OS according to the groups (Group A, patients received preoperative IM treatment; Group B, patients underwent surgery initially).

patients, including 2 (9.1%) patients with hepatic metastasis in which 1 patient with initial hepatic metastasis was diagnosed with hepatic relapse 18 months after the resection and switched to sunitinib treatment. She ultimately died in the 32nd month after the surgery.

The clinical and demographic characteristics of Group A were compared with Group B in Table 1. The 2 groups had no statistically significant differences in sex, age, tumor pathologic nor genetic mutation features. In addition, the median time of postoperative TKI therapy was similar in both groups. In Group B, 5 patients (17.2%) had tumor spread during the operation, and 14 patients (48.3%) underwent multi-organ resection, including the spleen, colon, liver, or uterine adnexa. These 2 proportions were significantly different compared with Group A ($P = 0.04$ and 0.026, respectively). The proportion of patients not achieving R0 resection in Group B, included 7 patients (24.1%) with R1 resection and 1 patient (3.4%) with R2 resection, was also greater than that in Group A but not statistically significant ($P = 0.099$). Furthermore, there was no case of perioperative death (i.e., in-hospital mortality) in the cohort study. Postoperative complications occurred in <15% of the patients, with no significant differences between the 2 groups.

As shown in Fig. 1, tumor progression after the surgery was observed in 1 patient (4.5%) in Group A and 8 patients (27.6%) in Group B, resulting in 3-year estimated PFS of 94.4% and 61.4%, respectively ($P = 0.045$). Figure 1 displays the Kaplan-Meier curve for OS, measured from the date of initial treatment. At the last follow-up, 1 (4.5%) patient had died of the disease in Group A, whereas in Group B, 3 (10.3%) patients had died of the disease, and 1 (3.4%) patient had died due to an unexplained cause. There was no difference in 3-year OS between the 2 groups (83.3% and 81.6%, respectively).

Univariate analysis of the pathologic features and the treatment variables, which could potentially influence RFS and OS, detected intraoperative tumor spread, curability, and preoperative IM treatment as prognostic factors correlating with PFS ($P = 0.009$, 0.003, and 0.033, respectively). Patients who were treated by the preoperative IM, who achieved R0 resection and who were without the intraoperative tumor rupture had better PFS, with hazard ratios of 1.318, 1.805, and 2.174, respectively. No factors were associated with adverse OS. Multivariate analysis yielded no significant outcomes due to the relatively small number of patients in each cohort.

Systematic review and meta-analysis

From our computerized search and after extensive cross-checking, 86 relevant articles were extracted and reviewed by 2 independent reviewers. Thirteen articles were ultimately eligible for inclusion in this analysis, and data were extracted from these studies.[15–27] The details of individual studies are given in Table 2. Because these articles were nonrandomized studies, the DerSimonian–Laird test (random-effects model) was used to estimate the bias in the selected articles.

Compared with recurrent/metastatic GIST, the patients with primarily unresectable GIST had superior resection status and PFS. Incomplete resection (R1/R2) was significantly less frequent in the locally unresectable GIST subgroup than the recurrent/metastatic GIST (RR, 0.39; 95% CI, 0.20–0.75; $P = 0.005$; Fig. 2, top). Correspondingly, the patients with recurrence or metastasis had a higher risk of progression within 2 years after the surgery (RR, 0.35; 95% CI, 0.07–1.74; $P = 0.20$; Fig. 2, bottom).

The difference in surgical findings between the SD and PD subgroups was also significant. All the results in the SD subgroup were superior to the PD

Table 2 Descriptions and summary of studies eligible for the meta-analysis

Author	Location	Type of study	Number of patients		Response to IM		Surgery outcomes
			Unresectable	Recurrent/metastatic	SD	PD	
Raut CP 2006[15]	USA	Retrospective	9	60	23	46	PFS, OS
Bonvalot S 2006[16]	France	Retrospective	5	17	22	0	PFS, OS
Rutkowski P 2006[17]	Poland	Prospective	3	29	24	8	PFS
Andtbacka RH 2007[18]	USA	Retrospective	11	35	21	25	DFS, OS
DeMatteo RP 2007[19]	USA	Retrospective	0	40	20	20	PFS, OS
Gronchi A 2007[20]	Italy	Retrospective	3	35	30	8	PFS, DSS
Sym SJ 2008[21]	Korea	Retrospective	8	26	24	10	PFS, OS
Eisenberg BL 2009[22]	USA	Prospective	30	22	48	4	PFS, OS
Yeh CN 2010[23]	Taiwan	Retrospective	0	38	14	24	PFS, OS
Mussi C 2010[24]	Italy	Retrospective	0	80	49	31	PFS, DSS
Blesius A 2011[25]	France	Prospective	25	0	22	3	PFS, OS
Tielen R 2012[26]	Netherlands	Retrospective	0	55	35	20	PFS, OS
Zaydfudim V 2012[27]	USA	Retrospective	0	32	23	9	PFS, OS

SD, stable disease; PD, progressive disease; PFS, progression-free survival; DFS, disease-free survival; DSS, disease-specific survival; OS, overall survival.

subgroup, including resectability rate (RR, 0.32; 95% CI, 0.18–0.55; $P < 0.0001$) (Fig. 3, top), PFS (RR, 0.45; 95% CI, 0.37–0.56; $P < 0.00001$; Fig. 3, middle) and OS (RR, 0.13; 95% CI, 0.04–0.42; $P = 0.0008$; Fig. 3, bottom).

Furthermore, the incidence of PD during the IM treatment was greater in recurrent/metastatic GIST patients, and for this subset of patients, there have been more controversies on the effects of the surgery. Therefore, the differences in resectability rates and PFS between SD and PD patients with recurrent/metastatic GIST were analyzed in our series. As shown in Fig. 4, surgery had a minor effect on recurrence or metastasis in the PD subgroup, with a higher rate of bulky residual disease remaining after the surgery (RR, 0.32; 95% CI, 0.17–0.61; $P = 0.0005$) and a higher risk of progression within 2 years after the surgery (RR, 0.44; 95% CI, 0.35–0.55; $P < 0.00001$) than the SD subgroup.

Discussion

In our study, preoperative IM therapy benefitted the patients with advanced GIST more, in terms of fewer intraoperative tumor ruptures and multivisceral resections, than those without prior IM therapy. The PFS of these patients was also superior to those who underwent surgery initially. However, 2 distinct clinical scenarios that may produce different prognoses for postimatinib surgery were included in Group A of our clinical case-series analysis: first, locally advanced tumors or tumors in "difficult" locations, and second, presence of metastasis. Because Group A had a low patient number, a meta-analysis was then conducted in which we further divided advanced GIST patients into an unresectable and a metastasis subgroup or a stable disease and a progressive disease subgroup to identify which subset of advanced patients could benefit from postimatinib surgery. For patients with primary disease, neoadjuvant IM decreases the size

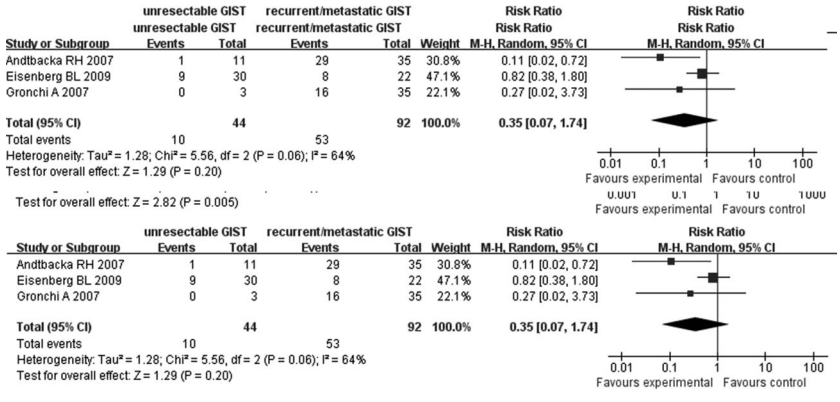

Fig. 2 Comparison of prognosis between unresectable and recurrent/metastasis GIST. (Top) Incomplete resection (R1/R2 resection) after preoperative IM treatment; (bottom) recurrence within 2 years after the surgery.

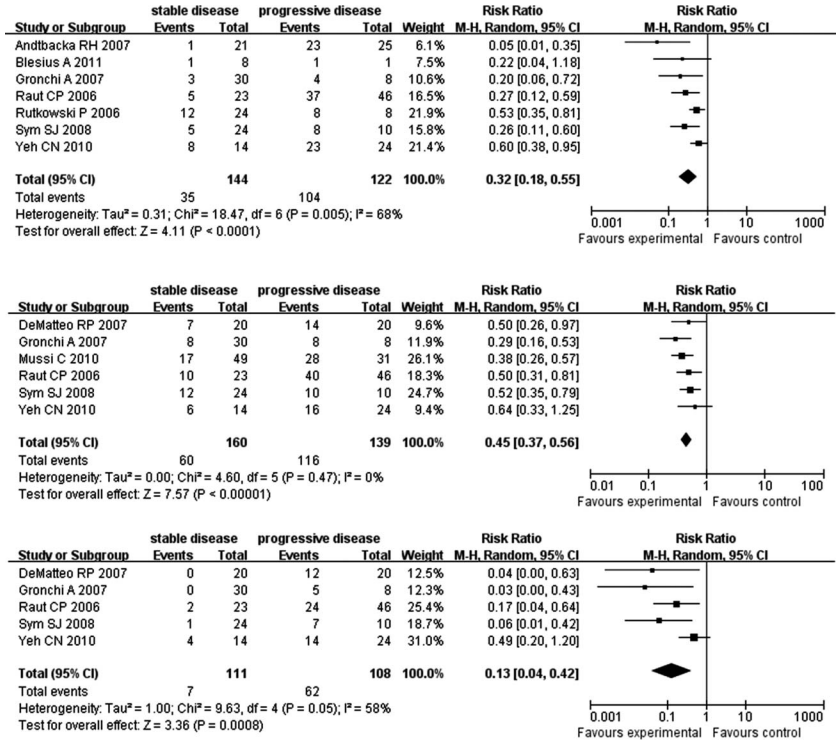

Fig. 3 Prognosis comparison between the advanced GIST patients with stable disease and progressive disease after the preoperative IM treatment. (Top) Incomplete resection (R1/R2) following the IM therapy; (middle) recurrence within 2 years after the surgery; (bottom) death within 2 years after the surgery.

of responsive tumors leading to less morbidity in surgery with organ- or function-preservation and to render previously inoperable tumors operable. Our meta-analysis shows that preoperative IM treatment had a positive effect in advanced GIST patients. However, compared to the satisfactory results of primary GIST, the outcomes of metastatic GIST were poor. In our systemic analysis, we found a higher risk of recurrence within 2 postoperative years in the metastatic group ($P = 0.20$), as well as fewer complete resections ($P = 0.005$). However, some studies have indicated that some metastatic patients still benefit from surgery, even though IM treatment or incomplete resection was performed.[20,28] A control study between unresected patients who received IM treatment alone and patients who received IM treatment followed by resection also showed that resection of residual tumors after preoperative IM treatment in patients with metastatic GIST is feasible.[29] We think the difference between our study and these studies is primarily related to the relatively limited number of patient in

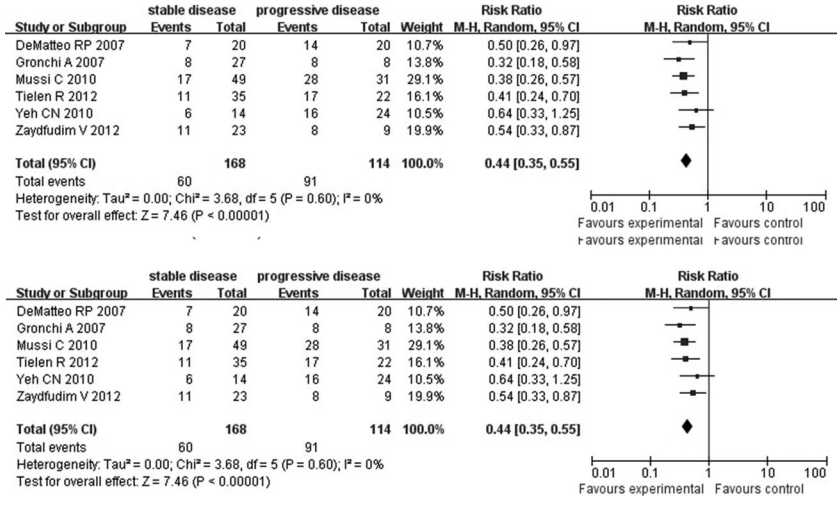

Fig. 4 Prognosis comparison between the recurrent/metastatic GIST patients with stable disease and progressive disease after the preoperative IM treatment. (Top) Incomplete resection (R1/R2) following the IM therapy; (bottom) recurrence within 2 years after the surgery.

our study. Therefore, currently, IM is still the standard treatment of choice for patients with metastasis, and surgery is not curative but only secondary to IM treatment. Particularly for metastatic GIST not controlled by preoperative IM treatment, it is evident that surgery offers poor results.[26,27] Therefore, these patients should be treated with high doses of IM, according to the tolerance, or with second-line agents such as sunitinib; surgery is indicated only for palliative reasons to control complications, such as pain, bleeding, bowel obstruction, or rupture of tumor masses. It is worth noting that the patients with advanced GISTs still gain the opportunity for surgical resection after sunitinib treatment.[30,31]

In the meta-analysis study, we also showed that patients who were responsive to or had stable disease after initial IM treatment could benefit from the surgery, with a higher rate of complete curability and prolonged PFS and OS compared to those who did not undergo the subsequent surgery, regardless of whether they had primarily unresectable, recurrent or metastatic GIST. In contrast, surgery had a limited role in patients with advanced GIST who initially regressed under IM treatment but then developed progression in later course. The analysis indicated that the type of surgical resection, that is, its "quality" (R0, R1, or R2), depending on the type of response to IM, and these differences have prognostic implications. A recent study of 35 patients at the MD Anderson Cancer Center[18] found that patient survival in those who achieved R0 resection was 100% at the 30th months, compared to 80% at 12 months in those who achieved R1 or R2 resection. Other reports[15,23] also found a link among IM response, surgery quality and survival. However, a study[19] indicated that selected patients with local progression also benefit from incomplete resection in overall survival if tumor nodules that progress on IM therapy are removed. We think that it is difficult to evaluate the degree of progression accurately only on the basis of radiologic evidence. Some tumor nodules shown by CT scan as local progression frequently have micrometastases that is difficult to be identified by current imaging technology. In addition, univariate analysis in the present study demonstrated that patients with R1/R2 resection or with intraoperative tumor rupture had a poor PFS. The exact value of partial resection, especially for the patients in progression, is uncertain and should be evaluated in future studies. At present, incomplete resection or "debulking surgery" is preferable only in selected patients to alleviate symptoms.

Given the collective evidence reviewed previously, we suggest that the IM treatment is capable of creating best timing for surgical resection leading directly to the patient's prognosis. However, the optimal time to treat patients with IM before undergoing surgery has not been established. Theoretically, the surgery should be performed after the maximum response and before the development of secondary resistance. This is usually approximately 6 to 12 months.[20,32] However, secondary KIT mutations have been identified only 10 months after neoadjuvant IM therapy.[33] Hence, some authors argue that it is not always necessary to wait for the maximum response; especially for patients with primarily unresectable GIST, surgery should be performed as soon as there is sufficient shrinkage.[34] In our study, the median IM preoperative treatment time was 6 months (range, 2–14 months). All the cases received early surgical treatment, and the outcomes were satisfactory. For metastatic patients, more time should be allowed to achieve the maximum IM benefit. In these patients, a treatment response assessment by PET or CT is key in choosing the optimal time for surgery. Cessation of tumor shrinkage on successive imaging or CT scans or the formation of new nodules or tumor growth after a period of shrinkage may represent the beginning of secondary resistance and should prompt evaluation for surgery.

Bonvalot *et al*[16] reported that 3% of the patients treated with the neoadjuvant IM therapy-developed complications, particularly in relation to the rupture of large tumor masses that became necrotic under treatment. This is largely due to the edema of the tumor tissues caused by the drug leading to higher friability. In these cases, emergency surgery seems to be associated with increased mortality and postoperative morbidity, and most of the patients cannot obtain complete en bloc resection. The poor outcomes of the emergency surgery have been confirmed by other reports.[15,16] Therefore, elective surgery should be considered for patients at higher risk of complications during pharmacologic debulking. One argument often brought forward against surgery in metastatic or recurrent GIST is that potential complications outweigh the rather minor clinical benefit. In our series, however, all the patients tolerated the prescribed preoperative IM therapy without severe complications, and the rate of surgical morbidity was comparable with that of the control group as well. This is consistent with the results of a similar series.[22]

Therefore, there is no strong reason to assume that preoperative IM treatment would lead to the increased surgical morbidity.

Considering that postoperative IM treatment has been approved for adjuvant treatment in patients with a medium or high risk of recurrence by the FDA[5] and ESMO,[6] all advanced patients who undergo post-imatinib surgery, whether or not they achieve a complete cytoreduction, should be given postoperative IM. Blay *et al*[35] presented the data of a randomized trial evaluating continuous vs. intermittent use of IM in metastatic GIST and found that continuous IM produced a better progression-free survival. In 2 studies we reviewed,[17,19] postoperative recurrence or progression was not rare in patients who discontinue further IM treatment after the complete resection. In light of these findings, continuous treatment with IM may be optimal for many patients in the clinical setting, especially those with intraoperative tumor rupture or a failure to achieve R0 resection.

In conclusion, surgical excision is suitable for advanced GIST patients whose debulking has been controlled by IM, especially patients with primary advanced tumors, patients in whom the surgeon estimates that an R0 resection may be difficult to achieve, or patients in whom R0 resection would be easier to achieve if tumor cytoreduction were possible. Among recurrent/metastatic patients, elective surgical resection may be favorable in patients who have IM-responsive disease, while surgery is generally not indicated for those resistant to IM treatment.

Acknowledgments

This work was supported by a grant from the National Natural Science Foundation of China (No. 81272743) and Priority Research Foundation of Shanghai Science Committee (No. 11411950800). Jia Xu and Tian-Long Ling contributed equally as cofirst authors.

References

1. Sleijfer S, Wiemer E, Verweij J. Drug Insight: gastrointestinal stromal tumors (GIST)–the solid tumor model for cancer-specific treatment. *Nat Clin Pract Oncol* 2008;**5**(2):102–111
2. Dematteo RP, Heinrich MC, El-Rifai WM, Demetri G. Clinical management of gastrointestinal stromal tumors: before and after STI-571. *Hum Pathol* 2002;**33**(5):466–477
3. 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**(1):51–58.
4. Demetri GD, von Mehren M, Blanke CD, Van den Abbeele AD, Eisenberg B, Roberts PJ *et al*. Efficacy and safety of imatinib mesylate in advanced gastrointestinal stromal tumors. *N Engl J Med* 2002;**347**(7):472–480
5. Yeh CN, Hwang TL, Huang CS, Lee PH, Wu CW, Chen-Guo K *et al*. Clinical practice guidelines for patients with gastrointestinal stromal tumor in Taiwan. *World J Surg Oncol* 2012;**10**: 246
6. Casali PG, Jost L, Reichardt P, Schlemmer M, Blay JY, ESMO Guidelines Working Group. Gastrointestinal stromal tumours: ESMO clinical recommendations for diagnosis, treatment and follow-up. *Ann Oncol* 2009;**20**(Suppl 4):64–67
7. Goodman VL, Rock EP, Dagher R, Ramchandani RP, Abraham S, Gobburu JV *et al*. Approval summary: sunitinib for the treatment of imatinib refractory or intolerant gastrointestinal stromal tumors and advanced renal cell carcinoma. *Clin Cancer Res* 2007;**13**(5):1367–1373
8. Dematteo RP, Ballman KV, Antonescu CR, Maki RG, Pisters PW, Demetri GD *et al*. Adjuvant imatinib mesylate after resection of localised, primary gastrointestinal stromal tumour: a randomised, double-blind, placebo-controlled trial. *Lancet* 2009;**373**(9669):1097–1104
9. Cohen MH, Johnson JR, Justice R, Pazdur R. Approval summary: imatinib mesylate for one or three years in the adjuvant treatment of gastrointestinal stromal tumors. *Oncologist* 2012;**17**(7):992–997
10. Sjölund K, Andersson A, Nilsson E, Nilsson O, Ahlman H, Nilsson B. Downsizing treatment with tyrosine kinase inhibitors in patients with advanced gastrointestinal stromal tumors improved resectability. *World J Surg* 2010;**34**(9):2090–2097
11. Hou YY, Zhou Y, Lu SH, Qi WD, Xu C, Hou J *et al*. Imatinib mesylate neoadjuvant treatment for rectal malignant gastrointestinal stromal tumor. *World J Gastroenterol* 2009;**15**(15): 1910–1913
12. Fletcher CD, Berman JJ, Corless C, Gorstein F, Lasota J, Longley BJ *et al*. Diagnosis of gastrointestinal stromal tumors: a consensus approach. *Hum Pathol* 2002;**33**(5):459–465
13. Therasse P, Arbuck SG, Eisenhauer EA, Wanders J, Kaplan RS, Rubinstein L *et al*. New guidelines to evaluate the response to treatment in solid tumors. European Organization for Research and Treatment of Cancer, National Cancer Institute of the United States, National Cancer Institute of Canada. *J Natl Cancer Inst* 2000;**92**(3):205–216
14. Higgins JPT, Green S. Cochrane Handbook for Systematic Reviews of Interventions, Version 5.0 (updated February 2008). The Cochrane Collaboration 2008. Available at: http://www.cochrane-handbook.org. Accessed December 5, 2014
15. Raut CP, Posner M, Desai J, Morgan JA, George S, Zahrieh D *et al*. Surgical management of advanced gastrointestinal stromal

tumors after treatment with targeted systemic therapy using kinase inhibitors. *J Clin Oncol* 2006;**24**(15):2325–2331
16. Bonvalot S, Eldweny H, Péchoux CL, Vanel D, Terrier P, Cavalcanti A *et al*. Impact of surgery on advanced gastrointestinal stromal tumors (GIST) in the imatinib era. *Ann Surg Oncol* 2006;**13**(12):1596–1603
17. Rutkowski P, Nowecki Z, Nyckowski P, Dziewirski W, Grzesiakowska U, Nasierowska-Guttmejer A *et al*. Surgical treatment of patients with initially inoperable and/or metastatic gastrointestinal stromal tumors (GIST) during therapy with imatinib mesylate. *J Surg Oncol* 2006;**93**(4):304–311
18. 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
19. DeMatteo RP, Maki RG, Singer S, Gonen M, Brennan MF, Antonescu CR. Results of tyrosine kinase inhibitor therapy followed by surgical resection for metastatic gastrointestinal stromal tumor. *Ann Surg* 2007;**245**(3):347–352
20. Gronchi A, Fiore M, Miselli F, Lagonigro MS, Coco P, Messina A *et al*. Surgery of residual disease following molecular-targeted therapy with imatinib mesylate in advanced/metastatic GIST. *Ann Surg* 2007;**245**(3):341–346
21. Sym SJ, Ryu MH, Lee JL, Chang HM, Kim TW, Kim HC *et al*. Surgical intervention following imatinib treatment in patients with advanced gastrointestinal stromal tumors (GISTs). *J Surg Oncol* 2008;**98**(1):27–33
22. 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):42–47
23. Yeh CN, Chen TW, Tseng JH, Liu YY, Wang SY *et al*. Surgical management in metastatic gastrointestinal stromal tumor (GIST) patients after imatinib mesylate treatment. *J Surg Oncol* 2010;**102**(6):599–603
24. Mussi C, Ronellenfitsch U, Jakob J, Tamborini E, Reichardt P, Casali PG *et al*. Post-imatinib surgery in advanced/metastatic GIST: is it worthwhile in all patients? *Ann Oncol* 2010;**21**(2): 403–408
25. Blesius A, Cassier PA, Bertucci F, Fayette J, Ray-Coguard I, Bui B *et al*. Neoadjuvant imatinib in patients with locally advanced non metastatic GIST in the prospective BFR14 trial. *BMC Cancer* 2011;**11**:72
26. Tielen R, Verhoef C, van Coevorden F, Gelderblom H, Sleijfer S, Hartgrink HH *et al*. Surgery after treatment with imatinib and/or sunitinib in patients with metastasized gastrointestinal stromal tumors: is it worthwhile? *World J Surg Oncol* 2012;**10**:111
27. Zaydfudim V, Okuno SH, Que FG, Nagorney DM, Donohue JH. Role of operative therapy in treatment of metastatic gastrointestinal stromal tumors. *J Surg Res* 2012;**177**(2):248–254
28. Haller F, Detken S, Schulten HJ, Happel N, Gunawan B, Kuhlgatz J *et al*. Surgical management after neoadjuvant imatinib therapy in gastrointestinal stromal tumours (GISTs) with respect to imatinib resistance caused by secondary KIT mutations. *Ann Surg Oncol* 2007;**14**(2):526–532
29. Bauer S, Hartmann JT, de Wit M, Lang H, Grabellus F, Antoch G *et al*. Resection of residual disease in patients with metastatic gastrointestinal stromal tumors responding to treatment with imatinib. *Int J Cancer* 2005;**117**(2):316–325
30. Ruka W, Rutkowski P, Szawłowski A, Nowecki Z, Debiec-Rychter M, Grzesiakowska U *et al*. Surgical resection of residual disease in initially inoperable imatinib-resistant/intolerant gastrointestinal stromal tumor treated with sunitinib. *Eur J Surg Oncol* 2009;**35**(1):87–91
31. Pantaleo MA, Di Battista M, Catena F, Astorino M, Saponara M, Di Scioscio V *et al*. Surgical debulking of gastrointestinal stromal tumors: is it a reasonable option after second-line treatment with sunitinib? *J Cancer Res Clin Oncol* 2008;**134**(5): 625–630
32. Loughrey MB, Mitchell C, Mann GB, Michael M, Waring PM. Gastrointestinal stromal tumour treated with neoadjuvant imatinib. *J Clin Pathol* 2005;**58**(7):779–781
33. Haller F, Detken S, Schulten HJ, Happel N, Gunawan B, Kuhlgatz J *et al*. Surgical management after neoadjuvant imatinib therapy in gastrointestinal stromal tumours (GISTs) with respect to imatinib resistance caused by secondary KIT mutations. *Ann Surg Oncol* 2007;**14**(2):526–532
34. Blay JY, Bonvalot S, Casali P, Choi H, Debiec-Richter M, Dei Tos AP *et al*. Consensus meeting for the management of gastrointestinal stromal tumors. Report of the GIST Consensus Conference of 20–21 March 2004, under the auspices of ESMO. *Ann Oncol* 2005;**16**(4):566–578
35. Blay JY, Le Cesne A, Ray-Coquard I, Bui B, Duffaud F, Delbaldo C *et al*. Prospective multicentric randomized phase III study of imatinib in patients with advanced gastrointestinal stromal tumors comparing interruption versus continuation of treatment beyond 1 year: the French Sarcoma Group. *J Clin Oncol* 2007;**25**(9):1107–1113