Role of Resection Following Focal Progression with Standard Doses of Imatinib in Patients with Advanced Gastrointestinal Stromal Tumors: Results of Propensity Score Analyses

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Disclosures of potential conflicts of interest may be found at the end of this article.

Key Words. Gastrointestinal stromal tumor • Focal progression • Imatinib • Surgery

ABSTRACT

Background. There are limited data on the clinical benefits of adding surgical resection in patients with focally progressive gastrointestinal stromal tumor (GIST). This study aims to compare the clinical outcomes of resection plus imatinib dose escalation or maintenance (S group) with imatinib dose escalation alone (NS group) in patients with advanced GIST following focal progression (FP) with standard doses of imatinib.

Materials and Methods. A total of 90 patients with advanced GISTs who experienced FP with standard doses of imatinib were included in this retrospective analysis. The primary endpoints were time to imatinib treatment failure (TTF) and overall survival (OS).

Results. Compared with the NS group (n = 52), patients in the S group (n = 38) had a higher proportion of primary tumor site involvement and lower tumor burden at FP. With a median follow-up duration of 31.0 months, patients in the S group had significantly better TTF and OS than patients in the NS group (median TTF: 24.2 vs. 6.5 months, p < .01; median OS: 53.2 vs. 35.1 months, p = .009). Multivariate analysis showed that S group independently demonstrated better TTF (hazard ratio [HR], 0.29; p < .01) and OS (HR, 0.47; p = .01). Even after applying inverse probability of treatment-weighting adjustments, S group demonstrated significantly better TTF (HR, 0.36; p < .01) and OS (HR, 0.58; p = .049).

Conclusion. Our results suggested that resection following FP with standard doses of imatinib in patients with advanced GIST provides additional benefits over imatinib dose escalation alone.

Implications for Practice: This is the first study to compare the clinical outcomes of resection plus imatinib dose escalation or maintenance (S group) with imatinib dose escalation alone (NS group) in patients with advanced gastrointestinal stromal tumor (GIST) following focal progression (FP) with standard doses of imatinib. These findings suggest that resection can be safely performed following FP, and the addition of surgical resection provides further clinical benefit over imatinib dose escalation alone. Based on these results, the authors recommend resection following FP in patients with advanced GIST provided that an experienced multidisciplinary team is involved in the patient’s treatment.

INTRODUCTION

Gastrointestinal stromal tumors (GISTs) are the most common mesenchymal tumors arising from the gastrointestinal tracts, resulting most commonly from KIT or PDGFRA activating mutations [1]. The stomach (60%) and small intestine (30%) are the most common primary sites, but GISTs can arise anywhere along the gastrointestinal tract [2]. Localized GIST is a potentially curable disease if complete resection can be achieved. However, the risk of recurrence may be as high as 90% after curative surgery if high risk prognostic factors are present. Moreover, about 15% of patients initially present with metastatic disease [3].
For patients with recurrent or metastatic GISTs, imatinib is the primary treatment of choice [4, 5]. However, although imatinib provides a durable period of disease control in these patients, with a median progression-free survival (PFS) of 2 years and median overall survival (OS) of 5 years, most patients eventually experience disease progression because of secondary resistance [5]. After disease progression with standard doses of imatinib (400 mg per day), the drug can be escalated up to 800 mg per day before switching to subsequent line tyrosine kinase inhibitors (TKIs) such as sunitinib malate and regorafenib [6–8], although its antitumor efficacy is modest with a disease control rate of 33% and a median PFS of 2.8 months [9, 10]. Sunitinib malate and regorafenib have been approved as second- and third-line TKIs for metastatic GIST [11, 12]. Nevertheless, responses to these TKIs are also limited, with a median PFS of 6.8 months for sunitinib and 4.8 months for regorafenib [11, 12], indicating that medical treatment using TKIs alone rarely achieves a complete response in patients with advanced GISTs.

In an effort to improve the survival outcomes of advanced GIST, several retrospective studies have demonstrated a survival benefit from adding surgical resection to imatinib at maximal response, including partial response and stable disease, or at focal progression in patients with unresectable, recurrent, or metastatic GIST. Here, some patients remained free from disease progression for a long time after surgery [13–17]. In contrast, An et al. demonstrated that initial debulking surgery before imatinib therapy was not beneficial, and surgery should be avoided as a primary approach prior to imatinib in the treatment of advanced GIST [18]. In addition, the survival outcomes of patients who receive surgery at general disease progression are disappointing, and surgery is also not recommended in these individuals [15–17]. Although the survival benefit has not been proven in randomized phase III trials because such trials have closed early from lack of accrual [19], the guidelines of the National Comprehensive Cancer Network, European Society of Medical Oncology, and Asian Consensus Guidelines suggest that surgery should be considered following maximal response to imatinib in patients with advanced GIST, based on the results of previous retrospective studies [6–8]. The clinical benefits of adding surgical resection in patients with focally progressive advanced GIST have been advocated in few retrospective studies, but these studies lack a control arm, limiting the level of evidence [16, 20].

The aim of this study was to compare the clinical outcomes of resection plus imatinib dose escalation or maintenance (S group) with imatinib dose escalation alone (NS group) in patients with advanced GIST following focal progression (FP) with standard doses of imatinib.

### Materials and Methods

#### Patients

Between April 2003 and October 2016, 98 patients with histologically documented distant recurrent or initially metastatic GISTs experienced FP with standard doses of imatinib as first-line treatment at Asan Medical Center, Seoul, Republic of Korea. Eight patients who received sunitinib without imatinib dose escalation after FP were excluded, and a total of 90 patients were thus included in this retrospective analysis. FP was defined as follows: (a) one- or two-site progression with an increase in size of one or two of the pre-existing tumor masses; (b) appearance of single new lesion, including the development of a new enhancing focus enclosed within a preexisting tumor mass which was low in density and non-enhancing, described as a “nodule within a mass” [21]. Patients with pseudoprogression due to hemorrhage or cystic degeneration were excluded. The Institutional Review Board of Asan Medical Center approved this study.

#### Treatment and Evaluation

Patients who received surgery with maintenance of standard doses of imatinib or dose escalation of imatinib were classified as the surgery group (S group). Patients who were treated with escalated doses of imatinib first and then received surgery within 3 months were also classified as the S group. The nonsurgery group (NS group) included patients who were treated with escalated doses of imatinib only. Radiofrequency ablation (RFA) was regarded as a surgical intervention, and patients with liver metastases who were treated with RFA, either alone or with surgery, were also included in the S group.

All the patients included in this study were initially treated with standard doses of imatinib. At FP, the computed tomography (CT) scans were reviewed by the multidisciplinary team, including a medical oncologist, surgeon, and interventional radiologist to assess the probability of resection. Surgery was conducted only if all the focally progressive lesions were resectable. The extent of resection was defined as macroscopically complete with a negative microscopic margin (R0), macroscopically complete with a positive microscopic margin (R1), or macroscopically incomplete (R2). Postoperative complications were classified according to the Aaccordion Severity Grading System of Surgical Complications [22].

Generally, upon resumption of eating after surgery, imatinib treatment was restarted with standard or escalated doses of imatinib. For dose escalation of imatinib, the doses were escalated up to 800 mg day. CT scans were performed every 2–3 months and at any time when tumor progression was suspected. Responses were assessed according to the Response Evaluation Criteria in Solid Tumors (RECIST) version 1.1.

#### Statistical Analysis

Time to treatment failure (TTF) was defined as the duration of time from FP date to the date of disease progression on last escalated dose level of imatinib, intolerance to imatinib, or death from any cause, whichever occurred first. OS was defined as the duration of time from FP date to the date of death from any cause. For patients who were treated with sunitinib after imatinib failure, PFS for sunitinib (PFS SU) was calculated from the start date of sunitinib to disease progression or death from any cause, whichever occurred first. OS for sunitinib (OS SU) was calculated from the start date of sunitinib to death from any cause. Survival rates and corresponding standard errors were estimated using the Kaplan-Meier method, and survival curves were compared using the log-rank test. Baseline characteristics of the groups were compared using Pearson’s chi-square test or
age, sex, primary tumor site, disease status at the start of 
treatment was estimated using a logistic regression model based on 
primary tumor site, disease status at the start of first-line 
imatinib, genotype of the primary tumor, best response to 
treatment (S group) vs. imatinib dose escalation alone (NS group) 
weighting (IPTW) [23]. The propensity to receive sur-
regression modeling using the inverse probability of treat-
groups, we performed weighted Cox proportional hazards 
baseline characteristics of the patients with GIST in the 
results and candidate prognostic factors including age, sex, 
genotype of the primary tumor, best response to 
treatment were included.

To account for baseline differences between S and NS 
groups, we performed weighted Cox proportional hazards 
regression modeling using the inverse probability of treat-
ity of treatment weighting (IPTW) [23]. The propensity to receive sur-
surgery (S group) vs. imatinib dose escalation alone (NS group) 
was estimated using a logistic regression model based on 
age, sex, primary tumor site, disease status at the start of first-
ilne imatinib, genotype of the primary tumor, best response to 
first-line imatinib, surgery before FP, number of involved 
metastatic organs at FP, involved organs at FP, initial tumor 
burden at FP, and treatment group (S vs. NS group) were 
cluded in the univariate analysis. In the multivariate analy-
variables exhibiting a potential association with survival 
(p < .25) in the univariate analysis, along with age, sex, and 
primary tumor site, were included.

To account for baseline differences between S and NS 
groups, we performed weighted Cox proportional hazards 
regression modeling using the inverse probability of treat-
nalysis, variables exhibiting a potential association with survival 
were compared by weighted Cox 
proportional hazards regression models with robust standard 
errors. All analyses were performed using SAS version 9.4 
(SAS Institute Inc., Cary, NC). All tests were two-sided, with 
< .05 considered statistically significant.

RESULTS

Patient Characteristics
The baseline characteristics of the patients with GIST in the 
S (n = 38) and NS (n = 52) groups are presented in Table 1. 
The baseline characteristics were similar between the two 
groups, but a higher proportion of patients in the S group 
had primary tumor site involvement at the time of FP 
(26.3% vs. 7.7%), and the largest tumor size at FP was 
smaller in the S group (median, 34 mm vs. 52 mm) compared 
with the NS group. Surgical interventions are described in 
Table 2. All RFA procedures completely ablated the target 
tumor masses. Even in patients who received R2 resection 
and/or RFA with visible residual lesions, all the focally progres-
sive lesions were resected and/or ablated. The 30-day postop-
erative complication rate was 16.1 % (n = 5) in 31 evaluable 
patients of the S group, which includes ileus (n = 4) and ure-
terinal injury (n = 1). Percutaneous nephrostomy for ureteral 
jugation was required in one patient. There were no periop-
erative deaths. Pathologic reports for surgical specimens were 
available for 28 out of 38 patients in the S group (Table 2). 
Pathologic reports were not available in five patients who 
received only RFA as a surgical intervention and in five who 
received surgery at another hospital other than Asan Medical 
Center. The majority of patients had tumors with a mitotic 

| Table 1. Baseline patient and disease characteristics (n = 90) |
|-------------------------------------------------------------|
| **Characteristics**                                         | S group (n = 38) | NS group (n = 52) | p value |
| Median age at FP (range), yr                               | 59 (37–78)      | 62.5 (31–77)     | .11     |
| Sex                                                        |                 |                 |
| Female                                                     | 15 (39.5)       | 15 (28.8)       | .29     |
| Male                                                       | 23 (60.5)       | 37 (71.2)       |         |
| Primary tumor site                                         |                 |                 |
| Stomach                                                    | 13 (34.2)       | 22 (42.3)       | .57     |
| Small bowel                                                | 24 (63.2)       | 27 (51.9)       |         |
| Others                                                     | 1 (2.6)         | 3 (5.8)         |         |
| Disease status at the start of first-line imatinib          |                 |                 |
| Initially metastatic                                       | 15 (39.5)       | 26 (50.0)       | .32     |
| Distant recurrence                                         | 23 (60.5)       | 26 (50.0)       |         |
| Genotype of primary tumor                                  |                 |                 |
| KIT exon 11 mutation                                       | 30 (78.9)       | 41 (78.8)       | .57     |
| Others                                                     | 8 (21.1)        | 7 (13.5)        |         |
| Not available                                              | 0 (0.0)         | 4 (7.7)         |         |
| Best response to first-line imatinib                       |                 |                 |
| Complete response                                          | 5 (13.2)        | 3 (5.8)         | .316    |
| Partial response                                           | 22 (57.9)       | 29 (55.8)       |         |
| Stable disease                                             | 8 (21.1)        | 15 (28.8)       |         |
| Disease progression                                         | 0 (0.0)         | 3 (5.8)         |         |
| Not evaluable                                              | 3 (7.9)         | 2 (3.8)         |         |
| Surgery before FP                                          |                 |                 |
| No                                                         | 26 (68.4)       | 37 (71.2)       | .69     |
| Cytoreductive surgery before first-line palliative imatinib treatmenta | 8 (21.1) | 12 (23.1) | |
| Residual lesion resectionb                                  | 4 (10.5)        | 3 (5.8)         |         |
| Number of involved metastatic organs at FP                 |                 |                 |
| 1                                                          | 25 (65.8)       | 39 (75.0)       | .34     |
| ≥2                                                         | 13 (34.2)       | 13 (25.0)       |         |
| Involved organs at FP                                      |                 |                 |
| Primary tumor site                                         | 10 (26.3)       | 4 (7.7)         | .02     |
| Liver                                                      | 24 (63.2)       | 32 (61.5)       | .88     |
| Extra-liver                                                | 17 (44.7)       | 28 (53.9)       | .39     |
| Initial tumor burden at focal progression                  |                 |                 |
| Median largest tumor size (range), mm                      | 34 (8–127)      | 52 (10–136)     | .04     |
| Median sum of total tumor size (range), mm                 | 60 (8–480)      | 79.5 (10–569)   | .34     |

aCytoreductive surgery before starting first-line palliative imatinib in distant recurrent or initially metastatic disease.
bResidual lesion resection following disease control with standard doses of imatinib in distant recurrent or initially metastatic disease.

Abbreviations: FP, focal progression; NS, nonsurgery; S, surgery.
Table 2. Description of surgical intervention and pathologic reports for surgical specimens in S group (n = 38)

| Surgical intervention and pathologic reports | No. of patients (%) |
|---------------------------------------------|---------------------|
| Types of intervention                       |                     |
| Surgery only                                | 29 (76.3)           |
| RFA only                                    | 5 (13.2)            |
| Surgery + RFA                               | 4 (10.5)            |
| Types of surgery                            |                     |
| Hepatic resection                           | 17 (44.7)           |
| Peritoneal mass resection                   | 13 (34.2)           |
| Bowel resection                             | 4 (10.5)            |
| Gastrectomy                                 | 5 (13.2)            |
| Extent of surgical intervention             |                     |
| R0/1 resection and/or RFA without visible residual lesion | 26 (68.4) |
| R2 resection and/or RFA with visible residual lesion | 12 (31.6) |
| 30-d postoperative complications<sup>a</sup> |                     |
| No                                          | 26 (68.4)           |
| Grade 1                                     | 3 (7.9)             |
| Grade 2                                     | 1 (2.6)             |
| Grade 3                                     | 1 (2.6)             |
| Not evaluable                               | 7 (18.4)            |
| Pathologic reports (n = 28)                 |                     |
| Mitotic index (mitoses per 50 HPF)          |                     |
| ≤5                                          | 6 (21.4)            |
| >5                                          | 22 (78.6)           |
| Histologic phenotype                        |                     |
| Spindle                                     | 15 (53.6)           |
| Epithelioid                                 | 3 (10.7)            |
| Mixed                                       | 10 (35.7)           |
| Cellularity                                 |                     |
| Low                                         | 1 (3.6)             |
| Moderate                                    | 9 (32.1)            |
| High                                        | 18 (64.3)           |
| Necrosis extent, median (range), %          | 20 (0–90)           |
| KIT expression                              |                     |
| Negative                                    | 2 (7.1)             |
| Focal                                       | 3 (10.7)            |
| Diffuse                                     | 23 (82.1)           |

<sup>a</sup>Complications were classified according to Accordion Severity Grading System of Surgical Complications.

Abbreviations: HPF, high-power field; R0, absence of tumor in resection margin; R1, microscopic presence of tumor in resection margin; R2, presence of any gross residual tumors; RFA, radiofrequency ablation.

With a median follow-up duration of 31.0 months (range 11.7–99.0) in surviving patients, the median TTF for the S and NS groups was 24.2 months (95% confidence interval [CI], 13.3–35.1) and 6.5 months (95% CI, 3.6–9.4), respectively (p < .001; Fig 1A). The median OS was 53.2 months (95% CI, 36.8–69.6) in the S group and 35.1 months (95% CI, 25.6–44.7) in the NS group (p = .009; Fig 1B).

Univariate and Multivariate Analyses of Survival Outcomes in All Patients

Table 3 summarizes the results of the univariate and multivariate analyses of the potential prognostic factors for TTF and OS. In the univariate analysis, sex showed potential association (p < .25) with TTF, and largest tumor size at FP, sum of total tumor size at FP, and treatment group (NS vs. S group) showed potential association with both TTF and OS. In the multivariate analysis, the S group was independently associated with better TTF (vs. NS group; HR, 0.29; 95% CI, 0.17–0.49, p < .001) and OS (vs. NS group; HR, 0.47; 95% CI, 0.27–0.83, p = .01). In addition, the sum of total tumor size was also independently associated with both TTF and OS.
Table 3. Univariate and multivariate analysis for TTF and OS (n = 90)

| Variables                     | TTF Univariate analysis | TTF Multivariate analysis | OS Univariate analysis | OS Multivariate analysis |
|-------------------------------|-------------------------|---------------------------|------------------------|-------------------------|
|                               | HR (95% CI)             | p value                   | HR (95% CI)            | p value                 |
| Age at FP                     |                         |                           |                        |                         |
| <60                           | Reference               |                           | Reference              |                         |
| ≥60                           | 1.16 (0.71–1.87)        | .56                       | 1.31 (0.79–2.17)       | .30                     |
|                               | Reference               |                           | Reference              |                         |
| Sex                           |                         |                           |                        |                         |
| Female                        | Reference               |                           | Reference              |                         |
| Male                          | 1.52 (0.88–2.61)        | .13                       | 1.37 (0.79–2.39)       | .27                     |
| Primary tumor site            |                         |                           |                        |                         |
| Stomach                       | Reference               |                           | Reference              |                         |
| Others                        | 1.04 (0.63–1.72)        | .87                       | 1.07 (0.62–1.85)       | .80                     |
|                               | Reference               |                           | Reference              |                         |
| Largest tumor size at FP      |                         |                           |                        |                         |
| ≤Median (46 mm)               | Reference               |                           | Reference              |                         |
| >Median (46 mm)               | 2.08 (1.27–3.39)        | .004                      | 1.47 (0.77–2.79)       | .24                     |
| Sum of total tumor size at FP |                         |                           |                        |                         |
| ≤Median (77.5 mm)             | Reference               |                           | Reference              |                         |
| >Median (77.5 mm)             | 2.00 (1.22–3.28)        | .006                      | 2.07 (1.25–3.45)       | .005                    |
| Treatment group               |                         |                           |                        |                         |
| NS group                      | Reference               |                           | Reference              |                         |
| S group                       | 0.29 (0.17–0.50)        | <.001                     | 0.29 (0.17–0.49)       | <.001                   |

Abbreviations: CI, confidence interval; FP, focal progression; HR, hazard ratio; NS, nonsurgery-surgery; OS, overall survival; S, surgery; TTF, time to treatment failure.

Propensity Score and Inverse Probability of Treatment Weighting Analyses

IPTW analysis was performed to evaluate the effects of surgery after adjustment for differences in baseline characteristics. Model discrimination was assessed with c statistics (0.83), and model calibration was assessed with Hosmer-Lemeshow statistics (Chi-square = 4.70, degrees of freedom = 8, p = .79). The absolute standardized differences were used to evaluate the balance, and all absolute standardized differences after weighting was less than 0.2. Even after applying IPTW adjustment, patients in the S group demonstrated significantly better TTF (covariate-adjusted HR, 0.36; 95% CI, 0.21–0.61, p < .001) and OS (covariate-adjusted HR, 0.58; 95% CI, 0.336–0.998, p = .049) compared with the NS group.

Survival Outcomes of Sunitinib Treatment in Patients Treated with Sunitinib After Imatinib Treatment Failure

Among the 90 patients enrolled in this study, 67 experienced imatinib treatment failure. Of those, 62 patients were subsequently treated with sunitinib (22 patients in the S group and 40 in the NS group). There was no significant difference in ORR (13.6% vs. 13.5%, p = .989) and DCR (72.7% vs. 83.8%, p = .308) between the S and NS groups. With a median follow-up duration of 20.2 months (range, 2.1–55.9) in surviving patients treated with sunitinib, the median PFS SU in the S and NS groups was 7.4 months (95% CI, 2.8–12.0) and 6.3 months (95% CI, 4.5–8.2), respectively (p = .487; Fig 2A). The median OS SU was 26.6 months (95% CI, 7.0–46.3) in the S group and 20.8 months (95% CI, 17.8–23.7) in the NS group (p = .981; Fig 2B).

DISCUSSION

The goal of surgery in focally progressive advanced GIST is to stop disease progression by removing lesions that have gained resistance to imatinib. Although several retrospective studies have reported clinical benefits associated with adding surgeries to the treatment plans of patients with focally progressive GIST, lack of control group (i.e. imatinib alone without surgery) limits the level of evidence [16, 20]. This is the first study to compare the clinical outcomes of resection plus imatinib dose escalation or maintenance with imatinib dose escalation alone in patients with advanced GIST following FP with standard doses of imatinib. The addition of resection was significantly associated with better TTF and OS compared with imatinib dose escalation alone.

In this study, the S group was significantly associated with better TTF and OS compared with the NS group in both univariate and multivariate analyses. Previous studies have used PFS instead of TTF to evaluate the benefits of surgery, in which disease progression at a certain dose of imatinib was regarded as a disease progression event [16, 20, 24, 25]. However, considering that the purpose of surgery in patients with FP on imatinib is to delay the time of switching to an alternative TKI from imatinib, TTF would be a more appropriate endpoint. The median TTF of the S group in the current study was 24.2 months (vs. 6.5 months in the NS group, p < .001), indicating that the addition of surgery provides longer disease control with imatinib in patients with focally progressive advanced GIST. Previous studies have reported a median PFS of 7.7–11.3 months in patients who received surgery for focally progressive advanced GIST, which is shorter.
than the median TTF observed in the S group of the current study. The difference in outcome seems largely due to the inclusion of patients with focal progression on more later-line treatments such as imatinib dose escalation or sunitinib in the previous studies, whereas all of the patients in the current study were on standard doses of imatinib at the time of focal progression [15, 20]. Moreover, higher proportion of patients in the previous study (75%) had visible residual lesion after surgery including 16% of patients with bulky residual disease (presence of any residual disease ≥1 cm in diameter) [15]. By comparison, only 31.6% of patients had a visible residual lesion after surgical intervention in the current study, and even in these patients, all the focally progressive lesions have been successfully resected and/or ablated. The median OS of 53.2 months in the S group (vs. 35.1 months in the NS group, \(p = .009\)) was comparable to that reported in earlier studies (29.8–59.0 months) [15, 16, 24].

Although baseline characteristics between both the S and NS groups were similar, there were significant differences regarding the primary tumor site involvement and largest tumor sizes at FP. Tumor size is known to be a prognostic factor for both PFS and OS in patients with advanced GIST [26, 27]. Moreover, tumor size also affects the decision for surgery (i.e., patients with smaller tumors are more likely to be candidates for surgery). Thus, IPTW analysis was performed to account for the baseline differences between the two groups. Even after IPTW adjustment, TTF and OS were significantly better in the S group, compared with the NS group. This further supports that the addition of surgery provides survival benefits over imatinib dose escalation alone in patients with GIST following FP with standard doses of imatinib.

Among patients treated with sunitinib after imatinib treatment failure, there were no significant differences in PFS SU, OS SU, ORR, and DCR for sunitinib between the two groups, indicating that surgery had no influence on subsequent sunitinib treatment. Thus, it is likely that better OS in the S group was due to the prolongation of TTF by resection of imatinib-resistant clones.

One of the concerns associated with surgery for patients with metastatic or recurrent GIST is that complications may outweigh the clinical benefit in terms of survival. However, in this study, the rate of postoperative complications was low, with complications of any grade observed in less than 20% of evaluable patients in the S group. This is comparable to the results of a similar series (18%–33%) [15, 16, 24]. Most of the complications observed in this study were mild, and invasive intervention was required in only one patient with percutaneous nephrostomy for a left ureteral injury.

This study has several limitations. As anticipated for any retrospective study, selection bias was unavoidable. There were significant differences in baseline characteristics between the S and NS groups regarding primary tumor site and largest tumor size at FP. To minimize the impact of selection bias on the clinical outcomes of the current study, we used weighted Cox proportional hazards regression modeling with IPTW. In addition, the definition for FP varies among studies, and this might have affected the results of this study. However, to date, there is no standard definition for FP, and the definition used in this study was deemed acceptable following close review of definitions used in previous studies [15, 20, 21]. Moreover, our median follow-up duration was relatively short. Despite these limitations, this study has several strengths. The results of this study were based on one of the largest populations of patients with advanced GIST following FP with standard doses of imatinib. Furthermore, patients were uniformly treated with imatinib maintenance or dose escalation in both the S and NS groups. The relatively homogeneous patient population in the current study might have reduced potential confounding effects in the evaluation of the impact of surgery on survival outcomes.

**Conclusion**

Our findings suggest that resection plus imatinib dose escalation or maintenance can be safely performed following FP with standard doses of imatinib in patients with advanced GIST and provides additional benefits over imatinib dose escalation alone. Based on these results, resection following FP in patients with advanced GIST could be considered provided that an experienced multidisciplinary team including an experienced medical oncologist, surgeons, and interventional radiologists are involved in the patient’s treatment.
Although it would be ideal, recent experience shows that it is not feasible to conduct a randomized trial to evaluate the benefit of surgery in patients with focally progressive advanced GIST.

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Author Contributions
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References
1. Hirota S, Isozaki K, Moriyama Y et al. Gain-of-function mutations of c-kit in human gastrointestinal stromal tumors. Science 1998;279:577–580.
2. Miettinen M, Lasota J. Gastrointestinal stromal tumors: Pathology and prognosis at different sites. Semin Diagn Pathol 2006;23:70–83.
3. Nilsson B, Blumming P, Mesi-Kindblom JM et al. Gastrointestinal stromal tumors: The incidence, prevalence, clinical course, and prognostication in the preimatinib mesylate era–A population-based study in western Sweden. Cancer 2005;103:821–829.
4. Demetri GD, von Mehren M, Blanke CD et al. Efficacy and safety of imatinib mesylate in advanced gastrointestinal stromal tumors. N Engl J Med 2002;347:472–480.
5. Blanke CD, Demetri GD, von Mehren M et al. Long-term results from a randomized phase II trial of standard–versus higher-dose imatinib mesylate for patients with unresectable or metastatic gastrointestinal stromal tumors expressing KIT. J Clin Oncol 2008;26:620–625.
6. National Comprehensive Cancer Network. NCCN clinical practice guidelines in oncology: Soft tissue sarcoma, version 2. Fort Washington, PA: National Comprehensive Cancer Network; 2018. Available from: https://www.nccn.org/professionals/physician_gls/pdf/sarcoma.pdf. Accessed August 17, 2018.
7. Casali PG, Abecassis N, Bauer S et al. Gastrointestinal stromal tumours: ESMO–EURACAN Clinical Practice Guidelines for diagnosis, treatment and follow-up. Ann Oncol 2018;103(suppl 4):iv68–iv78.
8. Koo DH, Ryu MH, Kim KM et al. Asian consensus guidelines for the diagnosis and management of gastrointestinal stromal tumor. Cancer Res Treat 2016;48:1155–1166.
9. Zalcberg JR, Verweij J, Casali PG et al. Outcome of patients with advanced gastro-intestinal stromal tumours crossing over to a daily imatinib dose of 800 mg after progression on 400 mg. Eur J Cancer 2005;41:1751–1757.
10. Casali PG, Zalcberg J, Le Cesne A et al. Ten-year progression-free and overall survival in patients with unresectable or metastatic GI stromal tumors: Long-term analysis of the European Organisation for Research and Treatment of Cancer, Italian Sarcoma Group, and Australasian Gastrointestinal Trials Group Intergroup phase III randomized trial on imatinib at two dose levels. J Clin Oncol 2017;40:1713–1720.
11. Demetri GD, van Oosterom AT, Garrett CR et al. Efficacy and safety of sunitinib in patients with advanced gastrointestinal stromal tumour after failure of imatinib: A randomised controlled trial. Lancet 2006;368:1329–1338.
12. Demetri GD, Reichardt P, Kang YK et al. Efficacy and safety of sorafenib for advanced gastrointestinal stromal tumours after failure of imatinib and sunitinib (GRID): An international, multicentre, randomised, placebo-controlled, phase 3 trial. Lancet 2013;382:919–927.
13. Park SJ, Ryu MH, Ryoo BY et al. The role of surgical resection following imatinib treatment in patients with recurrent or metastatic gastrointestinal stromal tumors: Results of propensity score analyses. Ann Surg Oncol 2014;21:4211–4217.
14. Sym SJ, Ryu MH, Lee JL et al. Surgical intervention following imatinib treatment in patients with advanced gastrointestinal stromal tumors (GISTs). J Surg Oncol 2008;98:27–33.
15. Raut CP, Posner M, Desai J et al. Surgical management of advanced gastrointestinal stromal tumors after treatment with targeted systemic therapy using kinase inhibitors. J Clin Oncol 2006;24:2325–2331.
16. Fairweather M, Balachandran VP, Li GZ et al. Cytoreductive surgery for metastatic gastrointestinal stromal tumor treated with tyrosine kinase inhibitors: A 2-institutional analysis. Ann Surg 2018;268:296–302.
17. Bauer S, Rutkowski P, Hohenberger P et al. Long-term follow-up of patients with GIST undergoing metastasectomy in the era of imatinib - Analysis of prognostic factors (EORTC-STSG6 collaborative study). Eur J Surg Oncol 2014;40:412–419.
18. An HJ, Ryu MH, Ryoo BY et al. The effects of surgical cytoreduction prior to imatinib therapy on the prognosis of patients with advanced GIST. Ann Surg Oncol 2013;20:4212–4218.
19. Du CY, Zhou Y, Song C et al. Is there a role of surgery in patients with recurrent or metastatic gastrointestinal stromal tumours responding to imatinib: A prospective randomised trial in China. Eur J Cancer. 2014;50:1772–1778.
20. Al-Batran SE, Hartmann JT, Heidel F et al. Focal progression in patients with gastrointestinal stromal tumours after initial response to imatinib mesylate: A three-center-based study of 38 patients. Gastric Cancer 2007;10:145–152.
21. Ryu MH, Lee JL, Chang HM et al. Patterns of progression in gastrointestinal stromal tumor treated with imatinib mesylate. Jpn J Clin Oncol 2006;36:17–24.
22. Strasberg SM, Linehan DC, Hawkins WG. Theaccordion severity grading system of surgical complications. Ann Surg 2009;250:177–186.
23. Austin PC, Stuart EA. Moving towards best practice when using inverse probability of treatment weighting (IPTW) using the propensity score to estimate causal treatment effects in observational studies. Stat Med 2015;34:3661–3679.
24. Gao X, Xue A, Fang Y et al. Role of surgery in patients with focally progressive gastrointestinal stromal tumors resistant to imatinib. Sci Rep 2016;6:22840.
25. Mussi C, Ronellenfitsch U, Jakob J et al. Post-imatinib surgery in advanced/metastatic GIST: Is it worthwhile in all patients? Ann Oncol 2010;21:403–408.
26. Van Glabbeke M, Verweij J, Casali PG et al. Initial and late resistance to imatinib in advanced gastrointestinal stromal tumours are predicted by different prognostic factors: A European Organisation for Research and Treatment of Cancer–Italian Sarcoma Group–Australasian Gastrointestinal Trials Group Study. J Clin Oncol 2005;23:5795–5804.
27. Gastrointestinal Stromal Tumor Meta-Analysis Group (MetaGIST). Comparison of two doses of imatinib for the treatment of unresectable or metastatic gastrointestinal stromal tumours: A meta-analysis of 1,640 patients. J Clin Oncol 2010;28:1247–1253.