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# Imatinib-resistant gastrointestinal stromal tumors in the era of second- and third-line tyrosine kinase inhibitors: Does surgical resection have a role?

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ABSTRACT

*Background:* Imatinib resistance is associated with a poor prognosis in patients with gastrointestinal stromal tumors. Although novel tyrosine kinase inhibitors have improved outcomes in imatinib-resistant gastrointestinal stromal tumors, the role of resection remains unclear. We sought to investigate factors predictive of overall and progression-free survival in patients with imatinib-resistant gastrointestinal stromal tumors.

*Methods:* A query of our prospectively maintained Comprehensive Cancer Center registry was performed from 2003 to 2019 for patients with imatinib-resistant gastrointestinal stromal tumors. Clinicopathologic characteristics and medical and surgical treatments were collected; overall survival and progression-free survival after imatinib-resistance were analyzed with Kaplan-Meier and Cox proportional hazards modeling.

*Results:* A total of 84 patients developed imatinib resistance at a median age of 59 years. Median time to imatinib resistance after diagnosis and overall survival after imatinib resistance was 50 and 51 months, respectively. After being diagnosed with imatinib resistance, 17 (20%) patients underwent resection. On multivariable analysis, resection after imatinib resistance was independently associated with improved progression-free survival (hazard ratio 0.50; $P = .027$) but not overall survival (hazard ratio 0.62; $P = .215$). Similar findings were found on subgroup analysis of patients treated with second-line sunitinib ($n = 71$).

*Conclusion:* Long-term survival can be achieved in patients who develop imatinib-resistant gastrointestinal stromal tumors. Surgical resection of imatinib-resistant gastrointestinal stromal tumors is associated with improved progression-free survival and should be considered in selected patients.



## Introduction

Gastrointestinal stromal tumors (GIST) are mesenchymal neoplasms that originate from the interstitial cells of Cajal,[1] the majority of which are driven by oncogenic mutations in tyrosine kinase receptor genes, *KIT* and *PDGFRA*; the remaining 10% to 15% are driven by less common mutations, such as *SDH*, *NF1*, or others, and may have a more indolent clinical course.[2] Approximately 10% of patients with GIST have metastases at the time of diagnosis, with the liver and peritoneum being the most common sites (65% and

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21%, respectively).[3,4] For patients with metastatic disease, available therapies include tyrosine kinase inhibitors (TKI), including first-line imatinib, and either palliative or curative-intent surgical resection.

Approximately 10% to 15% of patients treated with imatinib will have primary imatinib resistance (ImR), experiencing progression within 3 to 6 months; the remainder develop secondary ImR, generally within 3 years from start of therapy.[5–7] Notably, however, wide variability in times to ImR are observed, with an estimated 10% of patients with metastatic disease able to remain on imatinib for over a decade without progression.[8] When secondary ImR does occur, the most common mechanism is the emergence of secondary *KIT* mutations in exons 13, 14, or 17.[9,10] The development of multiple TKIs in the past decade, such as sunitinib and regorafenib, have overcome many of these resistance mechanisms and added new layers of complexity to the management of patients with advanced imatinib-resistant disease. Currently, there are 4 FDA-approved TKIs for treatment of patients with advanced ImR GIST (sunitinib, regorafenib, avapritinib, and ripretinib). Prior to second- and third-line TKIs, curative-intent resection or cytoreduction of ImR GIST offered the only chance of altering disease trajectory for patients with imatinib-resistant GIST. In the modern practice environment, however, it is unknown whether patients derive an independent oncologic benefit to either overall survival (OS) or progression-free survival (PFS) with resection of ImR disease compared with the multiple lines of TKI therapy now available. Hence, we sought to evaluate factors associated with PFS and OS in patients with ImR GIST in our National Cancer Institute Comprehensive Cancer Center.

## Methods

### *Study population/patient data*

A query of the prospectively maintained Knight Cancer Registry was performed for consecutive patients with GIST treated at the Oregon Health & Science University (OHSU) between 2003 and 2018. Patients who developed ImR were identified, defined by a switch from imatinib to either a separate TKI or supportive care in the presence of multifocal progression of recurrent/metastatic lesions after at least 3 months of radiographically stable disease on imatinib therapy. Patients with unifocal progression resulting in an imatinib dose increase and/or resection of a unifocal ImR lesion were not considered ImR disease if the patient was continued on imatinib. This definition of ImR was chosen as some patients with liver or peritoneal metastatic disease experienced unifocal progression on imatinib and underwent either an imatinib dose increase and/or resection of the unifocal progressive lesion, followed by continuation of imatinib. We felt that neither of these events alone were sufficient to diagnose ImR, as some maintained stable disease on imatinib for a year or more until multifocal progression and a switch to second-line therapy occurred. Patients who never received imatinib therapy were not included. All included patients were treated at OHSU either before diagnosis of ImR disease or referred after the initial diagnosis of ImR disease. Patients referred to our institution after progression of ImR disease on second-line therapy were not included. All included patients with a localized primary disease at diagnosis underwent curative-intent resection, as did most patients with initially resectable metastatic and recurrent disease; ImR developed after subsequent recurrence. The decision to operate on patients with ImR disease was based on discussion in a multidisciplinary tumor board.

Data captured included patient demographics, clinicopathologic characteristics of primary tumors, duration of adjuvant therapy, timing and characteristics of recurrence, and oncologic outcomes, including dates and sites of progression and dates of mortality.

**Table I**
Clinicopathologic and treatment characteristics of $n = 84$ patients with imatinib-resistant gastrointestinal stromal tumor

| Variable | *n* (%) or median [IQR] |
|---|---|
| Age at diagnosis, y | 54 [42–63] |
| Age at ImR, y | 58.5 [47–70] |
| Sex | |
| Female | 35 (41.7) |
| Male | 49 (58.3) |
| Race/ethnicity | |
| White | 64 (76.2) |
| Non-White | 11 (13.1) |
| Unknown | 9 (10.7) |
| Neoadjuvant imatinib prior to primary resection | 16 (19) |
| AJCC T-stage at diagnosis | |
| I | 2 (2.4) |
| II | 12 (14.3) |
| III | 33 (39.3) |
| IV | 37 (44.0) |
| Driver mutation | |
| *KIT* | 65 (77.3) |
| Other | 9 (10.8) |
| Not tested | 10 (11.9) |
| Tumor rupture at primary resection | 7 (8.3) |
| Tumor histology | |
| Spindle cell | 72 (85.7) |
| Epithelioid | 7 (8.3) |
| Mixed | 5 (6.0) |
| Primary tumor size, cm | 7.5 [5.5–12] |
| Primary mitoses per 50 hpf | |
| 0–5 | 8 (9.5) |
| 6–10 | 20 (23.8) |
| >10 | 22 (26.2) |
| Unable to assess | 34 (40.5) |
| NIH risk assessment at diagnosis | |
| High | 42 (50.0) |
| Intermediate | 3 (3.6) |
| Low | 1 (1.2) |
| Very low | 1 (1.2) |
| Metastatic | 37 (44.0) |
| Curative-intent surgery for metastatic/recurrent disease before ImR | 40 (47.6) |
| Mon to ImR | 51 [25.5–77] |
| Site(s) of ImR disease | |
| Liver only | 37 (44.0) |
| Peritoneum only | 28 (33.3) |
| Liver and peritoneum | 12 (14.3) |
| Other location(s) | 7 (8.3) |
| Second-line therapy for ImR | |
| Sunitinib | 71 (84.5) |
| Other | 8 (9.5) |
| None | 5 (6.0) |
| Resection following ImR | 17 (20.2) |
| Peritoneal mass resection | 7 (8.3) |
| Major hepatectomy | 6 (7.1) |
| Minor hepatectomy | 2 (2.4) |
| Multisite metastasectomy | 2 (2.4) |

*AJCC,* American Joint Committee on Cancer; *hpf,* high-powered field; *ImR,* imatinib resistance; *IQR,* interquartile range; *NIH,* National Institutes of Health.

Given that ImR is by definition a progression event, disease progression was defined from the time of diagnosis of ImR, per the standard for studies of ImR GIST and using the Response Evaluation Criteria in Solid Tumours criteria.[11,12]

Staging for primary tumors was modified to reflect the eighth edition American Joint Commission on Cancer guidelines.[13] Surgical intervention for ImR disease was defined as any curative-intent or cytoreductive operation after the onset of ImR, as previously described. Patients without mutational testing were included and were presumed to have *KIT* driver mutations for the purposes of analysis. Starting in 2005, all patients with GIST treated at OHSU received *KIT* gene sequencing, followed by reflex *PDGFRA*

sequencing if *KIT* wild type. Patients negative for both mutations were evaluated for SDH-deficiency or other driver mutations according to the context of their clinical and family histories. Patients negative for *KIT, PDGFRA,* or *SDH* mutations were defined as "wild type." Liver resections for ImR disease were classified according to Brisbane Terminology.[14]

No subjects were excluded from the study based on sex, gender, or racial or ethnic origin. There were no age- or treatment-specific exclusion criteria. The study was reviewed and approved by the Institutional Review Board of OHSU and the Knight Cancer Institute Clinical Research Review Committee.

### *Statistical analysis*

Descriptive statistics of clinicopathologic variables were tabulated. Kaplan-Meier analysis was used to analyze OS (from date of ImR) and PFS (after ImR), and Cox proportional hazards modeling was used to calculate hazard ratios (HR) with 95% confidence intervals (95% CI) where appropriate. Variables with $P \leq .20$ on univariable analysis were included in the initial multivariable models to identify independent predictors of oncologic outcome; final multivariable models were arrived at by single backwards elimination of variables until further elimination resulted in a decrease in model fit with $P < .05$. Resection after a diagnosis of ImR disease was carried forward in all multivariable models regardless of significance thresholds, given that it was the specific covariable of interest. For Kaplan-Meier and Cox modeling, all patients not experiencing the event of interest were censored at last date of follow-up. All statistics were performed using SPSS Statistics 26 (IBM Corp, Armonk, NY).

## Results

### *Clinicopathologic characteristics and treatment*

Over the study period, 417 patients were treated at OHSU for GIST. Eighty-four patients (20.1%) met study criteria for ImR, which occurred at a median of 50 months after initiation of imatinib therapy (interquartile range: 25.5–77 months). The shortest time to imatinib resistance was 6 months. The median age was 59 years (Table I), and there was a slight male predominance ($n = 49$, 58%), while a majority were White ($n = 64$, 76%). Metastatic disease was present at initial diagnosis in 44% ($n = 37$) of patients. Of the 74 patients with mutational testing, 88% ($n = 65$) had a *KIT* mutation identified; 10 patients did not have mutational testing and were presumed to have a *KIT* mutation. Other driver mutations included *PDGFRA* ($n = 4$; 4.8%), *SDH* ($n = 3$; 3.7%), and wild type ($n = 2$; 2.4%). None of the patients with *PDGFRA* driver mutations had D842V point mutations. Approximately one fifth ($n = 16$; 19%) received neoadjuvant imatinib before resection of their primary non-metastatic tumor for a median of 2 months. Before the diagnosis of ImR, 48% of patients ($n = 40$) had a curative-intent resection for recurrent or metastatic disease. Most patients received sunitinib as second-line therapy for ImR ($n = 71$, 85%), while 5 patients were transitioned into hospice and received no further therapy or surveillance scans. Resection of ImR disease was performed in 17 (20%) patients, most commonly with peritonectomy ($n = 7$; 41%) or major hepatectomy ($\geq 3$ segments, $n = 6$; 35%). All patients undergoing surgical resection for ImR disease were also treated with perioperative second-line therapy, continued until progression. Median time to death or last follow-up was 33 months after ImR (range 2–166 months) and 94 months after GIST diagnosis (range 18–243 months).

### *Progression-free survival*

Of the 79 patients managed with second-line therapy and surveillance after diagnosis of ImR, 71 (89.9%) experienced further disease progression at a median of 10 months (estimated 95% CI: 7–13 months). Of the 71 patients with progression, 36 (51%) received regorafenib, 12 (17%) received no further therapy, 8 (11%) received nilotinib, 4 (6%) received avapritinib, and 11 (15%) received various other regimens on trial or on compassionate use basis. On Kaplan-Meier analysis, patients having a surgical intervention and a second-line TKI showed significantly improved PFS compared to patients only receiving TKI (median PFS 12 vs 8 months; $P = .043$, Fig 1).

On univariable Cox regression (Table II), variables associated with PFS after diagnosis of ImR were metastatic disease at diagnosis (HR 1.74; $P = .024$) and years to ImR (HR 0.92; $P = .016$). Surgical intervention after ImR (HR 0.60; $P = .09$) and primary tumor size (HR 1.01; $P = .163$) were not associated with PFS but were included in the preliminary multivariable model based upon prespecified statistical inclusion criteria. After single backwards elimination, surgical intervention after ImR (HR 0.50; $P = .027$) was independently associated with improved PFS on multivariable modeling. The association of increased time to ImR improved PFS did not reach statistical significance in the final multivariable model (HR 0.93 per year; $P = .064$). Sex, primary location, and tumor rupture were not associated with PFS (all $P > .2$). Of note, there were insufficient patients with non-*KIT* mutations to include driver mutation in the multivariable model and generate stable estimates.

### *Overall survival*

Overall, 54 patients (67.5%) died during the study period. The median OS was 51 months from development of ImR (95% CI: 32–70 months) and 110 months from GIST diagnosis (95% CI: 86–136 months). On Kaplan-Meier analysis, combined surgical intervention and TKI therapy of ImR disease was not associated with improved OS compared to TKI therapy alone (Fig 2, 5-year OS 76% vs 51%; $P = .065$).

On univariable analysis of 79 patients managed with second-line therapy (Table III), variables associated with OS were age at time ImR (HR 1.04 per additional year of age; $P < .001$), male sex (HR 1.92; $P = .029$), primary tumor rupture (HR 3.43; $P = .003$), and a prior curative-intent procedure of either primary or oligometastatic disease before ImR (HR 0.43; $P = .003$). A gastric primary location (HR 0.62; $P = .128$), metastatic disease at diagnosis (HR 1.48; $P = .152$), and surgical intervention for ImR disease (HR 0.55; $P = .092$) were included in the initial multivariable model. After single backwards elimination, age at ImR (HR 1.04; $P = .001$) was the only independent predictive factor for OS. Tumor rupture (HR 2.49; $P = .063$) was not significantly associated with OS but ultimately remained in the final multivariable model during stepwise elimination. On final multivariable modeling of OS, surgical intervention was not associated with improved OS when added to the model (HR 0.62; $P = .215$). Again, there was an insufficient number of patients with non-*KIT* mutations to include driver mutation in the multivariable model and generate stable estimates.

### *Subgroup analysis of patients treated with second-line sunitinib*

Recognizing that heterogeneous second-line treatment regimens can cloud the potential impact of ImR disease resection on outcomes, we performed a subgroup analysis of patients treated with second-line sunitinib per current standard of care ($n = 71$). In this group, receipt of surgical intervention was the only variable associated with improved PFS (HR 0.50, 95% CI: 0.27–0.93; $P =$

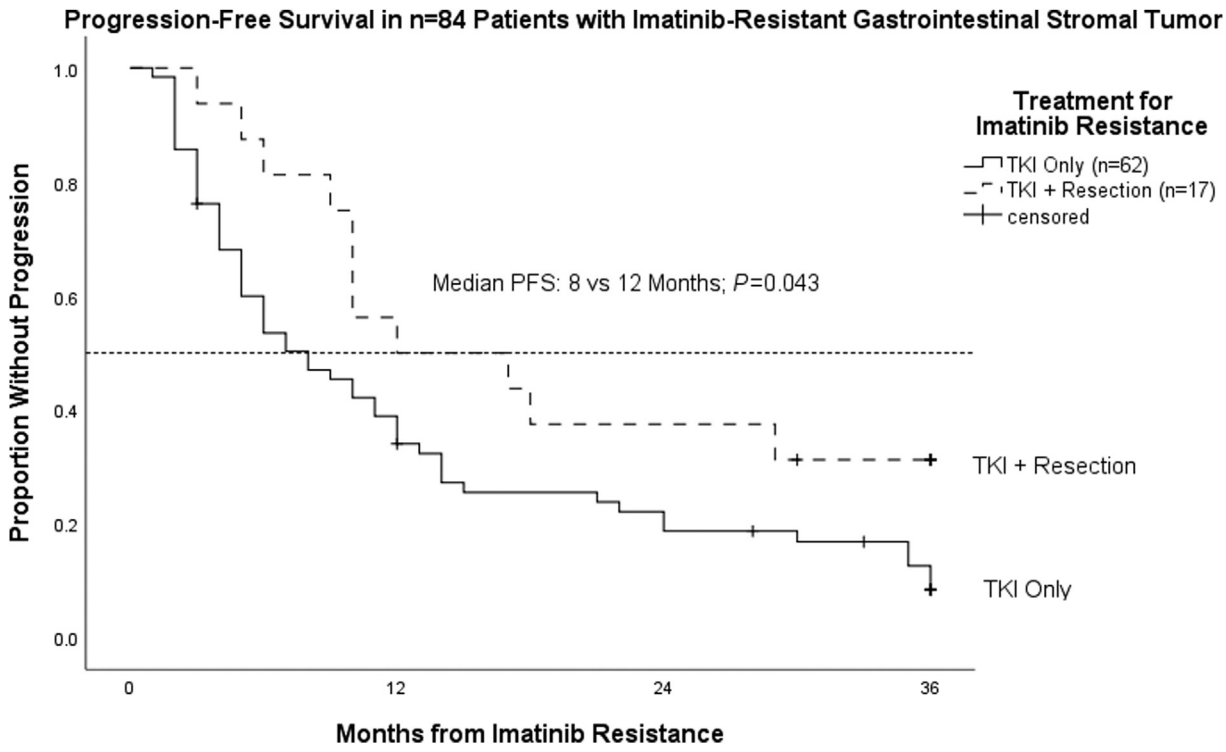


**Fig 1.** Kaplan-Meier plot of PFS after diagnosis of imatinib-resistant gastrointestinal stromal tumor. Patients receiving second-line TKI therapy plus surgical resection of imatinib-resistant disease display superior PFS than those receiving second-line TKI therapy alone (log-rank $P = .043$). *PFS,* progression-free survival; *TKI,* tyrosine kinase inhibitor.

**Table II**
Uni and multivariable regression of variables associated with progression-free survival in ImR GIST

| Variable | Univariable HR (95% CI) | *P* value | Multivariable HR (95% CI) | *P* value |
|---|---|---|---|---|
| Age at ImR | 1.00 (0.99–1.02) | .708 | - | - |
| Male sex | 1.01 (0.63–1.63) | .965 | - | - |
| Gastric primary | 1.10 (0.68–1.79) | .695 | - | - |
| Metastatic disease at diagnosis | 1.74 (1.08–2.82) | .024 | E | - |
| Tumor rupture | 1.18 (0.47–2.93) | .727 | - | - |
| Primary tumor size (per centimeter) | 1.01 (1.00–1.01) | .163 | E | - |
| Y to ImR | 0.92 (0.86–0.98) | .016 | 0.93 (0.86–1.00) | .064 |
| Any surgery following ImR | 0.60 (0.33–1.08) | .090 | 0.50 (0.27–0.92) | .027 |

*CI,* confidence interval; *E,* eliminated from model on single backwards elimination; *GIST,* gastrointestinal stromal tumors; *HR,* hazard ratio; *ImR,* imatinib resistance.

.029). Additionally, surgical resection was significantly associated with improved OS on univariable analysis (HR 0.42, 95% CI: 0.19–0.96; $P = .039$) but did not reach statistical significance (HR 0.47, 95% CI: 0.21–1.08; $P = .076$) on multivariable analysis. Increasing patient age at time of ImR was the only variable significantly associated with worse OS in the multivariable model (HR 1.04/year, 95% CI: 1.01–1.07; $P = .011$). No other variables were associated with OS or PFS in this population.

## Discussion

Since the advent of TKI therapy for patients with GIST, the treatment landscape for this visceral sarcoma has been among the most rapidly evolving in solid tumor oncology, ushering in novel targeted therapies that have been applied to other cancers. TKIs have now become a standard part of the treatment for most patients with GIST, with imatinib most commonly used for patients with known or potentially imatinib-sensitive mutations. Unfortunately, 90% of patients with initially imatinib-sensitive GIST that are metastatic at diagnosis or recur after resection will progress to ImR within 10 years of starting imatinib therapy.8

To our knowledge, the present study represents the first investigation of the role of surgical resection in this population in the era of multiline TKI therapeutics and includes analysis of patients with *KIT*-mutated tumors who develop secondary ImR. Our results indicate that resection of ImR GIST is independently associated with improved PFS compared to second-line TKI therapy alone. Additionally, our data suggest that this improvement in PFS may translate into an improvement in OS, as surgical resection after ImR approached statistical significance for improvement in OS ($P = .08$ on subgroup analysis of patients with *KIT* mutation); our cohort was likely underpowered to show this result, in part due to the multifactorial influences on survival, such as patient age. This fact highlights the difficulty of studying imatinib-resistant GIST, which is a rare population requiring lengthy follow-up to fully assess the outcomes of interest, as evidenced by a median follow-up exceeding 7 years after GIST diagnosis and approaching 3 years after ImR in our cohort. With the expanding and recognized role of neoadjuvant (per the ACRIN 6665/RTOG 0132 trial)[15] and adjuvant

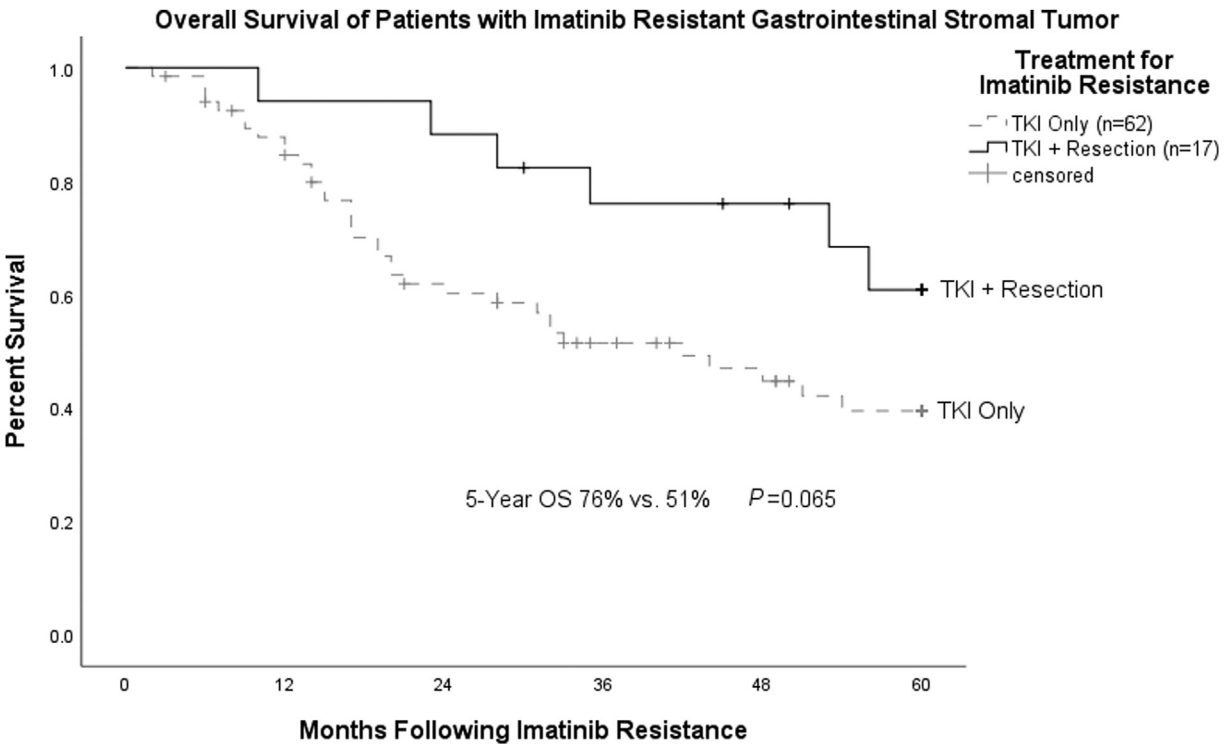


**Fig 2.** Kaplan-Meier plot of OS after diagnosis of imatinib-resistant gastrointestinal stromal tumor. Patients receiving second-line TKI therapy plus surgical resection of imatinib-resistant disease do not display significantly improved OS compared to those receiving second-line TKI therapy alone (log-rank $P = .065$). *OS,* overall survival; *TKI,* tyrosine kinase inhibitor.

**Table III**
Uni and multivariable regression of variables associated with overall survival in ImR GIST

| Variable | Univariable HR (95% CI) | *P* value | Multivariable HR (95% CI) | *P* value |
|---|---|---|---|---|
| Age at ImR | 1.04 (1.02–1.06) | < .001 | 1.04 (1.01–1.06) | .001 |
| Male sex | 1.92 (1.07–3.47) | .029 | E | - |
| Gastric primary | 0.62 (0.34–1.15) | .128 | E | - |
| Metastatic disease at diagnosis | 1.48 (0.87–2.52) | .152 | E | - |
| Tumor rupture | 3.43 (1.51–7.79) | .003 | 2.49 (0.95–6.47) | .063 |
| Primary tumor size | 1.00 (0.99–1.01) | .566 | - | - |
| Y to ImR | 0.93 (0.85–1.01) | .095 | E | - |
| Curative-intent procedure before ImR | 0.43 (0.25–0.76) | .003 | E | - |
| Any surgery following ImR | 0.55 (0.28–1.10) | .092 | 0.62 (0.30–1.32) | .215 |

*CI,* confidence interval; *E,* eliminated from model on single backwards elimination; *GIST,* gastrointestinal stromal tumors; *HR,* hazard ratio; *ImR,* imatinib resistance.

TKI therapy in patients with nonmetastatic GIST (per EORTC 62024, ACOSOG Z9001, and others),[15,16] there will likely be an increase in this population as more patients are exposed to therapy. Despite these limitations, our data provide the first suggestion that surgical intervention has a role in the management of this population, which will only become more frequent as additional TKI therapies are developed for GIST.

A relevant consideration in this population is whether some patients would be better served by resection during the period of imatinib sensitivity, rather than after ImR. While our study is not designed to answer this clinical question, that is a potential avenue for future research. Given the long period of imatinib sensitivity (exceeding 4 years in this population), the benefits of such an approach would have to be large to outweigh the risks of potentially morbid resections. Furthermore, as additional lines of TKI treatment are developed, the potential benefit of resection of moderate-to-large volume metastatic disease would likely diminish with each novel therapy.

The present study is limited as it is based in a prospectively maintained institutional database. As the study population represents all patients seen at OHSU before progression after ImR, the results are not subject to selection bias from patients referred for treatment only after progression of ImR disease. Despite the high-volume of GIST patients treated at our institution and the national and international referral base for this disease, the cohort of interest in the present study remains small, and our multivariable regressions were limited in their precision as a result. Additionally, due to our small cohort we were unable to generate regression models that distinguished between cytoreductive and curative-intent resections of ImR disease. It is possible that palliative resection may not hold oncologic benefit, and this remains a topic of further study. Similarly, we were unable to differentiate patients with high-volume ImR disease from those with low-volume disease due to a lack of a standard quantification scheme for liver and/or peritoneal disease. This may have impacted the decision to perform cytoreductive and/or

curative-intent resections and may be a confounder of the present results. Finally, we were unable to control for the heterogeneous third-line treatments that many patients received, such as regorafenib, which may have asymmetrically impacted the prognosis of patients treated with surgical resection after ImR. As additional lines of therapy are developed, the impact of surgical intervention in ImR disease may diminish.

In conclusion, we recommend that operative management be considered in patients with technically resectable ImR GIST, as it is associated with significantly improved PFS in select patients. Emphasis should also be placed on curative-intent resection of disease before the development of ImR, as this is a poor prognostic event with few highly efficacious treatments. Additional multicenter studies of this rare subpopulation are needed to more clearly identify the role of surgical resection in patients with ImR GIST.

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## Conflicts of Interest/Disclosure

Dr. Michael Heinrich receives consulting fees from Novartis, Deciphera Pharmaceuticals, Blueprint Medicines, and Theseus Pharmaceuticals. Dr. Michael Heinrich holds multiple patents on the diagnosis and/or treatment of GIST. One patent on treatment of GIST has been licensed by OHSU to Novartis. The other authors have no conflicts of interest or financial ties to disclose.

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