Surgical Management of Wild-Type Gastrointestinal Stromal Tumors: A Report From the National Institutes of Health Pediatric and Wildtype GIST Clinic

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ABSTRACT

Purpose

Wild-type gastrointestinal stromal tumors (WT-GISTs) that lack *KIT* or *PDGFRA* mutations represent a unique subtype of GIST that predominantly affects children. We sought to determine the effect on event-free survival (EFS) of staging variables, extent of resection, and repeat resection of tumors.

Methods

In 2008, a WT-GIST clinic was established at the National Cancer Institute, allowing the development of a large clinical database. We included participants who underwent resection of WT-GIST. Associations with EFS (ie, freedom from disease progression or recurrence) were evaluated using the Kaplan-Meier method and Cox proportional hazards modeling.

Results

Among 76 participants with WT-GISTs, the median follow-up was 4.1 years. Overall EFS ($\pm$ SE) was $72.6 \pm 5.4\%$ at 1 year, $57.6 \pm 6.2\%$ at 2 years, $23.7 \pm 6.0\%$ at 5 years, and $16.3 \pm 5.5\%$ at 10 years postoperatively. Hazard of disease progression or recurrence was significantly increased for patients with metastatic disease (adjusted hazard ratio [AHR], 2.3; 95% CI, 1.0 to 5.1; $P = .04$) and > 5 mitoses per 50 high-power fields (AHR, 2.5; 95% CI, 1.1 to 6.0; $P = .03$), whereas there was no significant effect of negative microscopic resection margins (AHR, 0.9; 95% CI, 0.4 to 2.2; $P = 0.86$). There was no association between type of gastric resection (ie, anatomic v partial/wedge) and EFS ($P = .67$). Repeated resection after the initial resection was significantly associated with decreasing postoperative EFS ($P < .01$). Five patients (6%) died after initial enrollment in 2008.

Conclusion

WT-GIST is an indolent disease, and most patients survive with disease progression. We found no improvement in EFS with more extensive or serial resections. Disease progression or recurrence may be more closely related to tumor biology than surgical management. These data suggest that resections for WT-GISTs be restricted to the initial procedure and that subsequent resections be performed only to address symptoms such as obstruction or bleeding.

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INTRODUCTION

Gastrointestinal stromal tumor (GIST) is a tumor of mesenchymal lineage that occurs at a rate of 14.5 cases per million person-years.¹ GISTs are presumed to arise from the interstitial cells of Cajal or their precursors,² most commonly resulting from mutation of a receptor tyrosine kinase, specifically *KIT* or *PDGFRA*.³⁻⁶ GISTs that lack *KIT* or *PDGFRA* mutations are considered wild-type GISTs (WT-GISTs). WT-GIST is a rare, incompletely understood subtype that disproportionately

affects children and adolescents.⁷ In a study of 27 patients with GIST diagnosed at 22 years of age or younger, Janeway et al⁷ found that 85% had wild-type tumor. In contrast, WT-GISTs comprise 10% to 15% of adult GISTs.^{4,8} On molecular and clinical levels, recent work has shown that WT-GIST behaves distinctly from its *KIT*/*PDGFRA*-mutated counterpart.⁹ Multimodality treatment of WT-GIST includes maintenance therapy with tyrosine kinase inhibitors, local control or palliation with tumor resection, and close observation with endoscopic and radiographic surveillance.¹⁰

ASSOCIATED CONTENT

Appendix

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The potential benefits of surgery must be tempered by the long-term morbidity of extensive resections in a young population. This is especially true for a disease that may persist for decades before recurrence or progression. Furthermore, the adult experience with GIST demonstrates a tendency to recur (especially in distant sites) despite complete resection.¹¹ Data supporting guidelines for the surgical management of WT-GIST are lacking. In particular, the effect of aggressive surgical resection and serial resections on event-free survival (EFS) has not been previously investigated. The WT-GIST clinic at the National Cancer Institute of the National Institutes of Health (NIH) was established in 2008 and has evaluated a large cohort of patients with WT-GIST. We analyzed data from this cohort to determine the optimal role of surgical intervention in the management of WT-GIST.

METHODS

The clinical records of 79 patients were collected and subsequently reviewed at the multidisciplinary Pediatric and Wildtype GIST Clinic, conducted at the NIH over 7 years.¹² The biannual clinic opened in 2008 as a collaborative effort among clinicians (including medical and pediatric oncologists, surgical oncologists, endocrinologists, geneticists, dermatologists, pathologists, and radiologists), researchers, allied health professionals (including social workers, psychologists, and dietitians), and patient advocates. Inclusion criteria were having either a GIST diagnosis before 19 years of age or, for adults ages 19 years or older, known WT-GIST. Participants with *KIT* or *PDGFRA* mutations were excluded. Those with succinate dehydrogenase (*SDH*) mutations were included in the analysis. Three patients who did not undergo surgery for WT-GIST were excluded from the analysis, leaving 76 participants in the final cohort. All patients in the NIH Pediatric and Wildtype GIST Clinic consented (and assented, where appropriate) to participation in the clinic and its studies. Demographic information, medical histories, and laboratory values were collected. The clinic also requested material for genomic studies. Radiotherapy was infrequently used, and dosimetry data were not collected.¹³ Operative reports were reviewed independently by two surgeons (A.L.M. and C.B.W.). Imaging studies were reviewed by radiologists who participated in the clinic. Pathology data were reviewed by NIH Pediatric and Wildtype GIST Clinic pathologists to confirm the diagnosis, determine the number of mitoses per 50 consecutive high-power fields, and assess resection margins of surgical specimens. Resection margins were classified as negative microscopic margins (R0), positive microscopic margins (R1), or positive gross margins (R2). Methods for determining tumor and germline *SDH* mutation status are described elsewhere.⁹ Mutation status of recurrent tumor was unknown, because tissue samples were not available. Further details of the Pediatric and Wild-Type GIST Clinic have been documented elsewhere.^{9,14,15}

We tabulated patient data, including biologic sex, age at diagnosis, extent of disease at presentation (ie, local, locoregional, or distant metastatic), and site of disease. Locoregional extent of disease indicates tumor involvement of nearby lymph nodes or adjacent structures. Disease stage was determined surgically and radiographically. As such, biopsy of sites of metastatic disease was not systematically performed, unless clinically indicated. We applied the NIH consensus criteria and Armed Forces Institute of Pathology (AFIP) risk scores to this cohort of participants with WT-GIST.^{16,17} The NIH consensus criteria risk score was originally developed to predict aggressive tumor behavior (specifically, risk of metastasis) for adults with GISTs. The NIH risk score incorporates metastatic disease, tumor size, and mitotic count into the following risk categories: very low risk, low risk, intermediate risk, high risk, and metastatic disease.¹⁶ Similarly, the AFIP risk score, as put forth by Miettinen and Lasota,¹⁷

estimates the risk of tumor-related death or metastasis. The AFIP criteria incorporate tumor size, mitotic count, and primary tumor site (gastric v small intestine) into the following risk categories: very low risk, low risk, intermediate risk, and high risk.

The primary outcome of this study was EFS. An event was defined as disease recurrence (after resection with no evidence of microscopic disease) or disease progression (after resection with evidence of microscopic or gross disease). No patient died before disease progression or recurrence; therefore, the competing risk of mortality was not considered. Secondary outcomes included extent of disease at recurrence and disease status (ie, no evidence of disease, alive with disease, or deceased) at most recent follow-up.

The univariable analysis of categorical factors associated with study end points was performed with the χ^2 test or Fisher's exact test, when appropriate. Linear trends in ordinal categorical data were assessed with the Cochran-Armitage test. Continuous factors independently associated with study end points were assessed with the two-tailed independent samples *t* test or Mann-Whitney *U* test, when appropriate. Kaplan-Meier (log-rank test) and Cox proportional hazards analyses assessed risk factors for progression or recurrence. Time to event was defined as the interval between surgery and date of disease progression or recurrence (or date of most recent follow-up imaging study). A two-tailed *P* value < .05 was considered statistically significant. All data were analyzed with SAS (SAS Institute, Cary, NC).

RESULTS

Seventy-six participants who underwent surgery and attended the NIH Pediatric and Wildtype GIST Clinic were included in the study. The majority of patients were female (76%; *n* = 58). Median (interquartile range [IQR]) age at diagnosis was 21.0 (12.1-32.3) years, and 47% (*n* = 36) were under 18 years of age at diagnosis. The majority of patients initially presented with local disease (62%; *n* = 47). Overall, the most common sites of local disease were stomach (83%; *n* = 63) and small intestine (13%; *n* = 10). Metastatic disease was present at initial diagnosis in 26% (*n* = 20). Of the 20 participants with metastatic disease at presentation, sites included liver (*n* = 13), omentum (*n* = 7), small intestine (*n* = 5), pelvis (*n* = 2), peritoneum (*n* = 2), vertebral body (*n* = 1), and large intestine (*n* = 1). Six participants had multiple sites of metastases. The remainder of patients (12%; *n* = 9) had locoregional spread to surrounding structures or lymph nodes at presentation. Of the nine participants with locoregional disease at presentation, seven were found to have lymphovascular invasion or infiltration of local lymph node basins. One patient was found to have gastric disease that extended to the diaphragm and esophagus. One patient was found to have gastric disease that extended to the omentum. For the latter two patients with disease spread to surrounding structures, pathology was unavailable, and their status as having locoregional disease was based on the surgeon's determination of need for an en-bloc resection to include these structures. For patients who presented with local disease, 93% (43 of 46), 4% (2 of 46), and 2% (1 of 46) had R0, R1, and R2 resection margins, respectively. For patients who presented with locoregional disease, 78% (7 of 9), 11% (1 of 9), and 11% (1 of 9) had R0, R1, and R2 resection margins, respectively. Finally, for patients who presented with metastatic disease, 47% (9 of 19), 5% (1 of 19), and 47% (9 of 19) had R0, R1, and R2 resection margins, respectively (*P* < .01 for difference in resection margins by extent of disease at presentation).

Median tumor size was 7.0 (IQR, 4.7-9.0) cm. Eight (11%) and 59 (78%) patients were administered neoadjuvant and adjuvant tyrosine kinase inhibitors, respectively. There was no difference in the rate of progression or recurrence with the use of neoadjuvant ($P > .99$) or adjuvant ($P = .23$) tyrosine kinase inhibitors. Five patients (6%) died after initial enrollment in 2008. Median follow-up from time of initial diagnosis was 4.1 (IQR, 1.5-8.2) years.

Fifty-four patients (71%) experienced an event of progression or recurrence. The median EFS was 2.5 years (95% CI, 1.7 to 3.5 years), as displayed in Figure 1. Factors significantly associated with progression or recurrence are listed in Table 1 and included increasing mitotic rate and elevated NIH risk score. The effect of the NIH score, which incorporates tumor size, mitotic rate, and presence of metastatic disease, is illustrated in Figure 2. (Kaplan-Meier curves for nonmetastatic disease at presentation and for > 5 mitoses per 50 high-power fields are presented in Appendix Figs A1 and A2, online only, respectively.) The AFIP criteria were not associated with significantly different Kaplan-Meier estimates of EFS (log-rank test, $P = .28$). Among patients with nonmetastatic disease, R0 resection (negative microscopic margins) was not significantly associated with improved EFS, as displayed in Appendix Figure A3, online only. Among the 41 patients who developed recurrent disease after R0 resection, recurrence was local for eight patients (19%), locoregional for four patients (10%), and metastatic for 29 patients (71%). In the multivariable analysis, metastatic disease at presentation and elevated mitotic rate were significantly associated with increased hazard of disease progression or recurrence, controlling for resection margins, age at diagnosis, gender, primary tumor location, and maximal tumor diameter (Table 2).

Evaluation of germline and tumor *SDH* mutation status was performed for 49 and 44 participants, respectively. On germline testing, *SDH* was deficient in 27 (55%) of 49 tested participants, whereas 17 (35%) of 49 participants were *SDH* competent without another mutation and five (10%) of 49 participants were *SDH* competent with other mutations. Of tumors tested, *SDH* was deficient in 23 (52%) of 44 tested participants, whereas 16 (36%) of 44 participants were *SDH* competent without another mutation, and five (11%) of 44 participants were *SDH* competent with other

Table 1. Event (recurrence or progression) After Initial Resection of WT-GIST

Variable	Event	No event	<i>P</i>
Sample size	54 (71)	22 (29)	
Age at diagnosis, years	18.9 (10.4-33.9)	23.4 (14.1-29.2)	.46
Female	42 (78)	16 (73)	.64
Primary gastric tumor	44 (81)	19 (86)	.75
Tumor extent at presentation			.21
Local	32 (59)	15 (68)	
Locoregional	5 (9)	4 (18)	
Metastatic	17 (31)	3 (14)	
Multifocal*	12 (32)	5 (26)	.64
Initial tumor size, cm	7.0 (4.3-10.0)	6.5 (5.0-9.0)	.97
Neoadjuvant medication	6 (11)	2 (9)	$> .99$
Adjuvant medication	44 (81)	15 (68)	.23
Mitoses per 50 HPF	16.5 (7.5-25.0)	4.0 (2.5-13.0)	$< .01$
> 5 mitoses per 50 HPF	37 (80)	10 (45)	$< .01$
Germline <i>SDH</i>			.15
Competent	18 (51)	4 (29)	
Deficient	17 (49)	10 (71)	
Tumor <i>SDH</i>			.08
Competent	17 (57)	4 (29)	
Deficient	13 (43)	10 (71)	
NIH risk score			$< .01$
Very low	0 (0)	0 (0)	
Low	2 (4)	0 (0)	
Intermediate	4 (4)	12 (55)	
High	28 (57)	7 (32)	
Metastatic	17 (35)	3 (14)	
AFIP risk score			.01
Low	6 (14)	10 (45)	
Intermediate	12 (28)	6 (27)	
High	25 (58)	6 (27)	
Resection margins			.50
R0	41 (79)	18 (82)	
R1	2 (4)	2 (9)	
R2	9 (17)	2 (9)	
No. of surgeries	2 (1-3)	1 (1-1)	$< .01$
Disease status at last follow-up			$< .01$
Alive with disease	35 (65)	3 (14)	
NED s/p treatment	14 (26)	19 (86)	
Deceased	5 (9)	0 (0)	
Follow-up years	6.1 (3.6-9.5)	1.1 (0.4-2.5)	$< .01$

NOTE. No. (%) or median (interquartile range).

Abbreviations: AFIP, Armed Forces Institute of Pathology; HPF, high-power fields; NED, no evidence of disease; NIH, National Institutes of Health; R0, negative microscopic margins; R1, positive microscopic margins; R2, positive gross margins; s/p, status post; *SDH*, succinyl dehydrogenase; WT-GIST, wild-type gastrointestinal stromal tumor.

*For disease not metastatic at presentation.

Fig 1. Event-free survival (without recurrence or progression) with 95% CI after initial resection of wild-type gastrointestinal stromal tumor: 1-year, 72.6% (SE = 5.4%); 2-year, 57.6% (SE = 6.2%); 5-year, 23.7% (SE = 6.0%); 10-year, 16.3% (SE = 5.5%); 15-year, 5.4% (SE = 3.6%); 20-year, 2.7% (SE = 2.6%); median (95% CI), 2.46 years (1.65 to 3.53 years).

mutations. Among tested participants who had an event, 17 (49%) of 35 participants were germline *SDH* deficient versus 10 (71%) of 14 among those with no event ($P = .15$) and 13 (43%) of 30 participants were tumor *SDH* deficient versus 10 (71%) of 14 among those with no event ($P = .08$). EFS was not significantly affected by tumor *SDH*-competent status (median *SDH*-deficient EFS, 4.6 years ν *SDH*-competent, 2.8 years; $P = .10$) or germline *SDH*-competent status (median *SDH*-deficient EFS, 4.6 years ν *SDH*-competent, 2.8 years; $P = .20$). Of five participants who died over the follow-up period of this cohort, the one participant who underwent *SDH* testing was found to be *SDH* competent in both tumor and germline. Two patients were found to be deficient in the neurofibromatosis 1 tumor suppressor gene, on the basis of tumor genotyping. Matching germline DNA was not available for analysis for either patient, although one had been diagnosed with neurofibromatosis on the basis

Fig 2. Event-free survival (without recurrence or progression) after initial resection of wild-type gastrointestinal stromal tumor, stratified by National Institutes of Health/Fletcher risk score. Log-rank $\chi^2 = 9.41$; $P < .01$.

Fig 3. Event-free survival (without recurrence or progression) after primary and subsequent resections of wild-type gastrointestinal stromal tumor. Log-rank $\chi^2 = 11.51$; $P < .01$.

of clinical criteria. In addition, two patients were *BRAF* deficient and one patient was *CBL* deficient. The findings of the tumor genotyping were reported to each patient.

Of 33 patients who underwent reoperation, five (15%) were symptomatic with bleeding ($n = 3$), pain ($n = 1$), or obstruction ($n = 1$). In the overall cohort, each subsequent resection after the initial resection was significantly associated with decreasing postoperative EFS (Fig 3; $P < .01$). In the overall cohort, during initial resection of gastric GIST, 12 (43%) of 28 patients underwent an anatomic resection with total gastrectomy ($n = 1$), subtotal gastrectomy ($n = 4$), or distal gastrectomy ($n = 7$). The remainder, 16 (57%) of 28 participants, underwent partial gastrectomy with wedge resection. There was no association between initial extent of gastric resection and EFS (log-rank test, $P = 0.67$). Likewise, there was no significant difference in rate of local recurrence after initial anatomic gastric resection (0 of 8; 0%) compared with non-anatomic gastric resection (2 of 9; 22%; $P = .47$).

DISCUSSION

We present data from a large cohort of patients with WT-GIST from the multidisciplinary NIH Pediatric and Wildtype GIST

Clinic. Patients with WT-GIST have prolonged survival but multiple recurrences, with 84% of patients experiencing an event at 10 years after diagnosis. Factors associated with tumor biology (ie, mitotic rate and presence of metastatic disease) were associated with decreased EFS, whereas surgical factors, such as microscopic resection margins and type of gastric resection (wedge v anatomic resection) were not significantly associated with EFS. Similarly, repeated resections led to diminishing returns, with decreased EFS compared with the initial resection.

This report includes 76 patients who were enrolled in the NIH Pediatric and Wildtype GIST Clinic on the basis of predefined criteria.^{9,14,15} Compared with *KIT*/*PDGFRA*-mutated tumors, WT-GISTs tend to occur at a younger age, affect female patients, and almost exclusively arise in the stomach.^{18,19} The natural history of WT-GIST has been suggested to be more indolent than that of *KIT*/*PDGFRA*-mutated GIST,^{20,21} although differences in follow-up duration and lack of direct comparison temper such conclusions comparing WT-GIST and *KIT*/*PDGFRA*-mutated GIST. In our population, the all-cause mortality rate was 6%, the median age at diagnosis was 21 years, over 75% of patients were female, and over 75% of tumors involved the stomach. Recent work elaborated molecular subtypes of WT-GIST.⁹ We report a nonsignificant trend between *SDH*-competent tumors and decreased EFS. Of the five participants who died, one was evaluated for *SDH* mutation and found to be *SDH* competent.

Despite a low overall mortality, disease progression and recurrence occurred frequently in our population. One-, 5-, and 10-year EFS was limited to 73%, 24%, and 16%, respectively. For this reason, WT-GIST must be viewed within the paradigm of a chronic disease. In comparison, *KIT*/*PDGFRA*-mutated GISTs have outcomes ranging from 39% 2-year EFS among patients with metastatic disease to 63% 5-year EFS among those with isolated primary gastric GISTs.^{22,23} Among our population of patients with WT-GIST, tumor biology strongly affected outcomes, given that presence of metastases and elevated mitotic rate significantly affected EFS. In contradistinction, surgical factors such as resection margin involvement did not affect EFS. For patients with *KIT*/*PDGFRA*-mutated GIST, resection with negative gross margins (R1 resection) has been shown to provide

Table 2. Multivariable Cox Analysis of Risk Factors for Disease Progression or Recurrence

Variable	Adjusted Hazard Ratio	95% CI	P
Metastasis	2.28	1.02 to 5.09	.04
> 5 mitoses per 50 HPF	2.54	1.08 to 5.99	.03
R0 resection	0.92	0.38 to 2.24	.86
Female	1.08	0.50 to 2.33	.85
Primary gastric tumor	1.34	0.49 to 3.66	.57
Primary tumor diameter (per cm)	0.99	0.92 to 1.06	.80
Age at diagnosis (per year)	1.00	0.97 to 1.03	.96

Abbreviations: HPF, high-power fields; R0, negative microscopic margins.

significant survival benefit.^{24,25} No significant difference in 4-year recurrence-free survival with overall GIST has been shown with negative microscopic margins (R0 resection), compared with grossly negative but microscopically positive margins (R1 resection).²⁶ This finding cannot be extrapolated to WT-GIST, however, given the low overall mortality rate. Furthermore, although WT-GIST may be less aggressive than its adult GIST counterpart in the short term, it is an insidious and tenacious entity that tends to progress or recur despite complete microscopic resection.¹⁰

Although we propose important caveats on the basis of these findings, surgery remains a cornerstone of treatment of non-metastatic WT-GIST and continues to be recommended by the National Comprehensive Cancer Network.²¹ In addition to contributing to local disease control, surgery at initial presentation is crucial to secure tissue for pathologic diagnosis and genotyping. Furthermore, given that a frequent manifestation of WT-GIST is gastrointestinal hemorrhage, surgery at presentation is often required. In the setting of recurrent disease, these data support the role of surgery in the event of symptoms such as pain, bleeding, perforation, obstruction, or other clinically significant issues. The use of surgery as a preventive treatment of growing tumors that may be likely to cause symptoms remains controversial. On the basis of our findings, we advise caution in the use of repeated, extensive, and formal anatomic resection for treatment of WT-GIST. When surgery is indicated, a limited operation with wedge resection may be the most appropriate option. On one hand, simple enucleation has been shown to confer a high risk of recurrence.²⁷ On the other hand, we found no significant association between anatomic (*v* nonanatomic or wedge) gastric resection and EFS. On the basis of the findings of this study, we suggest minimizing the extent of resection when possible, while still obtaining negative gross margins. Given the rarity of WT-GIST and the lack of definitive data, treating oncologists and surgeons should consider referral to centers of expertise for multidisciplinary consultation and surgical planning.

For patients with advanced WT-GIST, the decision of when to operate is especially challenging. Surgery for palliation of symptoms merits consideration. However, among asymptomatic patients with WT-GIST, the appropriate criteria for resection have not yet been determined. Several prognostic risk stratification systems have been developed for adult GIST, including the NIH consensus criteria.^{16,28} In this study, we found an association between decreased EFS and more severe NIH consensus criteria score. Further prospective work is warranted to assess the use of prognostic scores in preoperative risk stratification.

The potential morbidity of resection renders surgery less universally applicable compared with tyrosine kinase inhibitors, especially in the setting of metastatic disease, need for extensive resection, or poor risk profile. On the basis of the NIH consensus criteria. Recent investigations have assessed systemic therapy among patients with WT-GIST. Data published from this clinic

demonstrated no objective tumor response to imatinib, but a relatively superior response to sunitinib.⁹ A 2016 study by Ben-Ami et al²⁹ noted potential improvement of progression-free survival with regorafenib among patients with unresectable *SDH*-deficient GIST after failure of prior therapy with a tyrosine kinase inhibitor.

There were several limitations to our study. This was a retrospective analysis, with inherent biases, potential for confounding, and differential follow-up among patients with and without events. It is possible that event-free patients were right censored, potentially overestimating EFS. The mortality rate of 6% underestimates overall survival among all patients with WT-GIST, given that there is an unknown subset of patients who died before being eligible to enroll in the clinic (ie, survivorship bias). In general, biases were mitigated by a clinic protocol, in which clinical records were systematically obtained and primary radiology and pathology data were independently reviewed by the NIH Pediatric and Wildtype GIST Clinic. Patients in our analytic cohort were initially diagnosed over a period of decades, during which time there were changes in diagnosis and treatment. Notably, advances have included the development of tyrosine kinase inhibitors, improvements in imaging modalities, and evolution of intraoperative staging, such as the use of intraoperative ultrasound. We identified an association between repeated resection and decreased EFS; however, this relationship may be confounded by an association between more advanced disease and multiple resections.

In conclusion, this analysis suggests avoidance, when possible, of formal anatomic (eg, subtotal or total gastrectomy) and repeated resections. Over the follow-up period of this cohort, we report a low mortality and high likelihood of disease progression or recurrence, even after extensive resections. Among patients with WT-GIST, disease course depends more on mitotic rate and preexisting metastases than on extent of surgical resection. Overall EFS is low, regardless of resection margin status.

AUTHORS' DISCLOSURES OF POTENTIAL CONFLICTS OF INTEREST

Disclosures provided by the authors are available with this article at ascopubs.org/journal/jco.

AUTHOR CONTRIBUTIONS

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Final approval of manuscript: All authors

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Appendix

Fig A1. Event-free survival (without recurrence or progression) after initial resection of wild-type gastrointestinal stromal tumor, stratified by disease metastasis at presentation. Log-rank $\chi^2 = 10.34$, $P < .01$.

Fig A2. Event-free survival (without recurrence or progression) after initial resection of wild-type gastrointestinal stromal tumor, stratified by mitotic rate per 50 high-power fields (HPF). Log-rank $\chi^2 = 4.75$, $P = .03$.

Fig A3. Event-free survival (without recurrence or progression) after negative microscopic margins (R0) versus positive microscopic margins (R1) or positive gross margins (R2) initial resection of wild-type gastrointestinal stromal tumor among patients presenting with local or locoregional disease (ie, nonmetastatic disease at presentation). Log-rank = 0.005, $P = .94$.