Tumor Mitotic Rate, Size, and Location Independently Predict Recurrence After Resection of Primary Gastrointestinal Stromal Tumor (GIST)

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BACKGROUND. Gastrointestinal stromal tumor (GIST) is the most frequent sarcoma of the intestinal tract and often shows constitutive activation of either the KIT or PDGFRA receptor tyrosine kinases because of gain-of-function mutation. Although the efficacy of tyrosine kinase inhibitors in metastatic GIST depends on tumor mutation status, there have been conflicting reports on the prognostic importance of *KIT* mutation in primary GIST.

METHODS. A total of 127 patients were studied who presented to our institution from 1983 to 2002 with localized primary GIST and underwent complete gross surgical resection of disease. The majority of tumors originated in the stomach (58%) or small intestine (28%). By using polymerase chain reaction (PCR) and direct sequencing, a *KIT* mutation was found in 71% of patients and a *PDGFRA* mutation in 6%.

RESULTS. After a median follow-up of 4.7 years, recurrence-free survival was 83%, 75%, and 63% at 1, 2, and 5 years, respectively. On multivariate analysis recurrence was predicted by $\geq$5 mitoses/50 high-power fields, tumor size $\geq$10 cm, and tumor location (with patients having small bowel GIST doing the worst). In particular, a high mitotic rate conferred a hazard rate of 14.6 (95% confidence interval, 6.5–32.4). Specific *KIT* mutations had prognostic importance by univariate but not multivariate analysis. Patients with *KIT* exon 11 point mutations and insertions had a favorable prognosis. Those with *KIT* exon 9 mutations or *KIT* exon 11 deletions involving amino acid W557 and/or K558 had a higher rate of recurrence, whereas patients without a tyrosine kinase mutation had intermediate outcome.

CONCLUSIONS. In the absence of therapy with tyrosine kinase inhibitors, recurrence in completely resected primary GIST is independently predicted by mitotic rate, tumor size, and tumor location. ***Cancer* 2008;112:608–15.** © *2007 American Cancer Society.*

KEYWORDS: gastrointestinal stromal tumor, GIST, KIT, PDGFRA, mutation, surgery, survival.

Gastrointestinal stromal tumor (GIST) is the most common mesenchymal tumor of the intestinal tract. The tumor occurs typically in the stomach or small intestine, infrequently in the colon, rectum, or esophagus, and rarely outside of the gastrointestinal tract. A variety of mutations have been detected in GIST. The most common site involves *KIT* exon 11, whereas an exon 9 mutation occurs in approximately 5%.[1] In about 3% to 5% of GISTs there is instead a mutation in the platelet derived growth factor receptor alpha gene (*PDGFRA*).[2] In mice, targeted mutation of the KIT receptor has been shown to be sufficient for GIST development.[3,4]

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GIST has recently attracted widespread interest because of the development of effective targeted molecular agents against it. Over 80% of patients benefit from tyrosine kinase inhibitor therapy and the median survival from the diagnosis of metastatic GIST is now nearly 5 years.[5] Whereas the outcome of targeted therapy in metastatic GIST has been shown to correlate with mutation status,[6,7] it is unclear whether mutation status predicts the likelihood of recurrence after resection of a primary GIST. Several investigators have reported that *KIT* mutation confers a poor prognosis in primary GIST.[8–13] Because *KIT* mutations are known to be present even in small (<1–2 cm), incidental GISTs,[14] we postulated that *KIT* mutation itself may not actually influence outcome after resection of a primary GIST. The aim of this study was to determine the relative impact of clinicopathologic factors on recurrence in a large series of surgically resected primary localized GIST treated at a single institution.

MATERIALS AND METHODS

Clinicopathologic Variables

From 1983 to 2002 there were 127 patients who presented to our institution with primary GIST without metastasis, underwent complete gross resection, and had adequate archival tissue for mutational analysis. Patient, tumor, and treatment data were collected prospectively and entered into our sarcoma database.

Pathologic Analysis

All tumors included in the study were re-reviewed by a single sarcoma pathologist (C.R.A.) and the diagnosis of GIST was confirmed by positive staining for KIT (CD117) protein, as previously described.[15] Tumor morphology was classified as predominantly epithelioid or spindle-shaped. Mitotic rate was determined by counting the number of mitotic figures per 50 high power fields (HPF) and categorized as <5, 5–10, or ≥10.

Mutation Analysis

Mutation analysis was performed as detailed previously.[15] DNA was isolated from frozen tumor specimens using phenol chloroform extraction or from paraffin-embedded tissue using proteinase K digestion. One microgram of DNA was subjected to PCR using Platinum TaqDNAPolymerase High Fidelity (Life Technologies, Gaithersburg, Md). Oligonucleotide primers for *KIT* exons 9, 11, 13, and 17 or *PDGFRA* exons 12 and 18 have been published previously.[15–17] Tumors were first tested for *KIT* exon 9 and 11 mutations. Tumors lacking a mutation were then tested for *KIT* exon 13 or 17 mutation and *PDGFRA* exon 12 and 18 mutations. The PCR products were identified by agarose gel electrophoresis using a 2% MetaPhor agarose gel (BioWhittaker Applications, Rockland, Me) and purified with the QIAquick PCR Purification Kit (Qiagen, Valencia, Calif) before sequencing. Every ABI sequence was compared with a National Center for Biotechnology Information (NCBI) Human *KIT* gene nucleotide sequence and blasted using an NCBI Standard Nucleotide Blast Search to determine the location and type of mutation within a particular exon. If no mutation was found initially, another portion of tumor was tested. Tissue collection and molecular analyses were approved by the Institutional Review Board.

Statistics

Correlation between variables was assessed using the 2-sided Fisher exact test. For comparisons involving tumor location, 3 site categories and the 2-sided Pearson chi-square test were used. Actuarial recurrence-free survival from the date of surgical resection was calculated using the method of Kaplan and Meier. The relation of patient, tumor, and treatment characteristics to outcome was tested by univariate analysis using log-rank. SPSS statistical software (v. 11.5; Chicago, Ill) was used for univariate analysis. Multivariate analysis was performed with the Cox proportional hazards model. A P-value <.05 was considered statistically significant. SAS 9.1 (Cary, NC) was used for multivariate analysis.

RESULTS

Clinicopathologic Characteristics

The median age of the population was 67 years (range, 10–94) and there were 73 (57%) males. Tumor locations included the stomach in 74 (58%), small bowel in 35 (28%), rectum in 13 (10%), esophagus in 3 (2.4%), colon in 1 (0.8%), and an extraintestinal site in the pelvis in 1 (0.8%) (Table 1). There was 1 pediatric patient, a girl with multifocal gastric tumors. The median tumor size was 6 (0.3–50) cm. Most (74%) patients had a low mitotic rate. Cellular morphology was predominantly spindle-shaped in 112 (88%).

Treatment

Partial gastrectomy was the most common (51%) operation. Five patients underwent pancreaticoduodenectomy, 5 a proximal gastrectomy, 4 an esophagectomy, 2 a total gastrectomy, 5 an abdominoperineal resection, and 3 a pelvic exenteration. Perioperative mortality occurred in 4 patients (3.1%), 1 of whom

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TABLE 1
Clinicopathologic Characteristics of Patients With Primary GIST

Variable		No. (%)
Sex	Women	54 (43)
	Men	73 (57)
Age	<60	43 (34)
	≥60	84 (66)
Tumor location	Stomach	74 (58)
	Small intestine	35 (28)
	Colon/rectum	14 (11)
	Other	4 (3)
Tumor size	<5 cm	51 (40)
	5–10 cm	37 (29)
	≥10 cm	39 (31)
Mitotic rate	<5	94 (74)
	5–10	19 (15)
	≥10	14 (11)
Mutation	Any	98 (77)
	None	29 (23)
	KIT exon 11	85 (67)
	DEL557or8	35 (28)
	Other DEL	17 (13)
	INS	11 (9)
	PM	22 (17)
	KIT exon 9	4 (3)
	KIT exon 17	1 (1)
	PDGFRA	8 (6)

GIST indicates gastrointestinal stromal tumor; INS, insertion; DEL, deletion; PM, point mutation.

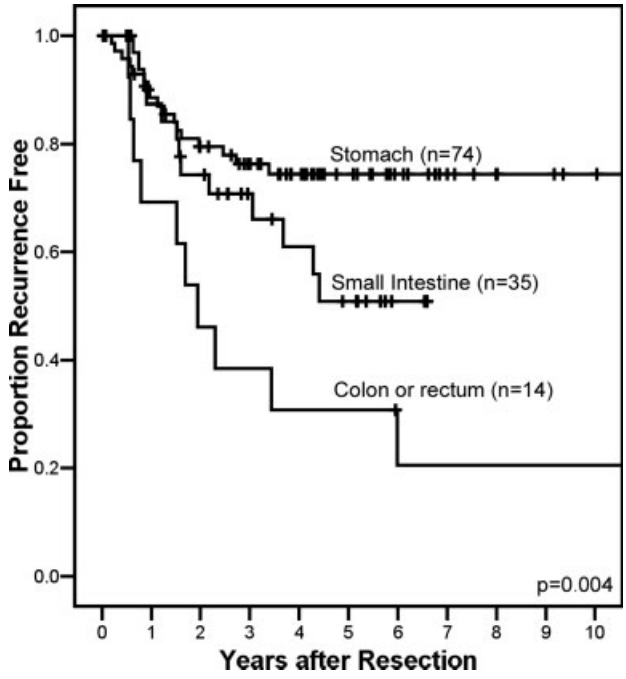

FIGURE 1. Recurrence-free survival in 127 patients with completely resected localized gastrointestinal stromal tumor (GIST) based on tumor location.

underwent operation primarily for an intraabdominal angiosarcoma. Positive microscopic margins occurred in 19 (15%) patients. No patient was treated with a tyrosine kinase inhibitor before developing recurrence.

KIT and *PDGFRA* Genotype

Of the 127 patients with localized primary GIST, 90 (71%) had a mutation in *KIT* (Table 1). Of patients with a *KIT* mutation, exon 11 was the most common site in 85 (94%). No patient had an exon 13 mutation. *KIT* exon 11 mutations were subtyped as deletions in 52 patients (61%), point mutations in 22 (26%), and insertions in 11 (13%). The *KIT* exon 11 deletions were further divided between those that resulted in an amino acid change or deletion at amino acid W557 and/or K558 (DEL557or8), and those that did not. In 29 (23%) patients a *KIT* or *PDGFRA* mutation could not be identified.

Recurrence Outcome and Univariate Analysis

With a median follow-up for survivors of 5.2 (0.02–12.8) years after resection of the primary tumor, 63 patients are alive without disease, 30 have died of disease, 22 died of other causes, and 12 are alive with disease. With a median follow-up for patients free of recurrence of 4.7 years, median recurrence-free survival was not reached with 83% recurrence-free at 1 year, 75% at 2 years, 63% at 5 years, and 60% at 10 years.

On univariate analysis, tumor location, size, and mitotic rate predicted recurrence-free survival. Patients with gastric GIST fared better than those with a small intestine or colon/rectum primary (Fig. 1). Tumor size was also an important predictor (Fig. 2). Patients with a mitotic rate of <5 did markedly better than those with ≥5 mitoses per 50 HPFs (Fig. 3). There was no difference in recurrence between patients with a mitotic rate of 5–10 versus those with ≥10 ($P = .67$). Age, sex, morphology, microscopic margins, and tumor rupture or intraabdominal hemorrhage did not predict recurrence. However, only 4 patients had tumor rupture. Positive microscopic margins occurred in 19 (15%) patients and were more likely in the rectum (38%) than the stomach (12%) or small intestine (9%).

The presence of any mutation or of any *KIT* mutation did not predict recurrence by univariate analysis ($P = .93$ and $P = .75$, respectively). However, the type of mutation was associated with recurrence-free survival (Fig. 4). We found that patients with *KIT* exon 11 DEL557or8 did worse than patients with other *KIT* exon 11 deletions ($P = .04$) or *KIT* exon 11 point mutations or insertions ($P < .001$). Patients

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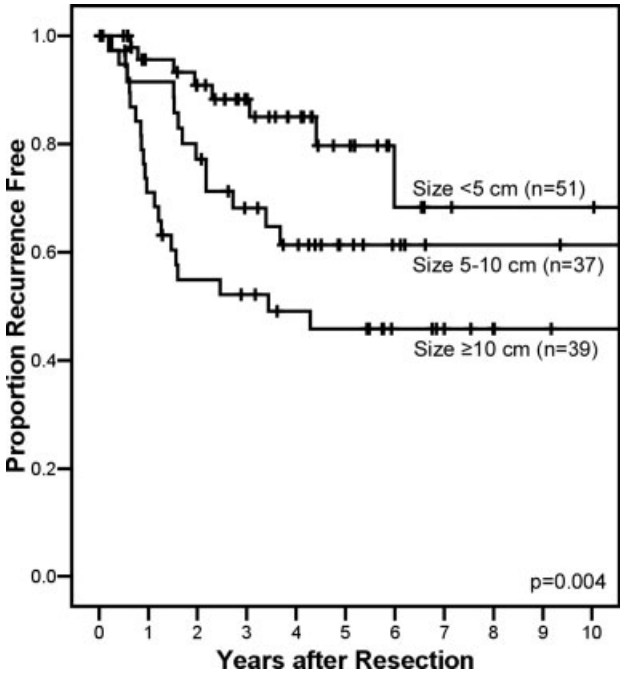

FIGURE 2. Recurrence-free survival in 127 patients with completely resected localized gastrointestinal stromal tumor (GIST) based on tumor size.

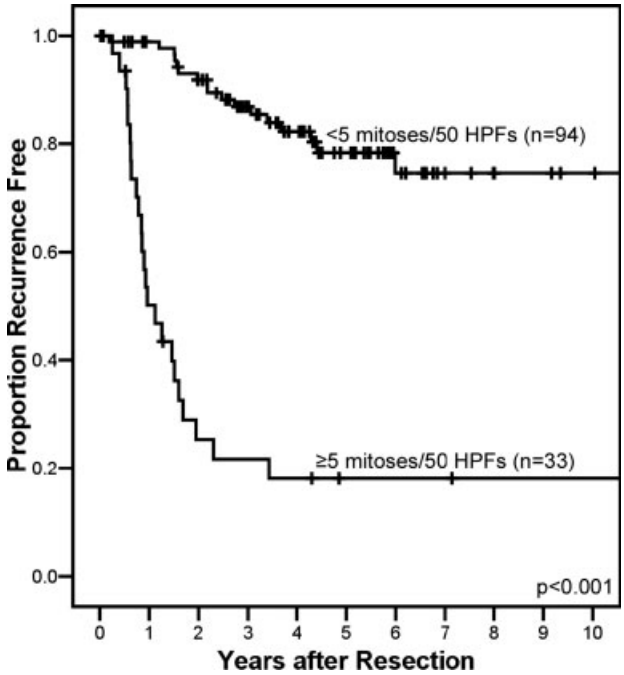

FIGURE 3. Recurrence-free survival in 127 patients with completely resected localized gastrointestinal stromal tumor (GIST) based on mitotic rate.

with *KIT* exon 11 point mutations or insertions had a better prognosis than patients whose tumor had no mutation ($P = .02$). The 4 patients with *KIT* exon 9 mutations each developed recurrent disease within 27 months. Patients with a *KIT* exon 11 deletion other than DEL557or8, a *PDGFRA* mutation, or no mutation had similar recurrence-free survival ($P = .82$). The 1 patient with a *KIT* exon 17 mutation was alive without recurrence at 36 months.

Multivariate Analysis

When variables that were significant on univariate analysis were entered into multivariate analysis, factors independently associated with recurrence were mitotic rate $\geq$5, tumor size $\geq$10 cm, and location (Table 2). Patients with a small bowel (hazard rate 3.3) or colon/rectum (hazard rate 1.2) GIST did worse than those with stomach GIST. We did not enter *KIT* exon 9 mutations into the multivariate analysis as there were only 4 patients with this mutation. *KIT* exon 11 DEL557or8 mutation did not independently predict recurrence on multivariate analysis. This was explained by the finding that the 18 patients with stomach tumors having this mutation did worse than the other patients with stomach GIST ($P = .002$), but the 8 patients with colon/rectum tumors and this mutation did better than the other 6

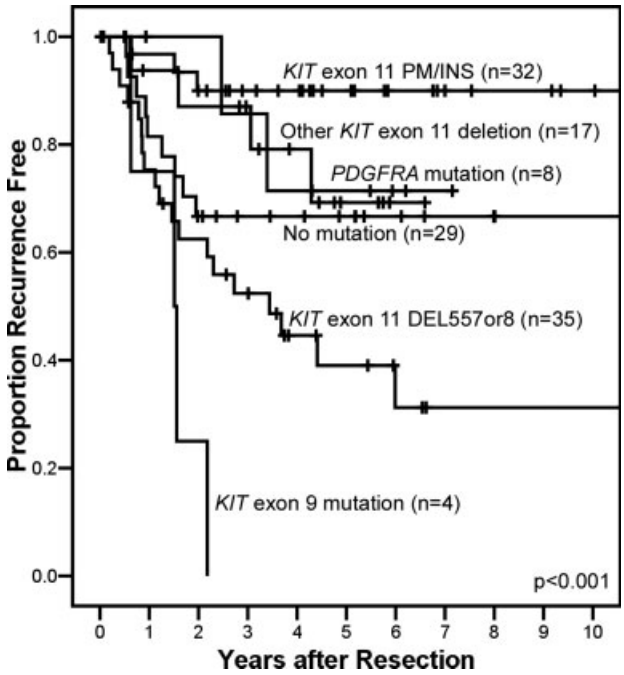

FIGURE 4. Recurrence-free survival in 127 patients with completely resected localized gastrointestinal stromal tumor (GIST) based on the type of mutation.

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TABLE 2
Predictors of Recurrence After Resection of Localized Primary GIST in 127 Patients

Variable	No.	Univariate *P*	Multivariate *P*	Hazard ratio (95% CI)
Tumor size ≥10 cm	39	.004	.007	2.5 (1.3–4.8)
Tumor location		.004	.009	
Stomach	74	—	—	Reference
Small bowel	35	—	—	3.3 (1.5–7.2)
Colon/rectum	14	—	—	1.2 (0.5–2.8)
Mitotic rate ≥5/50 HPF	33	<.001	<.001	14.6 (6.5–32.4)
Absence of KIT exon 11 PM/INS	94	.002	NS	—
KIT exon 11 DEL557or8	35	.001	NS	—
KIT exon 9 mutations	4	<.001	NA	

GIST indicates gastrointestinal stromal tumor; CI, confidence intervals; HPF, high-powered fields; NS, not significant; NA, not analyzed; PM/INS, point mutation or insertion; DEL557or8, deletion of amino acid W557 and/or K55.

patients with colon/rectum GIST ($P = .02$). For the 8 patients with small intestine tumors containing *KIT* exon 11 DEL557or8, there was a trend toward worse outcome ($P = .08$). When tumors in the colon/rectum were removed from the multivariate analysis there was a trend for tumors with *KIT* exon 11 DEL557or8 to have a worse outcome ($P = .08$, hazard ratio 2.11; 95% confidence intervals 0.9–4.8). Furthermore, when just patients with *KIT* exon 11 DEL557or8 were analyzed the outcome was similar regardless of tumor site ($P = .90$).

DISCUSSION

We found that tumor mitotic rate, size, and location each independently predicted recurrence-free survival after complete removal of primary, localized GIST. The effect of mitotic rate was dramatic, with a hazard rate of 14.6 for those with ≥5 mitoses/50 HPF. Although several large series of completely resected GIST have identified tumor size[10,12,18–20] and mitotic rate[10,12,19–21] as prognostic variables, the influence of anatomic location has been unclear. It has been observed that gastric GIST generally has a more favorable course than small intestine GIST and thus location is commonly held to be a prognostic variable.[22–26] However, tumor location has only been shown to be an independent predictor of outcome on multivariate analysis in 1 study.[12] In particular, we found that patients with colon/rectum GIST had a high rate of recurrence, with only 20% free of recurrence after long follow-up. Although we grouped colon and rectum GISTs together, only 1 patient had a colon primary and therefore no definitive statements can be made about this site.

Several associations were identified between specific mutations and recurrence on univariate analysis. In particular, patients with *KIT* exon 11 point mutations or insertions had a favorable prognosis, whereas those with *KIT* exon 11 DEL557or8 and those with *KIT* exon 9 mutations had a poor prognosis. The rate of exon 9 mutation was low,[3] consistent with a prior report.[12] It has been previously reported that *KIT* exon 11 point mutations are associated with longer recurrence-free survival after surgical resection of GIST.[27] We and others have previously reported the favorable prognosis of patients with *KIT* exon 11 insertions having internal tandem duplications at the 3′ end.[15,28] All but 1 of the 11 *KIT* exon 11 insertions in this series was an internal tandem duplication. We and others have also shown that patients with *KIT* exon 9 mutations are associated with worse prognosis.[15,29–31] The poor survival of patients with *KIT* exon 11 DEL557or8 was noted by Wardelmann et al.[32] in 2003. This has subsequently been confirmed in 2 other series of resected primary GIST.[12,33] In the series by Martin et al, worse recurrence-free survival was seen for the subset of *KIT* exon 11 with deletions involving both amino acids W557 and K558 (DEL557and8).[12] In the original series by Wardelmann et al.[32] there was also possibly a stronger association of worse survival with DEL557and8 as opposed to deletions involving only 1 of the amino acids. In contrast, we did not see a difference in recurrence-free survival between the 26 patients with *KIT* exon 11 DEL557and8 compared with the 9 with deletions involving only amino acid 557 or 558. We found a unique interaction between tumor location and *KIT* exon 11 DEL557or8 with regard to recurrence that has previously not been reported. *KIT* exon 11 DEL557or8 mutations were associated with a worse prognosis in the stomach when compared with other stomach GISTs. A trend ($P = .08$) for worse outcome also existed for small bowel GIST with DEL557or8. However, within colon/rectum GIST, DEL557or8 was actually associated with an improved prognosis. Nevertheless, it seems that the presence of a *KIT* exon 11 DEL557or8 predicts an outcome that is independent of tumor site because recurrence-free survival was superimposable for the 18 stomach, 8 small bowel, and 8 colon/rectum GISTs with this mutation.

It has been suggested that GISTs with *PDGFRA* mutations are associated with more favorable prognosis.[34] We did not find an association between *PDGFRA* mutations and recurrence in this study. It is possible that the strong association between *PDGFRA* mutations and gastric tumors accounts for this discrepancy, as gastric location was associated with a

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favorable prognosis. It has previously been noted that *KIT* exon 13 deletions are associated with malignant behavior[30] and were also found to be associated with poor recurrence-free survival in 2 patients with *KIT* exon 13 deletions compared with 46 patients without this mutation in a series of primary GIST.[27] We did not detect any *KIT* exon 13 mutations in the present report.

While there were correlations between specific mutations and recurrence-free survival on univariate analysis, we could not find an independent correlation with mutation on multivariate analysis. It is possible that associations between mutations and other prognostic variables and the relatively small number of patients with any given mutation prevented mutation from reaching significance. Similarly, for DEL557or8 the finding that colon/rectum tumors with this mutation actually had an improved prognosis favored site over mutation in our multivariate model, although tumors with this mutation appeared to have equivalent outcome regardless of their site.

Our finding that mutation analysis did not offer independent prognostic information for recurrence is in contrast to several previous reports.[9,10,12,19,27,33] Some of the discrepancy can be explained by small sample size[19,27] or the low prevalence of mutation[9,12,19] in these studies. The low number of events in all these series, including the present report, complicates multivariate analysis. We had 42 recurrences, as did Martin et al, and no other report assessing the impact of mutation on recurrence has had as many. As certain specific mutations but not others correlated with recurrence on univariate analysis (Fig. 4 and Table 2), it is likely that the relative frequency of these mutations within any 1 series greatly influences the prognostic significance of groups such as 'any mutation,' 'any *KIT* mutation,' or 'any *KIT* exon 11 mutation.' Consequently, it is difficult to make comparisons across studies using what we now realize to be artificial designations. The interplay with site may explain why *KIT* exon 11 DEL557or8 was not an independent predictor on multivariate analysis in the present series. In the studies where *KIT* exon 11 deletions were found to be independent predictors of worse outcome, either site was not used in the multivariate analysis[19] or there was a low number (3 [1.9%] and 2 [5.3%]) of colorectal tumors[12,33] compared with 14 (11%) in our series. If we excluded colon/rectum site as a variable in our analysis, *KIT* exon 11 DEL557or8 approached significance ($P = .08$) on multivariate analysis.

Overall, we were able to find a *KIT* or *PDGFRA* mutation in 77% of tumors. This is a relatively high mutation rate compared with other retrospective series.[8–13,19,27,33,35] In contrast, the mutation rate of *KIT* or *PDGFRA* in recent, large, prospective trials of patients with advanced GIST has been approximately 86% to 87%.[6,7] Variability in mutation rate is likely due to methodologic differences. In the current study we detected mutations in 87% of 72 cases in which we had frozen tissue and only 64% of the 55 cases in which we had only paraffin tissue ($P = .002$). It is likely that degradation of DNA in archival paraffin tissue accounted for this discrepancy. We estimate that the use of paraffin tissue resulted in our inability to detect 12–13 mutations. Nevertheless, when we excluded the 35 cases where only paraffin tissue was available and no mutation was found, our findings were unchanged. We did not test for the recently identified *PDGFRA* exon 14 mutations, although we expect only 1 or possibly 2 cases should have harbored such a mutation.[26]

A better understanding of the prognostic factors in surgically resected primary GIST may allow for appropriate risk stratification that can be used for determining postoperative follow-up strategies and the need for adjuvant therapy. The possibility to delay or prevent recurrence with adjuvant treatment is even more important now that it is clear that acquired resistance to imatinib mesylate (Gleevec, Novartis, Basel, Switzerland) is a frequent event in metastatic GIST, which has a median time to progression of younger than 2 years.[36–39] Although mutation did not independently predict recurrence-free survival, mutation is important in predicting response to tyrosine kinase inhibitors. Imatinib has proven to be highly effective in metastatic GIST[40–43] with a 2-year survival of approximately 70% and a median survival of 58 months,[5,44] but the benefit varies based on mutation status. Notably, patients with a *KIT* exon 11 mutation have the best outcome. In 324 patients with advanced GIST being treated with 400 or 800 mg imatinib daily on the US phase 3 trial, patients with an exon 11 *KIT* mutation had an objective response rate of 67% and a median time to treatment failure of 576 days. Meanwhile, patients with an exon 9 mutation had a 40% response rate and those without a *KIT* or *PDGFRA* mutation had a 39% response rate and these groups failed at a median of 308 days and 251 days, respectively.[6] In contrast, in patients with metastatic GIST who had mostly progressed on imatinib and were then treated with the multikinase inhibitor sunitinib malate (Sutent, Pfizer, New York, NY), those with *KIT* exon 9 mutations or no mutations fared best with 42% and 56%, respectively, having at least stable disease compared with 36% of those with *KIT* exon 11 mutations. Median survival for the 3 groups was 19.4, 20.9, and 5.1 months, respectively.

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In summary, tumor mitotic rate, size, and location are independent predictors of recurrence-free survival for completely resected primary, localized GIST. Risk stratification after surgical resection should be based on these variables.

REFERENCES

1. Andersson J, Bumming P, Meis-Kindblom JM, et al. Gastrointestinal stromal tumors with KIT exon 11 deletions are associated with poor prognosis. *Gastroenterology*. 2006;130: 1573–1581.
2. Heinrich MC, Corless CL, Duensing A, et al. PDGFRA activating mutations in gastrointestinal stromal tumors. *Science*. 2003;299:708–710.
3. Sommer G, Agosti V, Ehlers I, et al. Gastrointestinal stromal tumors in a mouse model by targeted mutation of the Kit receptor tyrosine kinase. *Proc Natl Acad Sci U S A*. 2003; 100:6706–6711.
4. Rubin BP, Antonescu CR, Scott-Browne JP, et al. A knock-in mouse model of gastrointestinal stromal tumor harboring kit K641E. *Cancer Res*. 2005;65:6631–6639.
5. Blanke CD, Joensuu H, Demetri GD, et al. Outcome of advanced gastrointestinal stromal tumor (GIST) patients treated with imatinib mesylate: Four-year follow-up of a phase II randomized trial *Gastrointest Cancers Symp*. 2006. Abstract 7.
6. Heinrich MC, Shoemaker JS, Corless CL, et al. Correlation of target kinase genotype with clinical activity of imatinib mesylate (IM) in patients with metastatic GI stromal tumors (GISTs) expressing KIT (KIT+) *J Clin Oncol*. 2005; 23(16S):7.
7. Debiec-Rychter M, Sciot R, Le Cesne A, et al. KIT mutations and dose selection for imatinib in patients with advanced gastrointestinal stromal tumours. *Eur J Cancer*. 2006;42:1093–1103.
8. Ernst SI, Hubbs AE, Przygodzki RM, Emory TS, Sobin LH, O'Leary TJ. KIT mutation portends poor prognosis in gastrointestinal stromal/smooth muscle tumors. *Lab Invest*. 1998;78:1633–1636.
9. Taniguchi M, Nishida T, Hirota S, et al. Effect of c-kit mutation on prognosis of gastrointestinal stromal tumors. *Cancer Res*. 1999;59:4297–4300.
10. Kim TW, Lee H, Kang Y-K, et al. Prognostic significance of c-kit mutation in localized gastrointestinal stromal tumors. *Clin Cancer Res*. 2004;10:3076–3081.
11. Liu XH, Bai CG, Xie Q, Feng F, Xu ZY, Ma DL. Prognostic value of KIT mutation in gastrointestinal stromal tumors. *World J Gastroenterol*. 2005;11:3948–3952.
12. Martin J, Poveda A, Llombart-Bosch A, et al. Deletions affecting codons 557–558 of the c-KIT gene indicate a poor prognosis in patients with completely resected gastrointestinal stromal tumors: a study by the Spanish Group for Sarcoma Research (GEIS). *J Clin Oncol*. 2005;23:6190–6198.
13. Cho S, Kitadai Y, Yoshida S, et al. Deletion of the KIT gene is associated with liver metastasis and poor prognosis in patients with gastrointestinal stromal tumor in the stomach. *Int J Oncol*. 2006;28:1361–1367.
14. Corless CL, McGreevey L, Haley A, Town A, Heinrich MC. KIT mutations are common in incidental gastrointestinal stromal tumors 1 centimeter or less in size. *Am J Pathol*. 2002;160:1567–1572.
15. Antonescu CR, Sommer G, Sarran L, et al. Association of KIT exon 9 mutations with nongastric primary site and aggressive behavior: KIT mutation analysis and clinical correlates of 120 gastrointestinal stromal tumors. *Clin Cancer Res*. 2003;9:3329–3337.
16. Spritz RA, Giebel LB, Holmes SA. Dominant negative and loss of function mutations of the c-kit (mast/stem cell growth factor receptor) proto-oncogene in human piebaldism. *Am J Hum Genet*. 1992;50:261–269.
17. Prakash S, Sarran L, Socci N, et al. Gastrointestinal stromal tumors in children and young adults: a clinicopathologic, molecular, and genomic study of 15 cases and review of the literature. *J Pediatr Hematol Oncol*. 2005;27:179–187.
18. DeMatteo RP, Lewis JJ, Leung D, Mudan SS, Woodruff JM, Brennan MF. Two hundred gastrointestinal stromal tumors: recurrence patterns and prognostic factors for survival. *Ann Surg*. 2000;231:51–58.
19. Bumming P, Ahlman H, Andersson J, Meis-Kindblom JM, Kindblom LG, Nilsson B. Population-based study of the diagnosis and treatment of gastrointestinal stromal tumours. *Br J Surg*. 2006;93:836–843.
20. Wu TJ, Lee LY, Yeh CN, et al. Surgical treatment and prognostic analysis for gastrointestinal stromal tumors (GISTs) of the small intestine: before the era of imatinib mesylate. *BMC Gastroenterol*. 2006;6:29.
21. Wong NA, Young R, Malcomson RD, et al. Prognostic indicators for gastrointestinal stromal tumours: a clinicopathological and immunohistochemical study of 108 resected cases of the stomach. *Histopathology*. 2003;43:118–126.
22. Crosby JA, Catton CN, Davis A, et al. Malignant gastrointestinal stromal tumors of the small intestine: A review of 50 cases from a prospective database. *Ann Surg Oncol*. 2001;8:50–59.
23. Fujimoto Y, Nakanishi Y, Yoshimura K, Shimoda T. Clinicopathologic study of primary malignant gastrointestinal stromal tumor of the stomach, with special reference to prognostic factors: analysis of results in 140 surgically resected patients. *Gastric Cancer*. 2003;6:39–48.
24. Emory TS, Sobin LH, Lukes L, Lee DH, O'Leary TJ. Prognosis of gastrointestinal smooth-muscle (stromal) tumors: dependence on anatomic site. *Am J Surg Pathol*. 1999;23: 82–87.
25. Miettinen M, Sobin LH, Lasota J. Gastrointestinal stromal tumors of the stomach: a clinicopathologic, immunohistochemical, and molecular genetic study of 1765 cases with long-term follow-up. *Am J Surg Pathol*. 2005;29:52–68.
26. Lasota J, Stachura J, Miettinen M. GISTs with PDGFRA exon 14 mutations represent subset of clinically favorable gastric tumors with epithelioid morphology. *Lab Invest*. 2006;86:94–100.
27. Singer S, Rubin BP, Lux ML, et al. Prognostic value of KIT mutation type, mitotic activity, and histologic subtype in gastrointestinal stromal tumors. *J Clin Oncol*. 2002;20: 3898–3905.
28. Lasota J, Dansonka-Mieszkowska A, Stachura T, et al. Gastrointestinal stromal tumors with internal tandem duplications in 3′ end of KIT juxtamembrane domain occur predominantly in stomach and generally seem to have a favorable course. *Mod Pathol*. 2003;16:1257–1264.
29. Lasota J, Kopczynski J, Sarlomo-Rikala M, et al. KIT 1530ins6 mutation defines a subset of predominantly malignant gastrointestinal stromal tumors of intestinal origin. *Hum Pathol*. 2003;34:1306–1312.
30. Lasota J, Wozniak A, Sarlomo-Rikala M, et al. Mutations in exons 9 and 13 of KIT gene are rare events in gastrointestinal

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stromal tumors. A study of 200 cases. *Am J Pathol*. 2000; 157:1091–1095.
31. Sakurai S, Oguni S, Hironaka M, Fukayama M, Morinaga S, Saito K. Mutations in c-kit gene exons 9 and 13 in gastrointestinal stromal tumors among Japanese. *Jpn J Cancer Res.* 2001;92:494–498.
32. Wardelmann E, Losen I, Hans V, et al. Deletion of Trp-557 and Lys-558 in the juxtamembrane domain of the c-kit protooncogene is associated with metastatic behavior of gastrointestinal stromal tumors. *Int J Cancer*. 2003;106:887–895.
33. Iesalnieks I, Rummele P, Dietmaier W, et al. Factors associated with disease progression in patients with gastrointestinal stromal tumors in the pre-imatinib era. *Am J Clin Pathol*. 2005;124:740–748.
34. Lasota J, Dansonka-Mieszkowska A, Sobin LH, Miettinen M. A great majority of GISTs with PDGFRA mutations represent gastric tumors of low or no malignant potential. *Lab Invest.* 2004;84:874–883.
35. Koay MH, Goh YW, Iacopetta B, et al. Gastrointestinal stromal tumours (GISTs): a clinicopathological and molecular study of 66 cases. *Pathology.* 2005;37:22–31.
36. Fletcher JA, Corless CL, Dimitrijevic S, et al. Mechanisms of resistance to imatinib mesylate (IM) in advanced gastrointestinal stromal tumor (GIST). *Proc Am Soc Clin Oncol.* 2003;22:815. Abstract 3275.
37. Chen LL, Trent JC, Wu EF, Fuller GN, Ramdas L, Zhang W, et al. A missense mutation in KIT kinase domain 1 correlates with imatinib resistance in gastrointestinal stromal tumors. *Cancer Res.* 2004;64:5913–5919.
38. Debiec-Rychter M, Cools J, Dumez H, et al. Mechanisms of resistance to imatinib mesylate in gastrointestinal stromal tumors and activity of the PKC412 inhibitor against imatinib-resistant mutants. *Gastroenterology.* 2005;128:270–279.
39. Antonescu CR, Besmer P, Guo T, et al. Acquired resistance to imatinib in gastrointestinal stromal tumor occurs through secondary gene mutation. *Clin Cancer Res.* 2005;11:4182–4190.
40. 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.
41. Druker BJ, Tamura S, Buchdunger E, et al. Effects of a selective inhibitor of the Abl tyrosine kinase on the growth of Bcr-Abl positive cells. *Nat Med.* 1996;2:561–566.
42. Buchdunger E, Zimmermann J, Mett H, et al. Selective inhibition of the platelet-derived growth factor signal transduction pathway by a protein-tyrosine kinase inhibitor of the 2-phenylaminopyrimidine class. *Proc Natl Acad Sci U S A.* 1995;92:2558–2562.
43. Joensuu H, Roberts PJ, Sarlomo-Rikala M, et al. Effect of the tyrosine kinase inhibitor STI571 in a patient with a metastatic gastrointestinal stromal tumor. *N Engl J Med.* 2001;344:1052–1056.
44. Verweij PJ, Casali PG, Zalcberg PJ, et al. Progression-free survival in gastrointestinal stromal tumours with high-dose imatinib: randomised trial. *Lancet.* 2004;364:1127–1134.

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