

## Outcome of Metastatic GIST in the Era before Tyrosine Kinase Inhibitors

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**Background:** Treatment of metastatic GIST with imatinib mesylate results in a 2-year survival of approximately 72%. The outcome of patients with metastatic GIST not treated with tyrosine kinase inhibitors is not well defined.

**Methods:** One hundred nineteen patients with metastatic GIST diagnosed prior to July 1, 1998 (approximately 2 years prior to the use of imatinib for GIST) were identified from an institutional database of patients with pathologically confirmed GIST. Mutational analysis was performed in cases with available tissue. The log rank test and Cox regression models were used to assess prognostic factors.

**Results:** Median survival was 19 months with a 41% 2-year survival and a 25% 5-year survival. Resection of metastatic GIST was performed in 81 patients (68%), while 50 (42%) received conventional chemotherapy. Twelve patients (10%) were eventually started on imatinib. Primary tumor size < 10 cm, < 5 mitoses/50 HPF in the primary tumor, epithelioid morphology, longer disease-free interval, and surgical resection were independent predictors of improved survival on multivariate analysis. Mutational status did not predict outcome. In patients who underwent resection, the 2 year survival was 53%, and negative microscopic margins also independently predicted improved survival.

**Conclusions:** Treatment with imatinib appears to improve 2-year survival of metastatic GIST by approximately 20% when compared to surgery alone. The combination of imatinib and surgery for the treatment of metastatic GIST therefore warrants investigation.

**Key Words:** Gastrointestinal stromal tumor—GIST—Imatinib mesylate—Gleevec—Surgery.

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Elucidating the natural history of gastrointestinal stromal tumor (GIST) has been hampered by its rarity and by its historic misclassification. The most reliable estimate of the incidence of GIST is 13 cases per million people per year,<sup>1</sup> which would result in a few thousand new cases annually in the United

States. In the past, GISTs were typically diagnosed as leiomyomas or leiomyosarcomas. Currently, GIST is thought to arise from the interstitial cells of Cajal, which function as intestinal pacemakers, and not from smooth muscle. GIST can now be reliably distinguished from leiomyoma and leiomyosarcoma by experienced pathologists based on histologic appearance, immunohistochemical staining (particularly for KIT (CD117)), and genetic analysis. In fact, GIST has a homogenous gene expression profile distinct from other sarcomas.<sup>2</sup>

Modern series have described the epidemiology of GIST as well as the survival and risk of recurrence after resection of primary resectable tumors.<sup>3–7</sup> GIST has a

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slight male predominance with a median age of onset in the sixth decade. Unfortunately, as many as 40% of patients develop recurrent disease after resection of a primary localized GIST. Size and mitotic index are the two strongest predictors of recurrence.

Soon after GIST was recognized as a distinct pathologic entity, an effective targeted agent, imatinib mesylate (Gleevec, Novartis Pharmaceuticals, Basel Switzerland), was incorporated into the care of patients with metastatic GIST.<sup>8</sup> While several uncontrolled studies have demonstrated the outcome of patients with metastatic GIST after treatment with imatinib,<sup>9-14</sup> the outcome of untreated metastatic GIST remains uncertain.

Prior to the development of imatinib, there was no effective treatment for metastatic GIST. Because of the small number of GIST patients in trials that included multiple types of sarcoma and the diagnostic confusion between GIST and leiomyosarcoma, it is impossible to determine the exact response rate of metastatic GIST to chemotherapy, but it appears to be less than 10%.<sup>15</sup> Prior to the use of imatinib, surgical resection was often employed due to the lack of other effective therapy. We previously reported the results of surgical resection for 60 patients who had either metastatic GIST or gastrointestinal leiomyosarcoma. Twenty patients had a complete gross resection, 36 had an incomplete resection, and 4 had a biopsy only. The median survival for the whole group of patients was 15 months, and disease-free interval was the only prognostic variable correlating with survival.<sup>16</sup> We have also published the results of liver resection for either metastatic GIST or gastrointestinal leiomyosarcoma. Of 56 patients who underwent resection for sarcoma metastatic to the liver, 34 had GIST or gastrointestinal leiomyosarcoma. There was no difference in outcome based on histology for patients undergoing liver resection for sarcoma with a 39 month overall median survival.<sup>17</sup>

The long-term results of treatment of metastatic GIST with imatinib have emerged from several large trials. Approximately 50% of patients with metastatic GIST have a measurable response after administration of imatinib, while about 75% will have at least stable disease.<sup>9-14</sup> Although the 2-year survival of patients with metastatic GIST treated with imatinib approximates 72%, half of the patients develop disease progression by 2 years.<sup>14</sup>

We undertook the present study to elucidate the outcome of patients with metastatic GIST prior to the era of imatinib. Our aim was to provide the context in which to interpret the current results in metastatic GIST with the use of tyrosine kinase inhibitors.

## METHODS

### Patients

Patients were identified by a review of a prospectively maintained database of GIST patients treated at Memorial Sloan-Kettering Cancer Center who were diagnosed with metastatic disease between January 1, 1981 and July 1, 1998. This date was chosen as it was approximately 2 years prior to the use of imatinib. All patients in the database have had tumor tissue re-reviewed since the year 2000 by a single experienced soft tissue pathologist [CRA] to confirm the diagnosis of GIST.

### Clinicopathological Variables

Medical records were reviewed for pertinent patient, tumor, and treatment variables. The extent of surgical resection was determined from operative reports and pathology records. If visible tumor was not resected or if margins were grossly involved, the resection was determined to be R2. If margins were microscopically positive or if an enucleative procedure was performed, the resection was coded as R1. If all disease was completely resected with tumor-free margins, the resection was considered R0.

### Mutational Analysis

All cases with available tumor tissue were analyzed for the presence of *KIT* and *PDGFR $\alpha$*  mutations, as described previously.<sup>18,19</sup> In short, genomic DNA was isolated by a standard phenol-chloroform organic extraction protocol from snap-frozen tumor tissue samples stored at  $-70^{\circ}\text{C}$  or from paraffin-embedded tissue. The known sites of *KIT* (exons 9, 11, 13, 14, and 17) and *PDGFR $\alpha$*  (exons 12 and 18) mutations were examined in all cases. PCR was performed using 1 microgram of genomic DNA and Platinum TaqDNA Polymerase High Fidelity (Life Technologies, Inc., Gaithersburg, MD). The primers and annealing temperatures were as previously described. Sequences of PCR products were compared with the National Center for Biotechnology Information human *KIT* and *PDGFR $\alpha$*  gene sequences.

### Statistical Analysis

Correlations were sought between clinicopathological variables and survival. Survival was measured from the time of diagnosis of metastatic disease until death or last follow-up. Survival curves were gener-

ated by the Kaplan-Meier method<sup>20</sup> and were compared by the log-rank test with *P* values  $\leq 0.05$  considered significant. SPSS 11.0 (SPSS, Chicago, IL) was used for univariate analysis. Variables that were significant in the univariate analyses were used in the multivariate analysis, and the final multivariate model was built using stepwise Cox regression. SAS 9.1 (SAS, Cary, NC) was used for multivariate analysis.

## RESULTS

### Patient and Tumor Characteristics

One hundred nineteen patients with pathologically confirmed GIST diagnosed prior to July 1, 1998 were identified. The patient and tumor characteristics of these patients are shown in Table 1. The median age was 58. There was a slight male predominance with 70 (59%) males and 49 (41%) females. Eighty-two patients (69%) had metachronous metastatic disease diagnosed a median of 2.4 years after resection of the primary tumor. There was an even distribution between gastric and small bowel GISTs, with a small minority of patients having a large bowel primary (8%), and one patient having an omental primary (1%).

The patients tended to have large primary tumors, with a median tumor size of 11.5 cm. Only 12% of patients had tumors  $< 5$  cm in size. Mitotic activity also tended to be high with 48% of the tumors where mitotic activity could be assessed having  $> 10$  mitoses per 50 high powered fields. Tissue was available for mutational analysis in 89 patients. A *KIT* or *PDGFR $\alpha$*  mutation was identified in 61 (69%). *KIT* exon 11 mutations were the most common (79% of kinase mutations identified).

### Pattern of Spread

The initial site of GIST metastasis nearly always involved the peritoneal surface and/or the liver (Table 2). At some point (typically late in their disease), 16 (13%) patients had metastasis at other sites. The lung was involved in 10 patients (8%) and the bone in 6 patients (5%).

### Treatment Variables

The treatment modalities employed are shown in Table 3. Surgical resection was the most frequent treatment of metastatic GIST and was used in 81

TABLE 1. Patient and tumor characteristics

Median age (range)	58 (20–92)
Number of males (%)	70 (59%)
Number metachronous (%)	82 (69%)
Median disease-free interval in years (range)	2.4 (0.2–11.3)
Site of origin	
Stomach	51 (43%)
Small bowel	50 (42%)
Large bowel	9 (8%)
Omentum	1 (1%)
Unknown	8 (7%)
Median size of primary tumor in cm (range)	11.5 (3–35)
Primary tumor size categories	
$< 5$ cm	14 (12%)
5–10cm	51 (43%)
$> 10$ cm	45 (38%)
Unknown	9 (8%)
Mitotic index of primary tumor*	
$< 5$	31 (26%)
5–10	24 (20%)
$> 10$	51 (43%)
Unknown	13 (11%)
Morphology	
Spindled	95 (80%)
Epithelioid	20 (17%)
Mixed	3 (3%)
Unknown	1 (1%)
Mutation <sup>†</sup>	
<i>KIT</i> exon 11	48 (54%)
Point mutations	14 (29%)
Insertions	2 (4%)
Deletions	32 (67%)
<i>KIT</i> exon 9	11 (12%)
<i>PDGFR<math>\alpha</math></i>	2 (2%)
No mutation	28 (31%)
Margin status of primary tumor <sup>‡</sup>	
Microscopic	
Negative	52 (63%)
Positive	4 (5%)
Unknown	26 (32%)
Gross	
Negative	57 (70%)
Unknown	25 (30%)

\* Mitoses/50 high-powered fields.

<sup>†</sup> In 89 patients with available tissue.

<sup>‡</sup> For patients who did not have metastasis at the time of resection of the primary tumor.

patients (68%). Multiple resections over the course of disease were common as 33 patients (41% of surgical patients) underwent repeat resections (Table 4). While only 17 patients (21%) had an R0 resection at the time of the first operation, as many patients had multiple operations, 25 patients (31%) had an R0 resection, and 42 patients (52%) had at least an R1 (complete gross) resection at some time in the course of their disease.

Chemotherapy was used in 56 patients (47%). Systemic chemotherapy was used in 50 patients (42%) and intraperitoneal chemotherapy was used in 7 patients (6%). Doxorubicin was the most commonly employed systemic agent and was given to 37 patients (74% of those getting systemic chemotherapy). The

**TABLE 2.** Sites of metastasis

Site	Number of Patients (%)
First site of metastasis	
Peritoneum only	58 (49%)
Liver only	35 (29%)
Peritoneum and liver only	22 (18%)
Other	3 (3%)
Unknown	1 (1%)
Cumulative sites of metastasis	
Peritoneum only	33 (28%)
Liver only	24 (20%)
Peritoneum and liver only	46 (39%)
Other	16 (13%)
Lung	10 (8%)
Bone	6 (5%)

**TABLE 3.** Treatment modalities

Modality	Number of Patients (%)
Surgical resection	81 (68%)
Liver resection	32 (27%)
Percutaneous ablation liver lesion	13 (11%)
Embolization	12 (10%)
Radiofrequency ablation	1 (1%)
Alcohol injection	1 (1%)
Any chemotherapy	56 (47%)
Systemic chemotherapy	50 (42%)
Intraperitoneal chemotherapy	7 (6%)
Any radiation	14 (12%)
External beam	12 (10%)
Brachytherapy	4 (3%)

**TABLE 4.** Surgical variables

Variable	Number of Patients (%)
Multiple resections	33 (41%)
2 resections	20 (25%)
3 resections	8 (10%)
4 resections	4 (5%)
5 resections	0 (0%)
6 resections	1 (1%)
R status first resection	
R0	17 (21%)
R1	23 (28%)
R2	28 (35%)
Unknown	13 (16%)
Best R status	
R0	25 (31%)
R1	17 (21%)
R2	26 (32%)
Unknown	13 (16%)

other commonly used systemic chemotherapeutic agents are shown in Table 5.

Twelve patients (10%) were eventually started on imatinib. As patients in this series were selected for having metastatic GIST diagnosed at least 2 years prior to when imatinib began to be used in the

**TABLE 5.** Common systemic chemotherapeutic agents used

Agent	Number of Patients (%)
Doxorubicin	37 (74%)
Dacarbazine	16 (32%)
Cyclophosphamide	14 (28%)
Cisplatin	8 (16%)
Ifosfamide	8 (16%)
Paclitaxel	6 (12%)
Gemcitabine	5 (10%)
Vinblastine	5 (10%)

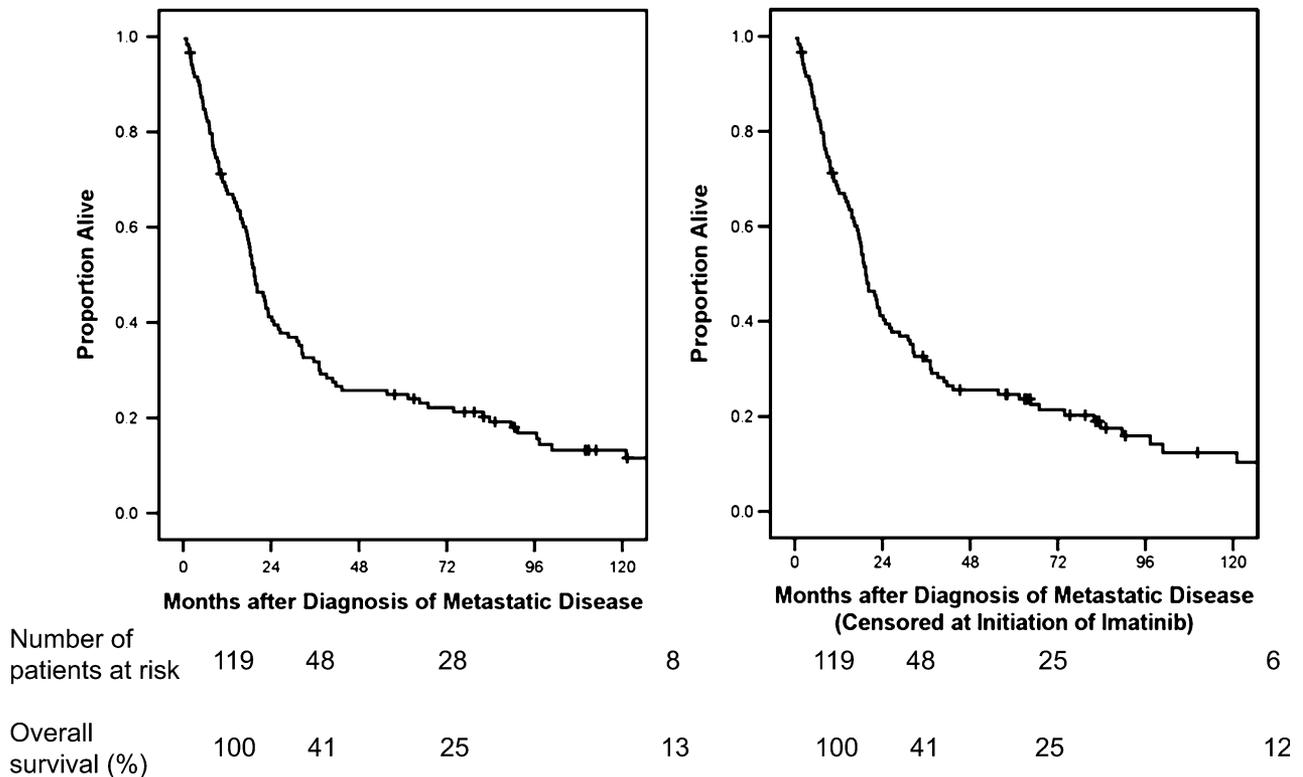
treatment of GIST, these patients were typically started on imatinib late in the course of their disease, a median of 70 months (35–161) after the diagnosis of metastatic GIST.

Fourteen patients (12%) received radiation therapy at some point in the course of their disease. In 5 cases, radiation was given for treatment of localized primary disease (as an adjuvant to resection in 4 cases and because the primary was initially thought to be unresectable in 1 case). In another 5 cases, radiation was given for treatment of localized intraperitoneal recurrence (as an adjuvant to resection in 4 cases and as the primary treatment for an unresectable recurrence in 1 case). Radiation was used for liver recurrences in 2 cases (in 1 case after debulking and in 1 case with liver only disease after progression on chemotherapy). Bone metastases were radiated in 2 patients (prior to resection in 1 patient and as palliation for bone pain in 1 patient).

**Survival and Prognostic Variables**

Median survival for the entire group of 119 patients with metastatic GIST diagnosed before July 1, 1998 was 19 months with a 41% 2-year survival and a 25% 5-year survival. To assess whether the use of imatinib on a small number of patients late in their disease course affected the overall survival in this series, survival was also analyzed censoring patients at the time they started imatinib. Survival was essentially unchanged in this analysis (see Fig. 1). Therefore, for the remainder of the analyses, patients were censored only if alive at the time of last follow-up.

Variables associated with survival are shown in Table 6. While decreased age and female gender were associated with improved survival on univariate analysis ( $P = 0.01$ ,  $P < 0.01$ , respectively), they were not independent of the other prognostic variables on multivariate analysis. Independent predictors of improved survival on multivariate analysis were primary tumor size  $< 10$  cm ( $P < 0.01$ ), mitotic rate of



**FIG 1.** Survival of patients with metastatic GIST in the era prior to imatinib. Survival is shown with patients censored at the time of last follow-up (left), and also with the 12 patients (10%) who went on to receive imatinib censored at the time they began this treatment (right).

**TABLE 6.** Variables Associated with Survival for the Entire Cohort ( $n = 119$ )

Variable (number of patients)	Median survival (mos.)	Univariate <i>P</i> -value	Multivariate <i>P</i> -value	Hazard Ratio
Age (in years) <sup>†</sup>	32 vs. 19 (for < 50 ( $n = 33$ ), > 50 ( $n = 86$ ))	0.01 <sup>†</sup>	ns <sup>†</sup>	
Gender				
Female (49) vs. male (70)	25 vs. 17	< 0.01	ns	
Primary tumor size				
< 5 (14) vs. 5–10 cm (51)	40 vs. 23	0.12		
5–10 (51) vs. > 10 cm (45)	23 vs. 14	< 0.01		
< 10 (65) vs. > 10 cm (45)	32 vs. 14	< 0.01	< 0.01	0.45
Mitotic index*				
< 5 (31) vs. 5–10 (24)	97 vs. 19	< 0.01		
5–10 (24) vs. > 10 (51)	19 vs. 12	0.10		
< 5 (31) vs. > 5 (75)	97 vs. 29	< 0.01	< 0.01	0.34
Morphology				
Epithelioid (20) vs. spindled (95)	31 vs. 16	< 0.01	< 0.01	0.48
Disease-free interval (in months) <sup>†</sup>	90 vs. 17 (for > 4 ( $n = 27$ ), < 4 ( $n = 92$ ) yrs.)	< 0.01 <sup>†</sup>	0.02 <sup>†</sup>	0.88 <sup>†</sup>
Surgical resection for metastatic disease				
Resected (81) vs. unresected (38)	27 vs. 8	< 0.01	< 0.01	0.25

\* Mitoses/50 high-powered fields.

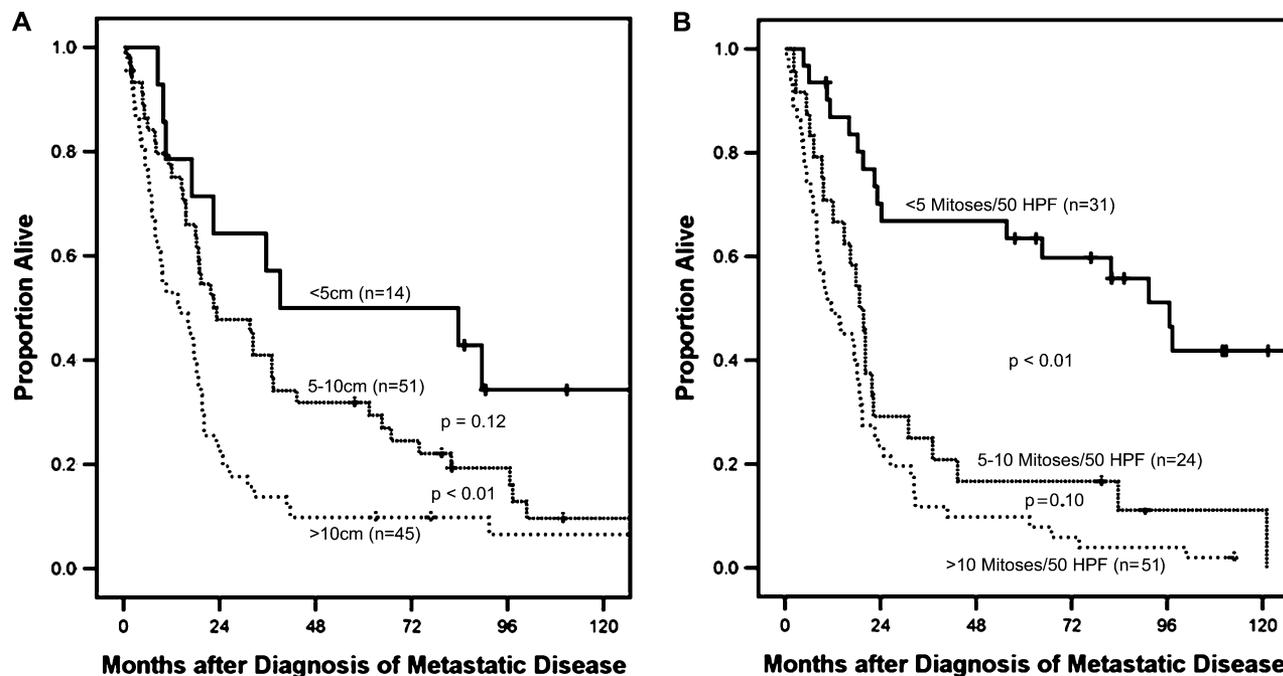
<sup>†</sup> Analyzed as a continuous variable.

ns = not significant.

the primary tumor < 5 mitoses/50 high-powered fields (HPF) ( $P < 0.01$ ), epithelioid cell morphology ( $P < 0.01$ ), shorter disease-free interval ( $P = 0.02$ ), and the use of surgical resection ( $P < 0.01$ ). The presence of either a *KIT* or *PDGFR $\alpha$*  mutation did

not predict outcome, nor did the exon or type (i.e. insertion, deletion, or point mutation) of *KIT* mutation.

Interestingly, size and mitotic rate of the primary tumor, which are the two most important predictors



**FIG 2.** Survival of patients with metastatic GIST in the era prior to imatinib as a function of (A) primary tumor size and (B) mitotic activity of the primary tumor. Patients with metastatic GIST and primary tumors 5–10 cm had improved survival compared to patients with primary tumors > 10 cm ( $P < 0.01$ ), while there was a trend toward improved survival for patients with tumors < 5 cm compared to patients with tumors 5–10 cm ( $P = 0.12$ ). Similarly, patients with metastatic GIST and primary tumors with < 5 mitoses/50 high powered fields (HPF) had improved survival compared to patients with tumors having 5–10 mitoses/50 HPF ( $P < 0.01$ ), while there was a trend toward improved survival for patients with tumors having 5–10 mitoses/50 HPF compared to those with tumors having > 10 mitoses/50 HPF ( $P = 0.10$ ).

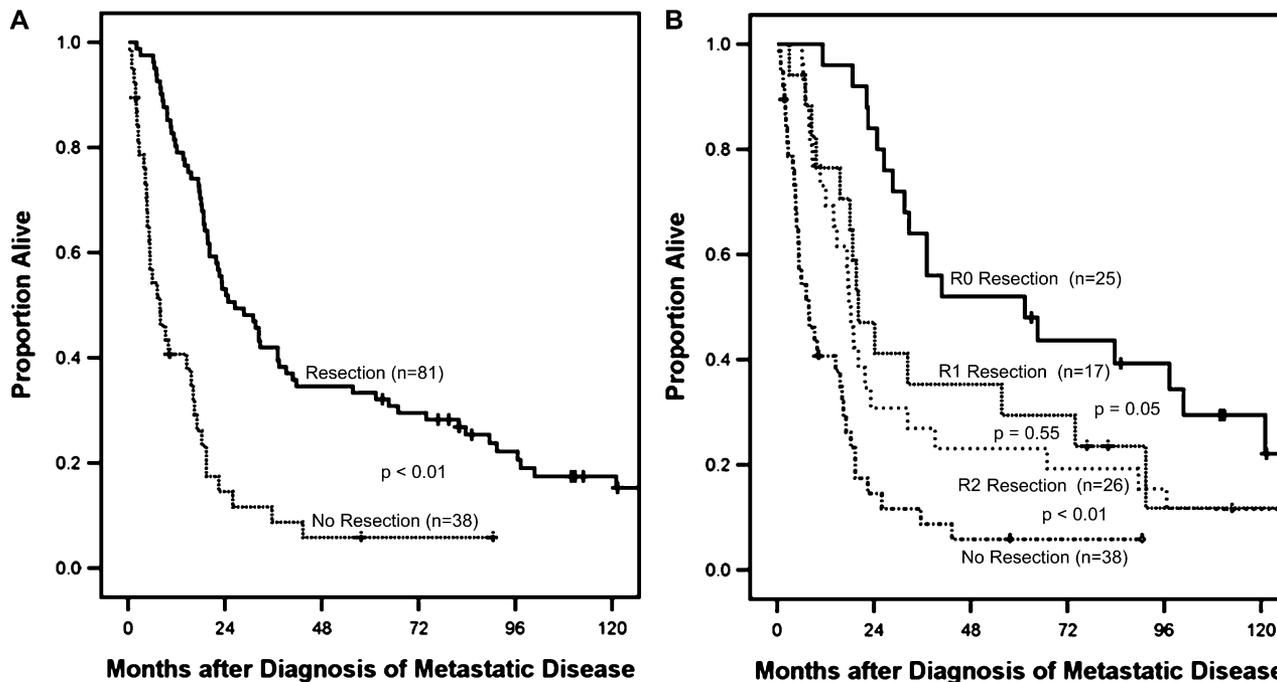
of recurrence, are also powerful predictors of survival after recurrence (hazard ratio = 0.45 for tumor size < 10 cm, hazard ratio = 0.34 for mitotic rate < 5 mitoses/50 HPF) (see Fig. 2). Surgical resection in the setting of metastatic disease, however, was the most powerful independent predictor of improved survival (hazard ratio = 0.25) (see Fig. 3). The benefit of surgery, however, was modest with a median survival of 27 months, a 53% 2-year survival, and a 33% 5-year survival.

We further analyzed the subset of 81 patients who underwent surgical resection. The variables associated with survival on univariate and multivariate analysis are shown in Table 7. On multivariate analysis, the factors independently associated with improved survival for patients who underwent surgical resection for metastatic GIST included primary tumor size < 10 cm ( $P < 0.01$ ), mitotic index < 5 mitoses/50 HPF in the primary tumor ( $P < 0.01$ ), epithelioid morphology ( $P = 0.04$ ), and disease-free interval < 4 years ( $P = 0.05$ ). These factors were associated with prognosis for the entire cohort. In addition, the ability to obtain an R0 resection at some point in the disease course was important ( $P <$

0.01). The relation of best R status for resection of metastatic disease is shown in Fig. 3. Notably, the outcome for patients who obtained an R0 resection at some point in their disease course was a median survival of 61 months, an 84% 2-year survival, and a 52% 5-year survival. There was also a statistically significant improved survival associated with debulking procedures where all disease could not be grossly resected (R2 resection), compared with no resection in the setting of metastatic disease ( $P < 0.01$ ).

## DISCUSSION

Imatinib mesylate, a targeted inhibitor of the tyrosine kinase activity of KIT, was the first agent with significant activity to be used in the treatment of metastatic GIST. Data from uncontrolled prospective trials indicate that imatinib results in a response rate of approximately 50%, with at least 75% of patients having prolonged stable disease. Imatinib rapidly became the standard of care for the treatment of patients with metastatic GIST. Because GIST is a rare tumor that was only recognized as



**FIG 3.** Impact of surgical resection for metastatic GIST in the era prior to imatinib. (A) Overall survival is shown for patients with metastatic GIST stratified by whether they underwent resection. (B) Survival is shown based on the best R status achieved during any operation for metastatic GIST. Patients who achieved an R0 resection had an improved survival compared to those who achieved an R1 resection ( $P = 0.05$ ). There was no survival difference between patients who achieved an R1 or R2 resection ( $P = 0.55$ ). An R2 resection was associated with a survival benefit compared to no resection ( $P < 0.01$ ).

**TABLE 7.** Variables associated with survival for patients who underwent resection ( $n = 81$ )

Variable (number of patients)	Median survival (mos.)	Univariate $P$ -value	Multivariate $P$ -value	Hazard Ratio
Age				
< 50 (25) vs. > 50 (56) years old	32 vs. 23	0.04	ns	
Gender				
Female (36) vs. male (45)	42 vs. 20	0.02	ns	
Size				
< 10 (34) vs. > 10 cm (40)	37 vs. 19	< 0.01	< 0.01	0.35
Mitotic index*				
< 5 (24) vs. > 5 (50)	97 vs. 37	< 0.01	< 0.01	0.17
Morphology				
Epithelioid (14) vs. spindled (65)	32 vs. 23	0.03	0.04	0.27
Disease-free interval				
> 4 (21) vs. < 4 (60) years	90 vs. 20	< 0.01	0.05	0.34
Best R status for resection of metastatic disease				
R0 (25) vs. R1 (17)	61 vs. 20	0.05		
R1 (17) vs. R2 (26)	20 vs. 18	0.55		
R0 (25) vs. R1 and R2 (43)	61 vs. 19	0.01	< 0.01	0.32
Liver resection for metastatic disease				
Yes (32) vs. no (49)	39 vs. 20	0.12	ns	
Use of chemotherapy				
No (40) vs. yes (41)	56 vs. 22	0.03	ns	

\* Mitoses/50 high-powered fields.

ns = not significant.

distinct pathologic entity just prior to the application of imatinib, the outcome of patients with metastatic GIST in the era prior to imatinib is not well defined.

This study describes the pattern of metastatic spread, treatment, and outcome of 119 patients diagnosed with metastatic GIST. The first site of GIST metastasis was nearly always within the abdo-

men. Reflecting the referral bias to our center, the majority of patients in this single institutional experience (68%) were treated with surgical resection. To some extent, however, this also represents the lack of effective alternative therapies. While chemotherapy was employed in nearly half of patients, it did not appear to be associated with any survival benefit, which is consistent with other reports.<sup>15</sup>

In this study, the survival of patients with metastatic GIST in the era before imatinib was 41% at 2 years and 25% at 5 years with a median survival of 19 months. In contrast, the use of imatinib in metastatic GIST is associated with an approximately 72% 2-year survival<sup>14</sup> and the median survival is 58 months.<sup>21</sup> Consequently, imatinib appears to improve survival at 2 years by at least 30%. It should be noted that in the imatinib trials, many of the patients went on to receive sunitinib malate (Sutent, SU11248, Pfizer, New York) after progression.<sup>22,23</sup> Thus, the apparent benefit compared to our historic data may be the result of the sequential treatment with 2 tyrosine kinase inhibitors. While improved imaging may allow the earlier diagnosis of patients with metastatic disease, it is unlikely to be the sole cause for the improved survival in modern series of imatinib-treated patients compared to our data.

In the EORTC phase III study of imatinib in metastatic GIST,<sup>21</sup> survival of patients receiving imatinib was compared to historical data in which subjects with "gastrointestinal leiomyosarcoma" were treated with doxorubicin. These control patients had a 2 year survival of about 18%, which is similar to what we found in patients who did not undergo resection. That the survival of our entire group was much higher may reflect that patients with limited metastatic disease were more likely to have been referred to our institution for surgery. It should also be kept in mind that many patients on the early trials of imatinib may have been late in their disease course, whereas most patients are now diagnosed with metastatic disease when they have a low tumor burden. Therefore, the results with imatinib may even improve.

We identified several independent prognostic variables of survival in patients with metastatic GIST. These were predominantly biologic variables: primary tumor size < 10 cm, < 5 mitoses/50 HPF in the primary tumor, epithelioid cell morphology, and shorter disease-free interval. The differential benefit of imatinib as it relates to these factors is unknown.

Notably, the mutational status of the tumor was not associated with prognosis after the development of metastases in the era prior to imatinib. In contrast, mutational status appears to have prognostic signifi-

cance both in primary GIST in the pre-imatinib era as well as in metastatic GIST treated with imatinib. For primary GIST, there is some inconsistency as to the overall influence of mutation status and in particular *KIT* exon 11 mutations.<sup>24-32</sup> However, in several well performed studies further subgrouping *KIT* exon 11 mutations, tumors with exon 11 deletions consistently had a worse outcome,<sup>26,29,32</sup> which we have also confirmed (unpublished data). These data can be reconciled with ours if mutational status is important in predicting recurrence but is not important in determining outcome after recurrence in the absence of imatinib. It should also be noted that the mutation rate reported in some other series is higher than ours,<sup>26,33-35</sup> which may reflect a lower sensitivity in identifying mutations in archived tissues. Analyses of the imatinib trials have shown that clinical response to imatinib is influenced by *KIT* genotype. Patients whose tumors contain *KIT* exon 11 mutations have the greatest chance of tumor response and longest survival.<sup>33-35</sup> Our data suggest that imatinib, not the underlying biology of the disease, accounts for the difference in outcome based on genotype.

In this study, surgical resection of metastatic GIST was associated with a survival benefit independent of the other predictive variables. It is impossible to say from this retrospective study that surgery, and not patient selection, is the actual cause of the improved survival. Nevertheless, the effect was only modest with a median survival of 27 months, a 53% 2-year survival, and a 33% 5-year survival. Thus, in patients with metastatic GIST who could otherwise undergo resection, imatinib achieves an approximately 20% greater 2-year survival. In the group of patients who underwent surgical resection, the biological variables of primary tumor size, primary tumor mitotic rate, epithelioid morphology, and disease-free interval were important in predicting outcome. Not unexpectedly, the ability to achieve an R0 resection also was an independent predictor of outcome. This too, however, may be a function of the extent of disease and not a function of the extent of the treatment. Nevertheless, the data suggest that surgery has an effect in the treatment of metastatic GIST. Consequently, a multimodality approach to metastatic GIST that includes tyrosine kinase inhibition and surgery deserves investigation.

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