Annals of Surgical Oncology **14**(1):14–24
DOI: 10.1245/s10434-006-9034-8

Surgical Resection of Gastrointestinal Stromal Tumors After Treatment with Imatinib

Robert H. I. Andtbacka, MD, CM,[1] Chaan S. Ng, MD,[2] Courtney L. Scaife, MD,[5] Janice N. Cormier, MD, MPH,[1] Kelly K. Hunt, MD,[1] Peter W. T. Pisters, MD,[1] Raphael E. Pollock, MD, PhD,[1] Robert S. Benjamin, MD,[3] Michael A. Burgess, MD,[3] Lei L. Chen, MD, PhD,[3] Jonathan Trent, MD,[3] Shreyaskumar R. Patel, MD,[3] Kevin Raymond, MD,[4] and Barry W. Feig, MD[1]

[1]Department of Surgical Oncology, The University of Texas M. D. Anderson Cancer Center, Unit 444, 1515 Holcombe Blvd., Houston, TX 77030, USA
[2]Department of Radiology, The University of Texas M. D. Anderson Cancer Center, Houston, TX 77030, USA
[3]Department of Medical Oncology, The University of Texas M. D. Anderson Cancer Center, Houston, TX 77030, USA
[4]Department of Pathology, The University of Texas M. D. Anderson Cancer Center, Houston, TX 77030, USA
[5]Department of Surgery, University of Utah, Salt Lake City, UT 84112, USA

Background: Surgical resection of gastrointestinal stromal tumors (GISTs) has been the most effective therapy for these rare tumors. Imatinib has been introduced as systemic therapy for locally advanced and metastatic GIST. In this study, the surgical resection rates and long-term outcomes of patients treated with preoperative imatinib for locally advanced primary, recurrent, or metastatic GISTs were evaluated.

Methods: Patients were retrospectively assessed for completeness of surgical resection and for disease-free and overall survival after resection.

Results: Forty-six patients underwent surgery after treatment with imatinib. Eleven were treated for locally advanced primary GISTs for a median of 11.9 months, followed by complete surgical resection. All eleven were alive at a median of 19.5 months, and ten were free of disease. Thirty-five patients were treated for recurrent or metastatic GIST. Of these, eleven underwent complete resection. Six of the eleven patients had recurrent disease at a median of 15.1 months. All eleven patients were alive at a median of 30.7 months. Patients with a partial radiographic tumor response to imatinib had significantly higher complete resection rates than patients with progressive disease (91% vs. 4%; $P < .001$). Of the 24 patients with incomplete resection, 18 initially responded to imatinib but were unable to undergo complete resection after they progressed before surgery.

Conclusions: Preoperative imatinib can decrease tumor volume and is associated with complete surgical resection in locally advanced primary GISTs. Early surgical intervention should be considered for imatinib-responsive recurrent or metastatic GIST, since complete resection is rarely achieved once tumor progression occurs.

Key Words: Gastrointestinal stromal tumor—Imatinib—Surgery—Outcome.

INTRODUCTION

Gastrointestinal stromal tumors (GISTs) are the most common soft tissue tumors of the gastrointestinal system. GISTs originate from mesenchymal stem cells that are believed to differentiate toward intestinal cells of Cajal, a network of pacemaker cells

Received August 23, 2005; accepted March 6, 2006; published online October 28, 2006.
Presented in part at the Annual Meeting of the Society of Surgical Oncology, Atlanta, GA, March 2005.
Address correspondence and reprint requests to: Robert H. I. Andtbacka, MD, CM; E-mail: robert_andtbacka@hotmail.com

that coordinate peristalsis in the gastrointestinal system.[1,2] Most GISTs express KIT (a tyrosine kinase receptor) on their cell surface, which helps to distinguish them from other gastrointestinal mesenchymal tumors.[3]

Historically, treatment of recurrent or metastatic GISTs with single or multi-agent chemotherapy resulted in disappointingly low response rates of $<10\%$.[4–6] The introduction of imatinib mesylate (STI571, Gleevec or Glivec, Novartis Pharmaceuticals, East Hanover, NJ), a small-molecule receptor tyrosine kinase inhibitor that targets KIT, has provided a much needed treatment regimen for patients with unresectable and metastatic GISTs. Clinical trials have demonstrated partial response rates of 40% to 69% and longer progression-free survival times in patients treated with imatinib for unresectable, recurrent, or metastatic GISTs.[7–10] Although complete responses are rare, many patients experience partial responses that often are maintained for extended periods of time.

The current clinical practice at The University of Texas M. D. Anderson Cancer Center for patients with either locally advanced, recurrent, or metastatic GIST is to use imatinib as first-line treatment and then consider surgical resection when the tumor has demonstrated adequate response to allow for complete resection of any residual disease. However, the indications, timing, and role of surgery for these patients are not well-established. Before the availability of imatinib, complete surgical resection of recurrent or metastatic GIST was achieved in only one third of patients, and the median postoperative disease-free survival and overall survival times for this subgroup was 12–19 months and 17.5–50 months, respectively. The five-year survival was approximately 20%.[11–15] We previously reported on the feasibility of tumor resection in patients with recurrent or metastatic GIST after imatinib treatment.[16] In that report, 16 of 17 patients underwent complete resection of all macroscopic disease. At the short median follow-up of six months, all 17 patients were alive, and 14 remained free of disease. It is not clear which patients may benefit the most from surgical resection after preoperative imatinib. In addition, the long-term effect of preoperative imatinib on postresection disease-free and overall survival times in patients with recurrent or metastatic GIST has not been established. Determining these factors would allow for improved treatment of patients with recurrent or metastatic GIST.

Surgery is currently the main treatment modality for patients with primary GIST. Two ongoing clinical trials are investigating the potential benefits of preoperative imatinib in patients with primary GISTs.[17,18] The effect of preoperative imatinib on surgical resection rates and postoperative outcome in patients with locally advanced primary GIST is unknown.

The purpose of our study was to better define the role of surgery and its long-term outcome in patients with locally advanced primary, recurrent, or metastatic GIST treated with imatinib preoperatively.

METHODS

Patients

Patients with locally advanced primary, recurrent, or metastatic GIST who were treated with imatinib were retrospectively identified from the M. D. Anderson Cancer Center prospective sarcoma database and the medical records database. Between January 2001 and October 2004, 46 patients with KIT-positive GIST, as determined by CD117 (DakoCytomation California Inc., Carpinteria, CA) immunohistochemical analysis underwent surgical exploration at M. D. Anderson for tumor resection after imatinib treatment and were included in this study. Permission to perform the study and a waiver of informed consent were obtained from the institutional review board.

Patient data collected from the sarcoma database, medical records database, and patient charts included age, sex, site of primary tumor, extent of disease at initial presentation, indication for preoperative imatinib treatment, dose and duration of imatinib treatment, surgical outcome, and disease status at last follow-up. For the purpose of analysis, patients were divided into two main groups, those with locally advanced primary GISTs and those with recurrent or metastatic GISTs.

Patients were assessed clinically and radiographically with CT imaging before and after surgery every 1–9 months depending on their response to treatment and the preference of the treating physician. Patients were followed-up to February 2005 and complete follow-up data were available for all 46 patients.

Definitions

Locally advanced primary GIST was defined as radiographic evidence of significant involvement of a single organ with tumor size ≥ 5 cm or extension of

the tumor to adjacent organs. Recurrent disease was defined as the presence of histologically or radiographically demonstrated recurrence of tumor after a previous surgical resection of the primary GIST. Disease appearing in the region of the previous intraperitoneal tumor was called ''recurrence,'' and disease that had spread to noncontiguous distant sites such as the liver or lung was called ''metastasis.''

Complete resection was defined as removal of all macroscopic disease, and incomplete resection was defined as the presence of residual macroscopic disease after resection. A complete pathologic response was defined as no evidence of residual tumor cells in the extirpated surgical specimen, whereas a partial pathologic response was defined as evidence of residual viable tumor cells within hyaline or myxoid areas consistent with treatment effect. No pathologic response was defined as evidence of viable tumor cells in the absence of treatment effect. Status of disease at last follow-up was determined using the most recent clinical and radiographic evaluation for that patient. If a patient had expired, the date of death and the disease status at death was recorded.

Disease-free survival time was defined as the time from post-imatinib resection of locally advanced primary, recurrent, or metastatic GIST to clinical or radiographic evidence of recurrent disease. Postoperative survival time was defined as the time from post-imatinib resection of locally advanced primary, recurrent, or metastatic GIST to the last documented follow-up or patient death. Overall survival time was defined as the time from initiation of imatinib for locally advanced primary, recurrent, or metastatic GIST to the time of last follow-up or patient death. Postoperative follow-up time was the time from post-imatinib surgery to the last follow-up or patient death. Total follow-up time was defined as the time from initiation of imatinib treatment to the last follow-up or patient death.

Surgery and Imatinib Treatment

Twenty-eight (61%) of the 46 patients underwent surgery as the initial treatment for their primary GIST; 26 of these patients were operated on at other institutions and subsequently referred to M. D. Anderson for follow-up, and two were operated on at M. D. Anderson. All 28 of these patients developed recurrent or metastatic GIST and were treated with imatinib at M. D. Anderson and subsequently underwent surgical exploration at M. D. Anderson. The remaining 18 (39%) patients received preoperative imatinib at M. D. Anderson for intact primary GIST before surgical resection; seven of these patients had synchronous metastasis and were included in the recurrent or metastatic GIST group. All 18 patients underwent surgical exploration at M. D. Anderson.

Patients with resectable primary GIST are not routinely treated with preoperative imatinib at M. D. Anderson. The patients in this study received preoperative imatinib for locally advanced primary GIST that were deemed to be unresectable or borderline resectable with en bloc resection of adjacent organs.

The duration of preoperative imatinib treatment was determined based on the radiographic response. Patients treated for locally advanced primary GIST underwent surgical resection after there were no further change in tumor size or enhancement between two consecutive radiographic imaging studies 2–3 months apart ($n = 10$), or the tumor caused increased pain ($n = 1$). Patients treated for recurrent or metastatic GIST received imatinib until no further change was observed between consecutive CT imaging 2–3 months apart and the surgeon deemed that further treatment would not change the surgical procedure. In patients who developed radiographic evidence of tumor progression on imatinib, the dose of imatinib was initially increased and if there was evidence of continued progression the patient then underwent surgery.

Evaluation of Tumor Response to Imatinib Treatment

An experienced radiologist (C.S.N.) retrospectively re-reviewed all radiographic data for the 46 patients in our study and categorized the longitudinal (i.e., over the entire preoperative imatinib treatment period) response to imatinib into four categories based on changes in tumor size, degree and extent of enhancement, and the presence or absence of solid nodules within the tumor:

1. Complete response: failure to identify a lesion previously identified on a radiographic image.
2. Partial response:

(a) Continuous regression: decreased tumor size or enhancement throughout treatment.
(b) Initial regression then stabilization: initial decrease in tumor size or enhancement followed by a period of no further change.

3. Stable disease: no evidence of change in tumor size or enhancement throughout treatment.
4. Progressive disease:

(a) Initial regression then progression: initial decrease in tumor size or enhancement followed by development of new lesions within or outside the tumor and increase in tumor size or enhancement over time.
(b) Continuous progression: increase in tumor size or enhancement throughout treatment.

The tumor volume in patients with locally advanced primary GIST was calculated from CT or magnetic resonance imaging (MRI) studies before and after imatinib treatment and was approximated using the formula for a sphere, $4\pi r^3/3$, where "r" represents the largest tumor radius. A change in tumor volume with preoperative imatinib treatment was expressed as an absolute change relative to the pre-treatment volume.

Statistical Analysis

Differences between proportions were tested with the chi-square test or Fisher's exact test as appropriate. The Wilcoxon's rank-sum test was used to analyze differences between medians. Survival times were calculated by the Kaplan–Meier method, and differences in survival times were tested using the log-rank test. A difference was accepted as significant when $P \leq .05$.

RESULTS

Patient and Tumor Characteristics

A total of 46 patients (22 men and 24 women) underwent surgery for GIST after preoperative treatment with imatinib. The median age of the patients was 55.7 years (range, 23.0 to 75.9 years) at diagnosis of primary GIST and 58.7 years (range, 28.4 to 80.9 years) at surgery after imatinib treatment. There was no significant difference in age distribution between the genders at either time point. Most patients were white (82%); 9% were black and 9% were Hispanic. The small bowel was the most common site for primary GIST (Table 1). At initial presentation with GIST, 74% of patients had a single tumor focus without metastasis, 7% had multiple intraperitoneal tumors without distant metastasis, and 19% had synchronous liver metastasis.

Preoperative Imatinib Treatment

At the initiation of imatinib treatment, the extent of GISTs was assessed by CT or MRI imaging.

TABLE 1. *Characteristics of primary GISTs (n = 46)*

Characteristic	No. (%)
Site of primary GIST	
Small bowel	21 (46%)
Stomach	13 (28%)
Colon	5 (11%)
Rectum	4 (9%)
Esophagus	1 (2%)
Unknown	2 (4%)
Extent of disease at diagnosis of primary GIST	
Single intraperitoneal tumor	29 (63%)
Multiple intraperitoneal tumors	3 (7%)
Single perirectal tumor	4 (9%)
Single periesophageal tumor	1 (2%)
Single intraperitoneal tumor and liver metastasis	7 (15%)
Multiple intraperitoneal tumors and liver metastasis	2 (4%)

GIST, gastrointestinal stromal tumor.

Thirty-five (76%) of the 46 patients were treated for recurrent or metastatic GIST; seven of these had an intact primary GIST with synchronous liver metastasis (one patient had an isolated liver metastasis, whereas six patients had multiple liver metastases) (Table 2). The remaining eleven patients (24%) were treated for locally advanced primary GIST. The median preoperative imatinib treatment duration for all 46 patients was 12.9 months (range, 2.8–38.1 months). For the 35 patients with recurrent or metastatic GIST, the median time of preoperative imatinib treatment was 15.2 months (range, 4.4–38.1 months), whereas the median time was significantly shorter for the eleven patients with locally advanced primary GIST (11.9 months; range, 2.8–15.0 months; $P = .02$). Thirty-two (70%) patients received 400 mg daily, six (13%) received 600 mg daily, and eight (17%) received 400 mg twice daily of imatinib at the time of surgery.

Response to Preoperative Imatinib Treatment

Tumor response to imatinib was evaluated in most patients with serial CT imaging. One patient with perirectal GIST was followed with serial MRI. Of the 46 patients treated, one (2%) patient with a GIST at the gastroesophageal junction had a complete radiographic response (Table 2), although on surgical exploration, this patient was found to have a 2-cm GIST with viable tumor cells. Nineteen (41%) patients had a partial response, one (2%) had stable disease, and 25 (55%) had progressive disease (Table 2). Of the 25 patients with progressive disease, seven exhibited continuous progression on imatinib, whereas 18 had disease that initially regressed but subsequently progressed on imatinib. In these 18 patients, the median time from initiation of imatinib

TABLE 2. *Radiographic response to preoperative imatinib treatment for GISTs (n = 46)*

Response	All patients (n = 46)	Patients with locally advanced primary GIST[a] (n = 11)	Patients with recurrent or metastatic GIST	
			Complete resection (n = 11)	Incomplete resection (n = 24)
Complete response (no., %)	1 (2%)	1 (9%)	0 (0%)	0 (0%)
Partial response (no., %)	19 (41%)	8 (73%)	10 (91%)	1 (4%)
Continuous regression (no.)	6	4	2	0
Initial regression then stable disease (no.)	13	4	8	1
Stable disease (no., %)	1 (2%)	1 (9%)	0 (0%)	0 (0%)
Progressive disease (no., %)	25 (55%)	1 (9%)	1 (9%)	23 (96%)
Initial regression then progression (no.)	18	0	0	18
Continuous progression (no.)	7	1	1	5

GIST, gastrointestinal stromal tumor.
[a] All 11 patients underwent complete resection.

to evidence of disease progression was 18.0 months (range, 5.3–37.4 months).

Radiographic response to imatinib was based on changes in tumor size, degree and extent of enhancement, and the presence or absence of solid nodules within the tumor over the entire preoperative treatment period. Of the 46 patients in our study, 38 patients showed an initial radiographic response to imatinib. In these 38 patients, 28 (73%) exhibited a reduction in both tumor size and enhancement, nine (24%) had only a reduction in size and one (3%) had only a reduction in enhancement. Of the 18 patients with GISTs that exhibited initial radiographic regression to imatinib treatment but subsequently progressed before surgery (Table 2), the progression was evidenced by new intratumoral nodules without substantial alterations in the overall size of the dominant lesions in five patients.

Twenty-one (46%) of the 46 patients also underwent [^{18}F]-fluorodeoxyglucose positron emission tomography (FDG–PET) imaging before imatinib treatment, and 18 of these underwent serial FDG–PET scanning during imatinib treatment. The CT and FDG-PET imaging results were concordant for 14 (78%) of these 18 patients. For the remaining four patients, the results were discordant in that the CT imaging indicated residual disease or disease progression and the FDG–PET imaging demonstrated no increased metabolic activity. Pathologic analysis of the surgical resection specimens indicated residual viable disease in all four patients. Hence, FDG–PET imaging underestimated the tumor burden in these four patients.

Completeness of Surgical Resection and Outcome After Preoperative Imatinib Treatment

Complete surgical resection after treatment with imatinib was accomplished in 22 (48%) of the 46 patients in our cohort, whereas 24 patients (52%) had an incomplete resection (Tables 2 and 3). Half of the complete resections were performed in patients with locally advanced primary GIST and half in patients with recurrent or metastatic GIST, whereas all of the incomplete resections occurred in patients with recurrent or metastatic GIST; this distribution was significantly different ($P < .001$) (Table 4). The median total follow-up time was the same for patients who underwent complete resection and those who underwent incomplete resection ($P = 0.8$). In contrast, the median postoperative follow-up time was significantly longer for patients who underwent complete resection ($P < .001$).

Resection of Locally Advanced Primary Tumors after Imatinib Treatment

All eleven patients treated with imatinib for locally advanced primary GIST underwent complete resection. One patient's tumor did not respond to imatinib and showed radiographic evidence of tumor progression before resection; the remaining ten patients had radiographic evidence of complete response (one patient), partial response (eight patients) or stable disease (one patient) (Table 2). The nine patients with a complete or partial response had an absolute median decrease in tumor volume of 85% (range, 27–99%). Subjectively, the treating surgeons felt that all nine patients were able to undergo less extensive surgery than was anticipated by the surgeon before imatinib treatment.

Pathologic evaluation of the surgical specimens from all eleven patients indicated complete response to imatinib in one patient and partial response in nine patients. The patient with radiographic evidence of tumor progression did not exhibit a pathologic treatment response.

The median total follow-up time for patients with locally advanced primary GIST was 31.4 months

TABLE 3. *Indications for preoperative imatinib treatment, follow-up times, and surgical outcomes, by completeness of resection of GIST (n = 46)*

Factor	Complete resection[a] (n = 22)	Incomplete resection (n = 24)	*P*
Indication for preoperative imatinib			< .001*
Primary GIST (no., %)	11 (50%)	0 (0%)	
Recurrence or metastasis (no., %)	11 (50%)	24 (100%)	
Total follow-up time			.8†
Median (months)	36.2	36.2	
Range (months)	15.5–48.1	11.6–48.0	
Postoperative follow-up time			< .001‡
Median (months)	23.4	11.8	
Range (months)	0.2–35.3	0.8–30.9	
Disease status at last follow-up			< .001†
No evidence of disease (no., %)	16 (73%)	0 (0%)	
Alive with disease (no., %)	6 (27%)	19 (79%)	
Dead with disease (no., %)	0 (0%)	5 (21%)	
Recurrences (no., %)	7[b] (32%)	NA	
Time to recurrence			
Median (months)	12.5	NA	
Range (months)	1.7–32.5	NA	
Time to death			
Median (months)	NA	12.0	
Range (months)	NA	0.8–13.8	

GIST, gastrointestinal stromal tumor; NA, not applicable.
[a] Removal of all macroscopic disease.
[b] One patient with recurrent disease underwent a second complete resection.
The following statistical analyses were used: * chi-square test, †Fisher's exact test, ‡Wilcoxon's rank-sum test.

(range, 15.5–42.5 months), and the median postoperative follow-up time was 19.5 months (range, 7.2–32.5 months). At last follow-up, all eleven patients were alive and ten (91%) were free of disease. The patient who exhibited radiographic evidence of tumor progression before surgery and no pathologic treatment response at the time of surgery developed recurrent GIST with multiple intraabdominal implants at twelve months postresection. The median disease-free survival time has not yet been reached for these eleven patients. Postoperatively, eight patients continue on adjuvant imatinib at a median of 15.1 months (range, 1.8–27.0 months).

Resection of Recurrent or Metastatic Tumors After Imatinib Treatment

Of the 35 patients with recurrent or metastatic GIST, eleven (31%) were able to have complete resection and 24 (69%) had incomplete resection. Tables 2 and 4 describe the differences between patients with recurrent and metastatic GIST who underwent complete and incomplete resections. Completeness of resection was associated with response to and duration of imatinib treatment, anatomic location and tumor burden. The median preoperative imatinib treatment time was significantly shorter for patients with complete resection than for patients with incomplete resection ($P = .03$). Patients who exhibited radiographic evidence of a partial response to imatinib at the time of resection were more likely to attain a complete resection (ten of eleven; 91%), whereas complete resection was rarely achieved in patients who had radiographic evidence of progressive disease (one of 24; 4%). This difference in resectability based on radiographic response was significant ($P < .001$). Patients who underwent complete resection were more likely to have multiple intraperitoneal recurrences, whereas patients who had an incomplete resection were more likely to have multiple liver and extraperitoneal metastases.

As indicated in Table 2, 23 (96%) of the 24 patients who had incomplete resection exhibited radiographic evidence of progressive disease at the time of resection. However, 18 of these 23 patients initially responded to preoperative imatinib but then progressed before surgical resection. The median time to progression in these 18 patients was 18.0 months (range, 5.3–37.4 months), and the median time from the diagnosis of progression until surgery was 5.7 months (range, 0.1–6.5 months). It is possible that some of the incompletely resected patients would have been able to undergo a complete resection had they been operated on when the GIST was still regressing on imatinib. To test this possibility, we compared the median preoperative imatinib treatment duration in the ten completely resected patients who exhibited a partial response to imatinib at the time of resection (ten months) and the median time to

TABLE 4. *Indications for, duration of, and surgical outcomes after preoperative imatinib treatment among patients with recurrent or metastatic disease, by completeness of resection of GIST (n = 35)*

Factor	Complete resection (n = 11)	Incomplete resection (n = 24)	*P*
Indication for preoperative imatinib			
Recurrence			
Single tumor (no., %)	0 (0%)	1 (4%)	
Multiple tumors (no., %)	3 (27%)	3 (12%)	
Isolated liver metastasis			
Single tumor (no., %)	2 (18%)	0 (0%)	
Multiple tumors (no., %)	0 (0%)	5 (21%)	
Recurrence and liver metastasis			
Single tumor (no., %)	3 (27%)	3 (12%)	
Multiple tumors (no., %)	3 (27%)	9 (38%)	
Recurrence and extraperitoneal metastasis (no., %)	0 (0%)	3 (12%)	
Duration of preoperative imatinib			.03‡
Median (months)	10.0	22.9	
Range (months)	6.9–37.5	4.4–38.1	
Recurrences (no., %)	6 (55%)	NA	
Time to recurrence			
Median (months)	15.1	NA	
Range (months)	1.7–32.5	NA	
Site of recurrence			
Local (no.)	1	NA	
Metastasis (no.)	3	NA	
Local and metastasis (no.)	2	NA	
Follow-up time since imatinib initiation			.10‡
Median (months)	39.1	36.2	
Range (months)	28.7–48.1	11.6–48.0	
Postoperative follow-up time			< .001‡
Median (months)	30.7	11.8	
Range (months)	0.2–35.3	0.8–30.9	
Status at last follow-up			< .001 *
No evidence of disease (no., %)	6[a] (55%)	0 (0%)	
Alive with disease (no., %)	5 (45%)	19 (79%)	
Dead with disease (no., %)	0 (0%)	5 (21%)	

GIST, gastrointestinal stromal tumor; NA, not applicable.
[a] GIST recurred in one patient with a single liver metastasis who was rendered free of disease after a second liver resection.
The following statistical analyses were used: * chi-square test, ‡ Wilcoxon's rank-sum test.

progression in the 18 patients whose disease initially regressed on imatinib but then progressed before surgery (18.0 months). This difference was statistically significant ($P = .04$). Of the 18 patients, only two had disease that progressed before ten months of treatment.

Pathologic evaluation of the eleven completely resected recurrent or metastatic GISTs indicated a complete response to imatinib in two patients and a partial response in nine patients. All eleven patients were alive at a median postoperative follow-up time of 30.7 months (range, 0.2–35.3 months) (Table 4). All patients received imatinib postoperatively for a median of 23.7 months (range, 1.7–33.8 months), and 10 (91%) had continued on imatinib at last follow-up. Six (55%) of the eleven patients had evidence of recurrent disease at a median of 15.1 months (range, 1.7–32.5 months), resulting in an overall postoperative median disease-free survival time of 24.7 months. Three of the six patients with recurrent disease underwent a second operation: one for palliative resection of multiple intraperitoneal tumors and ethanol injection for liver metastasis, one for radiofrequency ablation of multiple liver metastases, and one for resection of a stable single liver metastasis. The patient with a single stable liver metastasis was rendered free of disease by this second surgery and remained free of disease at 25.6 months after the second operation. At the time of last follow-up, six of the eleven patients, including the two patients with complete pathologic response, were free of disease at a median of 23.6 months (range, 0.2–31.6 months), whereas the other five patients have exhibited disease progression on imatinib.

Among the 24 patients with incompletely resected GIST, the median overall survival time had not been reached at the time of this analysis, and 19 (79%) of the 24 patients were alive at a median postoperative follow-up time of 11.8 months (range, 0.8–30.9 months) (Table 4). All 24 patients received imatinib postoperatively for a median of 10.0 months (range, 0.8–31.9 months). Of the 19 patients who are alive,

twelve have developed progressive disease on imatinib despite dose escalation, and five of these twelve have discontinued imatinib and have been enrolled in either a phase I or phase II clinical trial. The five patients who died with disease did so at a median of 12.0 months (range, 0.8–13.8 months) after surgery. One of the patients died 24 days after surgery from a myocardial infarction, whereas the other four died as a result of disease progression. Hence, the 30-day postoperative mortality rate for all 46 patients was 2.2%.

DISCUSSION

Our study demonstrated that preoperative imatinib resulted in decreased tumor volume in patients with locally advanced primary GIST, and this was associated with a high rate of complete surgical resection. In patients with recurrent or metastatic GIST, those with imatinib-responsive GISTs were more likely to undergo complete resection and had prolonged disease-free survival. Patients with recurrent or metastatic GIST that initially regressed on imatinib but then progressed before resection rarely underwent complete resection, indicating that early resection may be beneficial and should be considered for patients with imatinib-responsive recurrent or metastatic GIST. Preoperative imatinib treatment resulted in a reduction in both tumor size and tumor enhancement on radiographic evaluation, indicating that size alone may not be the best measure of tumor response.

Radiographic response of solid tumors to chemotherapeutic agents has traditionally been evaluated by measurement of the two-dimensional[19] or one-dimensional[20] change in tumor size on serial imaging. However, change in size alone, as defined by the Response Evaluation Criteria in Solid Tumors (RECIST),[20] has been shown to be a very inaccurate predictor of tumor response in GISTs treated with imatinib.[21–24] Evaluating other tumor changes such as enhancement, density and development of new intratumoral lesions have been shown to more accurately predict the response of GISTs to imatinib than size alone.[22] Currently, many investigators (including a group at M.D. Anderson)[25] are exploring the use of these radiographic variables to predict response to imatinib. In our study, treatment responses were assessed by changes in tumor size, enhancement and development of new intratumoral nodules. In addition, these changes were determined longitudinally over the entire preoperative treatment with imatinib. There was a reasonable concordance between a reduction in tumor size and tumor enhancement in tumors that responded to imatinib. In GIST which initially responded to imatinib but subsequently progressed, five out of 18 patients developed new intratumoral lesions without any change in the overall tumor size. Hence, at the present time, we believe that using more expanded criteria in assessing radiographic tumor response to imatinib is appropriate. We recognize that our findings are based on a relatively small number of patients and that prospective validation of the response criteria and the proposed response categories used in our study is necessary. Nonetheless, in our patient population, radiographic evidence of disease regression was associated with complete surgical resection, indicating that it may be used as a guideline by which patients are assessed for the appropriateness of surgery in order to render them free of disease.

Tumor metabolism can also be used as a marker of the response to imatinib. Several studies have indicated the benefits of using the metabolic activity measurements of FDG–PET imaging in assessing tumor response to imatinib,[22,26,27] whereas one study found FDG–PET to be less predictive of the pathologic tumor response.[16] In our study, four (22%) of 18 patients who underwent serial FDG–PET showed no evidence of active disease on PET scan just prior to surgery but were found to have evidence of residual tumor on both CT imaging and pathologic analysis. Hence, FDG–PET may be beneficial in evaluating the initial response to imatinib treatment but may be inaccurate as a predictor of residual disease at the time of resection.

Surgery remains the standard treatment for primary resectable GISTs. Ongoing trials by the Radiation Therapy Oncology Group (RTOG-S-0132)[18] and M. D. Anderson[17] are evaluating the potential benefits of preoperative imatinib in treating resectable localized or metastatic GIST. These trials are still accruing patients and results are not expected for several years. Only a few anecdotal case reports have been published on the potential benefits of preoperative imatinib for primary GIST.[28–30] In these case reports, preoperative imatinib treatment of unresectable GISTs resulted in tumor regression and enabled surgical resection. Our study is the first to report on the surgical outcome after preoperative imatinib treatment for locally advanced primary GIST in a larger group of patients. We found that nine (82%) of the eleven patients treated with preoperative imatinib had a substantial reduction in tumor volume, which would potentially decrease the extent of surgical

resection. Moreover, all eleven patients were able to have complete surgical resection, and one patient had a pathologic complete response.

Patients treated with preoperative imatinib for locally advanced primary GIST had a longer median disease-free survival time compared with historical controls. After a median postoperative follow-up of 19.5 months, only one of the eleven patients with locally advanced primary GIST developed recurrent disease, and the median disease-free survival time has not yet been reached. This outcome is much improved from that previously reported before imatinib was available. Ng et al.[12] reported an 18-month median disease-free survival time after complete resection of primary gastrointestinal leiomyosarcoma and a disease recurrence rate of 60% within two years. Other investigators have reported median disease-free survival times ranging from 7 to 20 months.[11,31] Whether the prolonged disease-free survival time we observed in our study is generalizable to a larger number of patients with primary GIST will need to be assessed in a larger cohort of patients. Eight of the eleven patients with locally advanced primary GIST in our study continued on imatinib postoperatively, and it is possible that the prolonged disease-free survival time is a result of postoperative rather than preoperative imatinib therapy. It is hoped that ongoing trials, including the RTOG-S-0132,[18] the M. D. Anderson trail,[17] two adjuvant trials sponsored by the American College of Surgeons Oncology Group (ACOSOG-Z9000 and -Z9001),[32,33] and an adjuvant trial conducted by the European Organization for Research and Treatment of Cancer (EORTC-62024)[34] will provide answers to these clinical questions.

Complete surgical resection can also be achieved in patients with recurrent or metastatic GISTs that respond to preoperative imatinib therapy. However, the optimal time to proceed with surgical resection in these patients has not been established. In our study, ten (91%) of the eleven patients who underwent complete resection had radiographic evidence of a partial response to imatinib at the time of surgery. In contrast, 23 (96%) of the 24 patients who had incomplete resection of their disease had radiographic evidence of progressive disease at the time of surgery. Interestingly, 18 of these 23 patients had initially demonstrated response to imatinib but developed progression on imatinib before surgery. The median time to progression in these 18 patients was 18.0 months, significantly longer than the median 10.0 months of preoperative imatinib treatment in the ten patients who had radiographic evidence of a partial response and had complete resection at the time of surgery. Hence, one could postulate that complete resection might have been achieved in the 18 patients who underwent incomplete resection had they undergone surgery when their recurrent or metastatic GIST was still demonstrating response to imatinib. This suggests that surgical intervention at an earlier time in the preoperative therapy with imatinib may be optimal in order to prevent tumor progression that ultimately results from imatinib resistance. Resistance to imatinib in recurrent or metastatic GIST is now being reported,[35–37] and the natural history of imatinib-treated recurrent or metastatic GIST has not yet been described. On the basis of the findings from our study, we believe that strong consideration should be given to early surgical intervention in patients with resectable recurrent or metastatic GIST whose disease is imatinib-responsive or stable on imatinib therapy. This may be especially true in those patients in whom further treatment with imatinib would not alter the extent of surgical resection required for complete resection. Although medical treatment of GIST has improved, surgery remains the only proven method to render these patients free of disease.

The overall complete resection rate after preoperative imatinib for patients with recurrent or metastatic GISTs in our study was 31%. This is similar to the complete resection rates of 30–34% that were reported before imatinib was available.[13–15] However, the postoperative median disease-free survival time in the eleven patients with recurrent or metastatic GIST who underwent complete resection was 24.7 months, which is longer than the 12–19 month disease-free survival reported in this group of patients before imatinib was available.[11,13,14] The median postoperative survival time after complete resection of recurrent or metastatic GIST before imatinib was available ranged from 17.5 to 50 months.[12,14,15] In the eleven patients who underwent complete resection in our study, the median postoperative survival time has not yet been reached, and all patients were alive at a median follow-up time of 30.7 months. These results are encouraging, but longer follow-up is needed in this group of patients before we can make any definitive conclusions.

The role for incomplete surgical resection (i.e., debulking) in recurrent or metastatic GIST has not been established. The median postoperative survival time after incomplete resection ranged from 2 to 20 months before imatinib was available.[11,12,14,15] In our study, the median postoperative survival time has not yet been reached, and 19 (79%) of the 24 patients who

underwent incomplete resection were alive at a median postoperative follow-up time of 11.8 months. Moreover, the median time since imatinib therapy was started in these 24 patients was 36.2 months, and the one-, two-, and three-year overall survival was 95.8%, 91.0% and 79.8%, respectively. This two-year survival is better than the reported two-year overall survival rate of 69–79% in patients with recurrent, metastatic, or unresectable GIST treated with imatinib alone.[7,10] It is possible that some patients may benefit from incomplete resection, especially those patients with recurrent or metastatic GIST that exhibit a mixed response to imatinib (e.g., some tumor nodules progress and others regress on imatinib). Resecting nodules that progress on imatinib therapy may be beneficial if this proves to prolong the overall survival time. Incomplete resection or "debulking surgery" can also be considered in select patients for alleviation of symptoms and palliation. Further studies are needed to determine which patients benefit from partial resection.

In summary, surgical resection after preoperative imatinib treatment is feasible and should be considered for patients with GISTs that are imatinib-responsive or stable on follow-up radiographic studies without evidence of progression. Preoperative imatinib for locally advanced primary GISTs can decrease tumor volume, is associated with a high rate of complete resection, and should be considered in these patients. In patients with recurrent or metastatic GISTs, strong consideration should be given to early resection of imatinib-responsive tumors, since disease-free survival can be prolonged in these patients. When surgical resection is delayed and imatinib resistance develops, complete resection is rarely achieved and the usefulness of surgical resection for these patients is questionable.

ACKNOWLEDGMENTS

We thank Elizabeth L. Hess of the M. D. Anderson Department of Scientific Publications for editing this manuscript and Dr. Joe Ensor of the M. D. Anderson Department of Biostatistics and Applied Mathematics for assistance with statistical analysis.

REFERENCES

1. Kindblom LG, Remotti HE, Aldenborg F, Meis-Kindblom JM. Gastrointestinal pacemaker cell tumor (GIPACT): gastrointestinal stromal tumors show phenotypic characteristics of the interstitial cells of Cajal. *Am J Pathol* 1998; 152(5):1259–69.
2. Miettinen M, Sarlomo-Rikala M, Lasota J. Gastrointestinal stromal tumors: recent advances in understanding of their biology. *Hum Pathol* 1999; 30(10):1213–20.
3. Fletcher CD, Berman JJ, Corless C, et al. Diagnosis of gastrointestinal stromal tumors: A consensus approach. *Hum Pathol* 2002; 33(5):459–65.
4. Le Cesne A, Judson I, Crowther D, et al. Randomized phase III study comparing conventional-dose doxorubicin plus ifosfamide versus high-dose doxorubicin plus ifosfamide plus recombinant human granulocyte-macrophage colony-stimulating factor in advanced soft tissue sarcomas: A trial of the European Organization for Research and Treatment of Cancer/Soft Tissue and Bone Sarcoma Group. *J Clin Oncol* 2000; 18(14):2676–84.
5. Nielsen OS, Judson I, van Hoesel Q, et al. Effect of high-dose ifosfamide in advanced soft tissue sarcomas. A multicentre phase II study of the EORTC Soft Tissue and Bone Sarcoma Group. *Eur J Cancer* 2000; 36(1):61–7.
6. Patel SR, Gandhi V, Jenkins J, et al. Phase II clinical investigation of gemcitabine in advanced soft tissue sarcomas and window evaluation of dose rate on gemcitabine triphosphate accumulation. *J Clin Oncol* 2001; 19(15):3483–9.
7. Verweij J, Casali PG, Zalcberg J, et al. Progression-free survival in gastrointestinal stromal tumours with high-dose imatinib: randomised trial. *Lancet* 2004; 364(9440):1127–34.
8. van Oosterom AT, Judson I, Verweij J, et al. Safety and efficacy of imatinib (STI571) in metastatic gastrointestinal stromal tumours: a phase I study. *Lancet* 2001; 358(9291):1421–3.
9. 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(7):472–80.
10. Rankin C, von Mehren M, Blanke C, et al. Dose effect of imatinib in patients with metastatic GIST—Phase III Sarcoma Group Study S0033 [Abstract]. *J Clin Oncol* 2004; 22(14S):9005.
11. Mudan SS, Conlon KC, Woodruff JM, Lewis JJ, Brennan MF. Salvage surgery for patients with recurrent gastrointestinal sarcoma: prognostic factors to guide patient selection. *Cancer* 2000; 88(1):66–74.
12. Ng EH, Pollock RE, Romsdahl MM. Prognostic implications of patterns of failure for gastrointestinal leiomyosarcomas. *Cancer* 1992; 69(6):1334–41.
13. Ng EH, Pollock RE, Munsell MF, Atkinson EN, Romsdahl MM. Prognostic factors influencing survival in gastrointestinal leiomyosarcomas. Implications for surgical management and staging. *Ann Surg* 1992; 215(1):68–77.
14. 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(1):51–8.
15. Clary BM, DeMatteo RP, Lewis JJ, Leung D, Brennan MF. Gastrointestinal stromal tumors and leiomyosarcoma of the abdomen and retroperitoneum: a clinical comparison. *Ann Surg Oncol* 2001; 8(4):290–9.
16. Scaife CL, Hunt KK, Patel SR, et al. Is there a role for surgery in patients with "unresectable" cKIT+ gastrointestinal stromal tumors treated with imatinib mesylate? *Am J Surg* 2003; 186(6):665–9.
17. Trent J, Hunt KK (2003) A prospective, randomized, phase II study of preoperative plus postoperative imatinib mesylate (Gleevec, formerly STI-571) in patients with primary, recurrent, or metastatic resectable, kit-expressing, gastrointestinal stromal tumor (GIST). Available: http://www.utmext01a.mdacc.tmc.edu/dept/prot/clinicaltrialswp.nsf/index/id03-0023 [accessed August 14, 2006].
18. Eisenberg B (2002) A phase II trail of neoadjuvant/adjuvant STI-571 (Gleevec NSC #716051) for primary and recurrent operable malignant GIST expressing the KIT receptor tyrosine kinase (CD117). Available: http://www.rtog.org/members/protocols/s0132/s0132.pdf [accessed August 14, 2006].

19. Miller AB, Hoogstraten B, Staquet M, Winkler A. Reporting results of cancer treatment. *Cancer* 1981; 47(1):207–14.
20. Therasse P, Arbuck SG, Eisenhauer EA, et al. New guidelines to evaluate the response to treatment in solid tumors. European Organization for Research and Treatment of Cancer, National Cancer Institute of the United States, National Cancer Institute of Canada. *J Natl Cancer Inst* 2000; 92(3):205–16.
21. Casali PG, Fumagalli E, Messina A, et al. Tumor response to imatinib mesylate in advanced GIST [Abstract]. *J Clin Oncol* 2004; 22(14S):9028.
22. Choi H, Charnsangavej C, de Castro Faria S, et al. CT evaluation of the response of gastrointestinal stromal tumors after imatinib mesylate treatment: a quantitative analysis correlated with FDG PET findings. *AJR Am J Roentgenol* 2004; 183(6):1619–28.
23. Shankar S, van Sonnenberg E, Desai J, Dipiro PJ. Van Den Abbeele A, Dimitri GD. Gastrointestinal stromal tumor: new nodule-within-a-mass pattern of recurrence after partial response to imatinib mesylate. *Radiology* 2005; 235(3):892–8.
24. Holdsworth CH, Manola J, Badawi RD, et al. Use of computerized tomography as an early prognostic indicator of response to imatinib mesylate in patients with gastrointestinal stromal tumors [Abstract]. *J Clin Oncol* 2004; 22(14S):3011.
25. Choi H, Charnsangavej C, Macapinilac HA, et al. Correlation of computerized tomography and positron emission tomography in patients with metastatic GIST treated at a single institution with imatinib mesylate [Abstract]. *Proc Am Soc Clin Oncol* 2003; 22:819.
26. Gayed I, Vu T, Iyer R, Johnson M, Macapinlac H, Swanston N, Podoloff D. The role of 18F-FDG PET in staging and early prediction of response to therapy of recurrent gastrointestinal stromal tumors. *J Nucl Med* 2004; 45(1):17–21.
27. Goerres GW, Stupp R, Barghouth G, et al. The value of PET, CT and in-line PET/CT in patients with gastrointestinal stromal tumours: long-term outcome of treatment with imatinib mesylate. *Eur J Nucl Med Mol Imaging* 2005; 32(2):153–62.
28. Katz D, Segal A, Alberton Y, Jurim O, Reissman P, Catane R, Cherny NI. Neoadjuvant imatinib for unresectable gastrointestinal stromal tumor. *Anticancer Drugs* 2004; 15(6):599–602.
29. Hiramatsu Y, Konno H, Kamiya K, et al. A case of gastric GIST treated preoperatively by imatinib mesylate. *Gan To Kagaku Ryoho* 2004; 31(8):1219–23.
30. Bumming P, Andersson J, Meis-Kindblom JM, et al. Neoadjuvant, adjuvant and palliative treatment of gastrointestinal stromal tumours (GIST) with imatinib: a centre-based study of 17 patients. *Br J Cancer* 2003; 89(3):460–4.
31. Conlon KC, Casper ES, Brennan MF. Primary gastrointestinal sarcomas: analysis of prognostic variables. *Ann Surg Oncol* 1995; 2(1):26–31.
32. DeMatteo RP (2001) A phase III randomized double-blind study of adjuvant STI571 (Gleevec) versus placebo in patients following the resection of primary gastrointestinal stromal tumor (GIST). Available: http://www.acosog.org/studies/synopses/Z9001_Synopsis.pdf [accessed April 20, 2005].
33. DeMatteo RP (2001) A phase II study of adjuvant STI571 (Gleevec) therapy in patients following completely resected high-risk primary gastrointestinal stromal tumor (GIST). Available: http://www.acosog.org/studies/synopses/Z9000_Synopsis.pdf [accessed August 14, 2006].
34. Casali PG (2004) Phase III randomized study of adjuvant imatinib mesylate versus observation only in patients with completely resected localized gastrointestinal stromal tumor at intermediate- or high-risk of relapse. Available: http://www.eortc.be/protoc/Details.asp?Protocol=62024 [accessed August 14, 2006].
35. Chen LL, Trent JC, Wu EF, et al. A missense mutation in KIT kinase domain 1 correlates with imatinib resistance in gastrointestinal stromal tumors. *Cancer Res* 2004; 64(17):5913–9.
36. Tamborini E, Bonadiman L, Greco A, et al. A new mutation in the KIT ATP pocket causes acquired resistance to imatinib in a gastrointestinal stromal tumor patient. *Gastroenterology* 2004; 127(1):294–9.
37. Wakai T, Kanda T, Hirota S, et al. Late resistance to imatinib therapy in a metastatic gastrointestinal stromal tumour is associated with a second KIT mutation. *Br J Cancer* 2004; 90(11):2059–61.