Surgical Management of Advanced Gastrointestinal Stromal Tumors: An International Multi-Institutional Analysis of 158 Patients

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BACKGROUND: Patients with advanced gastrointestinal stromal tumors (GIST) are at high risk for recurrence after surgery. The aim of this study was to characterize outcomes of advanced GIST treated with surgery from a large multi-institutional database in the tyrosine kinase inhibitor (TKI) era.

STUDY DESIGN: Patients who underwent surgery for an advanced GIST from 1998 through 2012 were identified. Demographic, clinicopathologic, perioperative, and survival data were collected and analyzed.

RESULTS: There were 87 patients with locally advanced GIST and 71 patients with recurrent/metastatic GIST. The vast majority (95%) of patients with locally advanced GIST required a multivisceral resection; most patients (87%) underwent a microscopically complete (R0) resection. Although 82% of patients had high-risk tumors according to modified NIH criteria or had recurrent/metastatic disease, only 56% of patients received adjuvant TKI therapy. Among patients with locally advanced GIST, 3-year recurrence-free survival and overall survival rates were 65% and 87%, respectively. In contrast, 3-year recurrence-free survival and overall survival rates among patients with recurrent/metastatic GIST were 49% and 82%, respectively. On multivariate analysis, predictors of worse outcomes included high mitotic rate and male sex for patients with locally advanced GIST, and age and lack of adjuvant TKI therapy were associated with adverse outcomes among patients with recurrent/metastatic GIST (all $p < 0.05$).

CONCLUSIONS: Resection of advanced GIST can be safely accomplished with high rates of R0 resection. Among patients with advanced GIST, TKI therapy was underused. Barriers to the use of TKI therapy in this population should be explored. (J Am Coll Surg 2014;219:439–449. © 2014 by the American College of Surgeons)

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Gastrointestinal stromal tumors (GISTs) are the most common mesenchymal tumor of the gastrointestinal tract, with an annual incidence of 10 to 15 cases per million.[1-3] Gastrointestinal stromal tumors most commonly arise from the stomach (50% to 60%) and small bowel (30% to 35%) and less frequently arise from the colon and rectum (5%) or esophagus (<1%).[4] Less than 5% of GISTs are not associated with the gastrointestinal tract—these tumors are most commonly found in the omentum, mesentery, and retroperitoneum.[4] Of note, 75% to 80% of patients with GIST have mutations in the receptor tyrosine kinase KIT (CD117), which lead to KIT overexpression.[5] In turn, imatinib mesylate (Gleevec; Novartis)—a tyrosine kinase inhibitor (TKI) targeted at

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Abbreviations and Acronyms

GIST = gastrointestinal stromal tumor
HPF = high-powered field
HR = hazard ratio
IQR = interquartile range
OS = overall survival
RFS = recurrence-free survival
TKI = tyrosine kinase inhibitor

KIT—is an effective treatment option for most patients with GIST.[6-8]

The main treatment modality for primary GIST is complete surgical resection. Surgery alone for primary GIST is associated with a 5-year recurrence-free survival (RFS) rate of 70%.[9,10] Although many patients with primary GIST have excellent prognoses, certain subsets of patients are at higher risk for recurrence. Typically, higher-risk patients include individuals with large tumors, a high mitotic rate, and history of tumor rupture at the time of surgery.[10-13] These factors have been combined in a number of consensus classification systems to select high-risk patients for adjuvant imatinib after surgery.[14-16] For those patients who do recur with metastatic disease, imatinib is the primary therapeutic option, as its use is associated with an improved overall survival (OS) compared with historic controls.[17] Imatinib has also been recommended in the neoadjuvant setting for patients with primary GIST that are locally advanced, with the goal of improving resectability and decreasing surgical morbidity by reducing the need for extensive multivisceral resections.[18-21] In fact, the National Comprehensive Cancer Network currently recommends neoadjuvant imatinib in cases where downstaging the tumor would decrease surgical morbidity.[22]

Most data on the topic of surgical management of advanced GIST come from small, single-institution experiences.[20,21,23-26] In addition, there has been no consistent definition of locally advanced GIST in the literature, leading to difficulty interpreting these data. Data on surgical management of metastatic GIST are similarly limited. Although a few small studies have advocated adjuvant surgery for patients with metastatic GIST to decrease tumor bulk,[27,28] a prospective trial addressing the efficacy of surgery after imatinib therapy in patients with recurrent/metastatic GIST was closed due to poor accrual.[29] The aim of the current study was to characterize outcomes after surgical resection among patients with advanced GIST. Specifically, we sought to define the perioperative, as well as long-term oncologic, outcomes of patients with locally advanced, recurrent, or metastatic GIST using a large multi-institutional database.

METHODS

Patient population and data collection

Between January 1998 and December 2012, six hundred and nine patients who underwent surgery for a GIST were identified from 7 major cancer centers in the United States (Johns Hopkins University, Baltimore, MD; Duke University, Durham, NC; Emory University, Atlanta, GA; Medical College of Wisconsin, Milwaukee, WI; and University of Virginia, Charlottesville, VA) and Canada (University Health Network, Toronto, ON and Sunnybrook Health Sciences Centre, Toronto, ON). The IRBs of each institution approved this study. Patients who underwent surgical resection of locally advanced or recurrent/metastatic GIST were included in the study. Locally advanced GIST was defined as a primary tumor with multivisceral involvement on preoperative imaging or at the time of surgery. There were 87 patients with locally advanced GIST and 71 patients with recurrent/metastatic GIST identified. All patients were evaluated with a baseline history and physical examination and appropriate imaging studies at the discretion of the treating physician before surgery. Pre- and postoperative therapy with TKIs was administered at the discretion of the treating physician. After surgery, all patients were followed with cross-sectional imaging of the abdomen every 3 to 6 months for 5 years and annually thereafter.

Standard demographic and clinicopathologic data were collected on each patient, including sex, age, and symptoms at the time of diagnosis. Data were collected on tumor characteristics, including site of the tumor, tumor size, involvement of other organs on preoperative imaging and presentation (locally advanced, recurrent, or metastatic). Operative details, including the operation performed, need for multivisceral resection, duration of surgery, estimated blood loss, and complications (graded using the Clavien-Dindo classification system) were recorded.[30] In addition, pathologic details, including tumor size on final pathology, mitotic rate, and margin status (negative [R0], microscopically positive [R1], macroscopically positive [R2]) were collected. Details of preoperative and postoperative therapy with a TKI, date of last follow-up, vital status, and recurrence-related information were collected on all patients. Data on response to therapy were also recorded using the Choi criteria.[31] Recurrence was defined as biopsy-proven recurrent GIST or a lesion deemed suspicious on cross-sectional imaging.

Statistical methods

Baseline characteristics and statistical analysis of the study population were summarized and stratified according to

whether the tumor was locally advanced or recurrent/metastatic. The data were correspondingly reported as numbers (percentage) or medians with interquartile ranges (IQR). Trends in TKI use over time were assessed using Pearson's correlation. Overall survival and RFS were estimated using the Kaplan-Meier method and differences in survival were examined with the log-rank test.[32] The association of relevant clinicopathologic variables with RFS and OS was assessed using Cox proportional hazards models; the prognostic power of covariates was expressed by calculating hazard ratios (HRs) with 95% CIs.[33] Recurrence-free survival was calculated from the date of surgery, and OS was calculated from the date of diagnosis. Date of diagnosis was used to calculate OS to avoid lead-time bias because of the use of neoadjuvant therapy. Date of surgery was used to calculate RFS because recurrence can only occur after resection. A sensitivity analysis was completed using date of diagnosis to calculate RFS to assess the impact of any lead-time bias on RFS. The variables considered in the analysis included age, sex, tumor site, tumor size at diagnosis, mitotic rate group, neoadjuvant TKI, margin status, tumor rupture, and adjuvant TKI. All analyses were carried out with STATA version 12.0 (Stata Corp), and a p value <0.05 was considered statistically significant.

RESULTS

Locally advanced gastrointestinal stromal tumors

There were 87 patients who underwent surgery for locally advanced GIST (Table 1). Most patients were symptomatic at presentation (n = 68 [80.9%]) and the most common presenting symptoms were pain (n = 38 [43.7%]), overt bleeding (n = 15 [17.2%]), and obstruction (n = 13 [14.9%]). The majority of tumors arose in the stomach (n = 62 [71.3%]), and a minority arose in the small intestine (n = 23 [26.4%]), rectum (n = 1 [1.1%]), and esophagus (n = 1 [1.1%]). Median tumor size at the time of diagnosis was 11.0 cm (IQR 5.5 to 15.0 cm).

Eighteen patients (20.7%) with locally advanced GIST received neoadjuvant therapy with imatinib for a median duration of 7 months (IQR 6 to 13 months) (Table 2). The proportion of patients who received neoadjuvant therapy with a TKI increased during the study period ($p < 0.001$; Fig. 1). On univariate analysis, younger age was predictive of receiving neoadjuvant therapy (odds ratio = 0.95; p = 0.01); sex, tumor size, mitotic rate, and presence of symptoms were not associated with receipt of neoadjuvant therapy (all $p > 0.05$). Using the Choi criteria, 16 (88.9%) patients had a favorable response to neoadjuvant therapy. Specifically, 2 patients (11.1%) had a complete response, 9 (50.0%) had a partial

Table 1. Preoperative Characteristics of Patients with Advanced Gastrointestinal Stromal Tumors

	Locally advanced (n = 87)	Recurrent/metastatic (n = 71)
Age, y, median (IQR)	63.9 (55.4–71.8)	54.5 (49.6–65.4)
Male sex, n (%)	53 (60.9)	34 (47.9)
White race, n (%)	29 (58.0)	43 (76.8)
Any symptom, n (%)	68 (80.9)	52 (73.2)
Pain	38 (43.7)	36 (50.7)
Overt bleeding	15 (17.2)	8 (11.3)
Obstruction	13 (14.9)	8 (11.3)
Abdominal distension	6 (6.9)	7 (9.9)
Occult bleeding	4 (4.6)	5 (7.0)
Site, n (%)		
Stomach	62 (71.3)	32 (45.1)
Duodenum	9 (10.3)	2 (2.8)
Small bowel	14 (16.1)	15 (21.1)
Rectum	1 (1.1)	4 (5.6)
Extragastrointestinal	0 (0.0)	3 (4.2)
Liver	0 (0.0)	12 (16.9)
Esophagus	1 (1.1)	0 (0.0)
Multifocal	0 (0.0)	2 (2.8)
Unknown	0 (0.0)	1 (1.4)
Size, cm, median (IQR)	11.0 (5.5–15.0)	8.8 (3.5–16.7)
Preoperative biopsy, n (%)	50 (57.5)	46 (64.8)

IQR, interquartile range.

Table 2. Preoperative Treatment of Advanced Gastrointestinal Stromal Tumors with a Tyrosine Kinase Inhibitor

Treatment	Locally advanced (n = 18)	Recurrent/metastatic (n = 27)
Preoperative TKI,* n (%)	18 (20.7)	27 (38.0)
Imatinib	18 (100)	27 (100.0)†
Sunatinib	0	3 (11.1)*
Duration of neoadjuvant, mos, median (IQR)	7 (6–13)	10 (6–13)
Response to neoadjuvant (Choi), n (%)		
Complete response	2 (11.1)	0 (0.0)
Partial response	9 (50.0)	12 (42.9)
Stable disease	5 (27.8)	7 (25.0)
Progressive disease	1 (5.6)	5 (17.9)
Unknown	1 (5.6)	3 (11.1)
Indication for neoadjuvant, n (%)		
Tumor size	7 (38.9)	NA
Morbidity of resection	5 (27.8)	NA
Multivisceral involvement	2 (11.1)	NA
Unresectable, n (%)	2 (11.1)	NA
Downstaging to attempt minimally invasive resection, n (%)	2 (11.1)	NA

*Percentage calculated using all patients in series.
†Three patients received both preoperative imatinib and sunitinib.
NA, not applicable; TKI, tyrosine kinase inhibitor.

response, 5 (27.8%) had stable disease, and 1 (5.6%) had progressive disease. The indications for neoadjuvant therapy were tumor size (n = 7 [38.9%]), anticipated morbidity of the resection (n = 5 [27.8%]), multivisceral involvement (n = 2 [11.1%]), unresectable tumor (n = 2 [11.1%]), and downstaging to attempt laparoscopic resection (n = 2 [11.1%]).

The vast majority of patients (n = 83 [95.4%]) who underwent surgery for locally advanced GIST required a multivisceral resection (Table 3). A median of 3 organs per

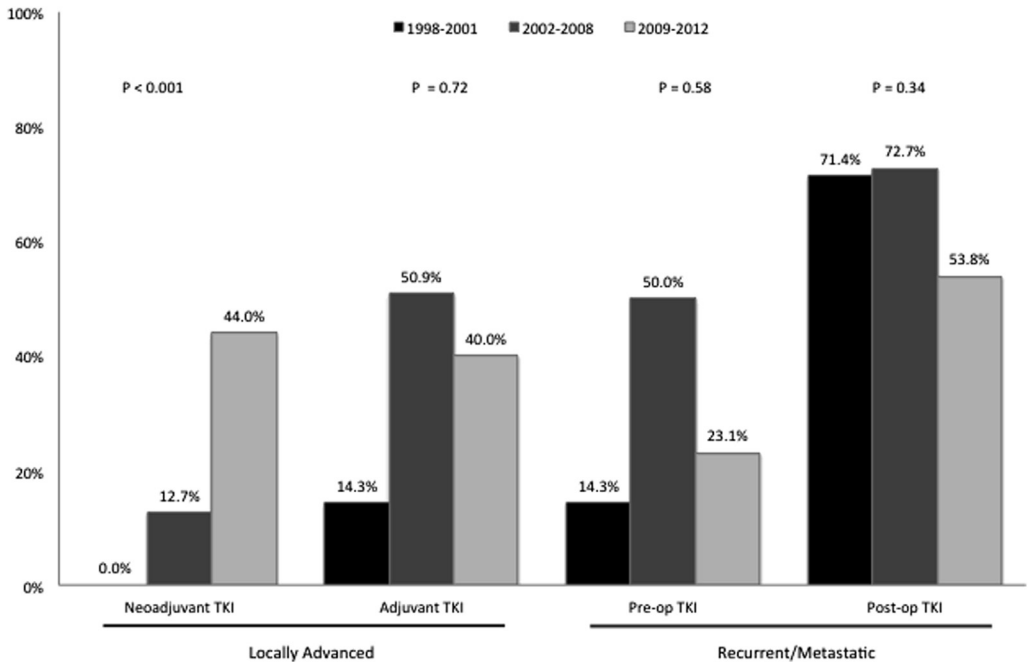

Figure 1. Proportion of patients with advanced gastrointestinal stromal tumors who received treatment with a neoadjuvant or adjuvant tyrosine kinase inhibitor stratified by year of diagnosis.

Table 3. Operative and Pathologic Details and Postoperative Tyrosine Kinase Inhibitor Therapy for Patients Undergoing Surgery for Advanced Gastrointestinal Stromal Tumors

	Locally advanced (n = 87)	**Recurrent/metastatic (n = 71)**
Multivisceral resection, n (%)	83 (95.4)	50 (70.4)
Organ resected,* n (%)		
Stomach	62 (71.3)	29 (40.9)
Spleen	32 (36.8)	14 (19.7)
Liver	13 (14.9)	39 (54.9)
Colon/rectum	20 (23.0)	23 (32.4)
Pancreas	38 (43.7)	10 (14.1)
Gallbladder	27 (31.0)	11 (15.5)
Small bowel	19 (21.8)	14 (19.7)
Duodenum	12 (13.8)	11 (15.5)
Esophagus	2 (2.3)	0 (0.0)
No. of organs resected, median (IQR)	3 (2−3)	2 (1−3)
EBL, mL, median (IQR)	500 (300−1,400)	525 (250−1,200)
Transfusion, n (%)	35 (40.2)	23 (32.4)
LOS, d, median (IQR)	9 (6−13)	7 (5−12)
Complication, n (%)		
Grade 1	7 (8.0)	2 (2.8)
Grade 2	25 (28.7)	24 (33.8)
Grade 3	6 (6.9)	9 (12.7)
Grade 4	3 (3.4)	6 (8.5)
Grade 5	1 (1.1)	0
Size of final path, cm, median (IQR)	11.0 (5.2−17.0)	9.1 (5.5−15.5)
Mitotic rate group (n = 117),† n (%)		
≤5/50 HPF	41 (51.3)	15 (40.5)
6−10/50 HPF	8 (10)	3 (8.1)
>10/50 HPF	31 (38.7)	19 (51.4)
R0 margin	76 (87.4)	49 (69.0)
Tumor rupture	2 (2.3)	5 (7.0)
KIT+	86 (98.9)	65 (91.5)
Exon mutation tested	17 (19.5)	11 (15.5)
No mutation	2 (11.8)	3 (27.3)
Exon 9	1 (5.9)	0 (0.0)
Exon 11	12 (70.6)	6 (54.5)
Exon 13	0	1 (9.1)
Exon 17	1 (5.9)	0 (0.0)
Exon 18 PDGFRA	1 (5.9)	1 (9.1)
Recurrence risk‡		
Very low	3 (3.5)	NA
Low	12 (14.0)	NA
Intermediate	13 (15.1)	NA
High	58 (67.4)	NA
Adjuvant TKI	39 (44.8)	49 (69.0)
Imatinib§	38 (97.4)	48 (98.0)
Sunatinib§	1 (2.6)	1 (2.0)
Duration of adjuvant therapy, mos, median (IQR)	12 (7−24)	12 (6−25)

*Total >100% due to multivisceral nature of the majority of resections.
†One hundred and seventeen patients had information available on the mitotic rate of the tumor: 80 of 87 of patients in the locally advanced group and 37 of 71 patients in the metastatic group.
‡Eighty-six of 87 patients had sufficient information available to calculate recurrence risk using the modified NIH criteria.
§Percentage calculated using patients who received postoperative tyrosine kinase inhibitor.
EBL, estimated blood loss; IQR, interquartile range; LOS, length of stay; PDGFRA, platelet-derived growth factor receptor−α; TKI, tyrosine kinase inhibitor.

patient (IQR 2 to 3) were resected. The most common organs resected were stomach (n = 62 [71.3%]), pancreas (n = 38 [43.7%]), spleen (n = 32 [36.8%]), colon/rectum (n = 20 [23.0%]), and small bowel (n = 19 [21.8%]). Median estimated blood loss was 500 mL (IQR 300 to 1,400 mL); 35 patients (40.2%) received a perioperative blood transfusion. Nine patients (10.3%) had a grade 3 or higher postoperative complication and there was 1 postoperative death (1.1%). Median length of stay was 9 days (IQR 6 to 13 days). On univariate analysis, receipt of neoadjuvant therapy was not associated with rate of postoperative complications or with number of organs resected (both $p > 0.05$).

The median tumor size on final pathology was 11.0 cm (IQR 5.2 to 17.0 cm) (Table 3). Forty-one patients (51.3%), 8 patients (10.0%), and 31 patients (38.7%) had tumors with mitotic rate ≤5 mitoses/50 high-powered field (HPF), 6 to 10 mitoses/50 HPF, and >10 mitoses/50 HPF, respectively. The majority of patients (n = 76 [87.4%]) underwent an R0 resection. Tumor rupture occurred in 2 patients (2.3%). All but 1 patient (n = 86 [98.9%]) were KIT positive. Among patients who underwent mutational analysis (n = 17 [19.5%]), the most common mutation identified was an exon 11 mutation (n = 12 [70.6%]). The recurrence risk using the modified NIH consensus criteria was very low for 3 patients (3.5%), low for 12 patients (14.0%), intermediate for 13 patients (15.1%), and high for 58 patients (67.4%).[16]

Thirty-nine patients (44.8%) received adjuvant therapy with a TKI for a median of 12 months (IQR 7 to 24 months) (Table 3). Thirty-eight of these patients (97.4%) received imatinib and 1 (2.6%) received sunitinib. The proportion of patients who received adjuvant therapy with a TKI did not change during the time period examined ($p = 0.72$, Fig. 1).

Median follow-up time was 41.2 and 30.0 months, calculated from the date of diagnosis and the date of surgery, respectively. Median RFS for patients with locally advanced GIST was 59.8 months (Fig. 2). Calculated from the date of surgery, the 1-, 3-, and 5-year RFS rates were 90.1%, 64.7%, and 49.9%, respectively. Of note, when RFS was calculated from date of diagnosis, it was the same for patients treated with neoadjuvant TKI vs patients who did not receive preoperative treatment ($p = 0.55$). On univariate analysis, factors associated with recurrence were tumor size (HR = 1.06; $p = 0.02$) and mitotic rate >10 mitoses/50 HPF (HR = 4.18; $p = 0.001$) (Table 4). On multivariate analysis, male sex (HR = 4.32; $p = 0.02$) and mitotic rate >10 mitoses/50 HPF (HR = 5.59; $p = 0.01$) were associated with increased risk of recurrence. Median OS was not reached and the 1-, 3-, and 5-year OS rates were 95.2%, 86.5%, and 71.0%, respectively (Fig. 2). There were no factors that were associated with OS on univariate or multivariate analysis (Table 4).

Twenty-five patients had recurrences after undergoing surgical resection of locally advanced GIST (local only, n = 9 [36.0%]; hepatic only, n = 6 [24.0%], peritoneal only, n = 1 [4.0%]; retroperitoneal only, n = 1 [4.0%]; chest wall only, n = 1 [4.0%]; and multiple sites, n = 7 [28.0%]). Five of these patients (20.0%) were on a TKI at the time of recurrence. The vast majority of recurrences were treated medically with a TKI (n = 22 [88.0%]); however, 8 patients (32.0%) underwent surgery to treat the recurrence.

Recurrent/metastatic gastrointestinal stromal tumors

During the study period, there were also 71 patients who underwent surgery for recurrent/metastatic GISTs (Table 1). Twenty-seven patients (38.0%) with recurrent/metastatic GISTs underwent preoperative therapy with a TKI for a median duration of 10 months (IQR 6 to 13 months) (Table 2). The proportion of patients who received preoperative therapy with a TKI did not significantly vary during the study period ($p = 0.58$, Fig. 1). Using Choi criteria, the majority of patients had a favorable response to preoperative therapy; 12 (42.9%) had a partial response, 7 (25.0%) had stable disease, and 5 (17.9%) had progressive disease. Fifty patients (70.4%) who underwent surgery for recurrent/metastatic GIST required a multivisceral resection (Table 3). Fifteen patients (21.1%) had a grade 3 or higher complication and there were no postoperative mortalities. Median length of stay was 7 days (IQR 5 to 12 days).

Among patients with recurrent/metastatic disease, the median size of the largest resected tumor on final pathology was 9.1 cm (IQR 5.5 to 15.5 cm) (Table 3). Data assessing the mitotic rate was available for 37 patients (52.1%), the majority of which had a mitotic rate >10 mitoses/HPF (n = 19 [51.4%]). Forty-nine patients (69.0%) underwent a R0 resection. Tumor rupture occurred in 5 patients (7.0%). The vast majority of patients (n = 65 [91.5%]) were KIT positive. Among those who underwent a full mutational analysis (n = 11 [15.5%]), the most common mutation identified was an exon 11 mutation (n = 6 [54.5%]). Forty-nine patients (69.0%) received adjuvant therapy with a TKI for a median of 12 months (IQR 6 to 25 months) (Table 3). Similar to patients with locally advanced disease, the proportion of patients who received adjuvant therapy with a TKI did not vary significantly over time ($p = 0.34$; Fig. 1).

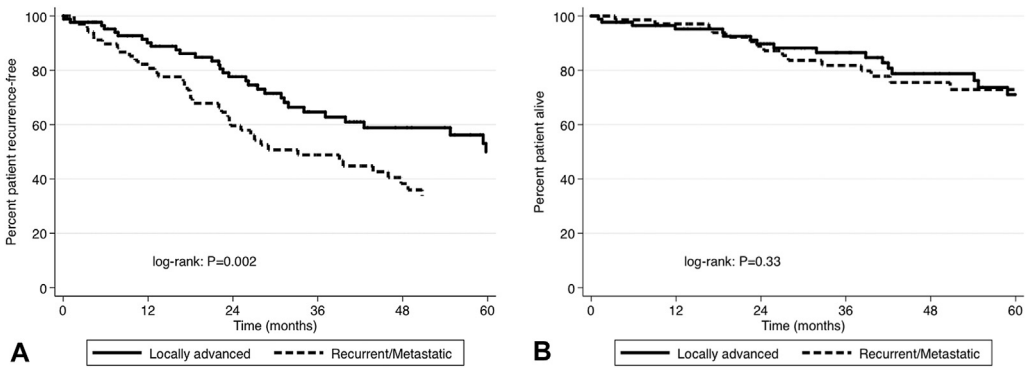

Figure 2. (A) Recurrence-free and (B) overall survival for patients after surgical therapy for advanced gastrointestinal stromal tumors.

Median follow-up time was 42.0 months and 25.6 months, calculated from the date of diagnosis and the date of surgery, respectively. Median RFS for patients with recurrent/metastatic GIST was 33.2 months (Fig. 2). When calculated from the date of surgery, the 1-, 3-, and 5-year RFS rates were 82.2%, 48.8%, and 33.7%, respectively. Of note, when RFS was calculated from date of diagnosis, it was the same for patients treated with preoperative TKI vs those patients who did not receive preoperative treatment ($p = 0.23$). On multivariate analysis, age (HR = 1.09; $p = 0.03$) and adjuvant therapy with a TKI (HR = 0.04; $p = 0.02$) were associated with recurrence. Median OS was 115.4 months and the 1-, 3-, and 5-year OS rates were 97.1%, 81.8%, and 72.9%, respectively (Fig. 2). Use of adjuvant TKI therapy was associated with OS on multivariate analysis (HR = 0.01; $p = 0.03$) (Table 5).

When analyses were limited to patients with recurrent/metastatic GIST who received preoperative TKI therapy, responsive or stable disease was found to be associated with improved RFS (HR = 3.90; $p = 0.03$) and OS (HR = 7.1; $p = 0.02$) (Fig. 3). Median RFS was 13.5 months for patients with progressive disease vs 71.9 months among patients with responsive or stable disease ($p < 0.01$). Similarly, median OS was 17.1 months for patients with progressive disease, and median OS was

Table 4. Univariate/Multivariate Analyses for Recurrence-Free and Overall Survival in Patients with Locally Advanced Gastrointestinal Stromal Tumors

	Recurrence-free survival						Overall survival					
	Univariate analysis			Multivariate analysis			Univariate analysis			Multivariate analysis		
	HR	95% CI	p Value	HR	95% CI	p Value	HR	95% CI	p Value	HR	95% CI	p Value
Age	1.02	1.00–1.05	0.08	1.02	0.98–1.07	0.31	1.03	0.99–1.07	0.12	1.03	0.97–1.09	0.30
Male sex	1.51	0.71–3.19	0.28	4.32	1.26–14.78	0.02	0.94	0.36–2.47	0.90	1.91	0.44–8.30	0.39
Site												
Stomach	Ref	—	—	Ref	—	—	Ref			Ref	—	—
Small bowel	1.59	0.64–3.98	0.32	2.46	0.69–8.70	0.16	1.10	0.31–3.87	0.88	2.64	0.54–12.98	0.23
Rectum	NA	—	—	NA	—	—	NA	—	—	NA	—	—
Others	0.42	0.10–1.76	0.23	0.83	0.13–5.22	0.84	0.45	0.06–3.42	0.44	1.51	0.10–22.37	0.76
Size at diagnosis	1.06	1.01–1.11	0.02	1.04	0.98–1.11	0.22	1.04	0.97–1.11	0.25	0.99	0.90–1.08	0.80
Mitotic rate group												
≤5/50 HPF	Ref	—	—	Ref	—	—	Ref	—	—	Ref	—	—
6–10/50 HPF	0.96	0.20–4.57	0.96	3.67	0.51–26.33	0.20	0.78	0.09–6.71	0.82	1.85	0.13–26.27	0.65
10+/50 HPF	4.18	1.82–9.59	0.001	5.59	1.65–18.95	0.01	2.65	0.91–7.77	0.08	2.70	0.57–12.75	0.21
Neoadjuvant TKI	0.73	0.25–2.09	0.55	0.58	0.13–2.65	0.48	0.82	0.18–3.65	0.79	1.25	0.13–12.50	0.85
R1 or R2 margin	1.56	0.64–3.82	0.33	1.94	0.64–5.93	0.24	0.96	0.22–4.23	0.96	1.39	0.27–7.19	0.70
Tumor rupture	1.96	0.47–8.22	0.36	5.19	0.66–40.76	0.12	1.67	0.22–12.64	0.62	3.55	0.19–67.09	0.40
Adjuvant TKI	0.89	0.45–1.79	0.75	0.33	0.09–1.27	0.11	0.46	0.16–1.30	0.14	0.28	0.05–1.67	0.16

HPF, high-powered field; HR, hazard ratio; NA, not applicable; TKI, tyrosine kinase inhibitor.

Table 5. Univariate/Multivariate Analyses for Recurrence-Free and Overall Survival in Patients with Recurrent/Metastatic Gastrointestinal Stromal Tumors

	Recurrence-free survival						Overall survival					
	Univariate analysis			Multivariate analysis			Univariate analysis			Multivariate analysis		
	HR	95% CI	p Value	HR	95% CI	p Value	HR	95% CI	p Value	HR	95% CI	p Value
Age	1.00	0.98–1.03	0.73	1.09	1.01–1.18	0.03	1.02	0.99–1.06	0.23	1.06	0.97–1.15	0.19
Male sex	1.16	0.65–2.08	0.61	0.53	0.07–3.80	0.53	1.67	0.71–3.91	0.24	5.00	0.13–194.47	0.39
Site												
Stomach	Ref	—	—	Ref	—	—	Ref	—	—	NA	—	—
Small bowel	0.68	0.29–1.60	0.38	0.60	0.07–4.96	0.64	1.11	0.37–3.29	0.87	NA	—	—
Rectum	1.44	0.48–4.31	0.51	0.23	0.00–15.09	0.49	2.11	0.44–10.06	0.35	NA	—	—
Others	1.76	0.90–3.44	0.10	0.48	0.05–4.98	0.54	0.86	0.30–2.43	0.78	NA	—	—
Size at diagnosis	1.01	0.96–1.05	0.79	0.98	0.81–1.18	0.84	1.07	1.01–1.14	0.03	0.87	0.65–1.16	0.34
Mitotic rate group												
≤5/50 HPF	Ref	—	—	Ref	—	—	Ref	—	—	Ref	—	—
6–10/50 HPF	NA	—	—	NA	—	—	NA	—	—	NA	—	—
10+/50 HPF	2.77	1.05–7.29	0.04	6.29	0.94–41.95	0.06	1.17	0.38–3.62	0.78	2.58	0.08–80.32	0.59
Neoadjuvant TKI	0.69	0.37–1.28	0.24	0.71	0.08–6.42	0.76	0.87	0.35–2.13	0.75	2.89	0.20–42.21	0.44
R1 or R2 margin	1.04	0.53–2.02	0.91	0.20	0.01–3.86	0.29	1.42	0.55–3.70	0.47	10.84	0.16–731.55	0.27
Tumor rupture	1.94	0.68–5.54	0.22	18.32	0.36–940.64	0.15	4.68	1.53–14.35	0.01	10.48	0.10–1131.43	0.33
Adjuvant TKI	0.84	0.44–1.60	0.59	0.04	0.003–0.62	0.02	0.50	0.21–1.20	0.12	0.01	0.00–0.62	0.03

HPF, high-powered field; HR, hazard ratio; NA, not applicable; TKI, tyrosine kinase inhibitor.

not reached in patients with responsive or stable disease ($p = 0.02$).

Forty-three patients had recurrences after undergoing surgical resection of recurrent/metastatic GIST. Fourteen of these patients (32.6%) were on a TKI at the time of recurrence. Recurrences were fairly evenly distributed: local only (n = 13 [30.2%]), hepatic only (n = 10 [23.3%]), peritoneal only (n = 8 [18.6%]), and multiple sites (n = 12 [27.9%]). Most recurrences were treated medically with a TKI (n = 36 [83.7%]), however, the majority of patients with recurrences were also treated with additional surgical therapy (n = 24 [55.8%]).

DISCUSSION

Although uncommon, GISTs are the most common mesenchymal tumor of the gastrointestinal tract. As such, surgeons need to be familiar with the management of not only early primary GIST, but also locally advanced and recurrent/metastatic disease. Surgical resection remains the cornerstone of treatment for primary GIST and also has an important role in the therapy of patients with more advanced disease. In addition, integration of surgery with systemic TKI therapy is critical to optimize the prognosis of patients with high-risk GIST. To date, most literature on the topic of patients with advanced GIST has included data from single-institutional series, which often suffer from small sample size and lack of generalizability. The current study is important because we used a broad, multi-institutional cohort of patients who underwent surgery for advanced GIST. Of note, preoperative TKI was administered to only 21% of patients with locally advanced GIST and 38% of patients with recurrent/metastatic GIST. Among all patients treated with a preoperative TKI, response was favorable, with 5% having a complete response, 49% a partial response, and 28% stable disease. Although most patients with advanced GIST required a multivisceral resection (84%), the perioperative morbidity (29%) and mortality (1%) were noted to be low. Prognosis after surgery for advanced GIST was also noted to be favorable, as 3-year survival rates among patients with locally advanced and recurrent/metastatic GIST were 87% and 82%, respectively. Similar to previously reported data on primary GIST, we noted that the factors most strongly associated with prognosis after surgical resection of advanced GIST included mitotic rate and treatment with adjuvant TKI.

Gastrointestinal stromal tumors can often present as large masses, which often displace and sometimes invade adjacent organ structures. In the current study, 87 patients had locally advanced GIST, defined as a primary tumor with multivisceral involvement on preoperative imaging or at the time of surgery. In general, neoadjuvant TKI is recommended for patients with locally advanced primary GIST when the tumor is deemed to be borderline resectable or when downstaging of the tumor might decrease surgical morbidity.[22] In the current study, only about 1 in 5 patients (21%) with locally advanced GIST underwent neoadjuvant

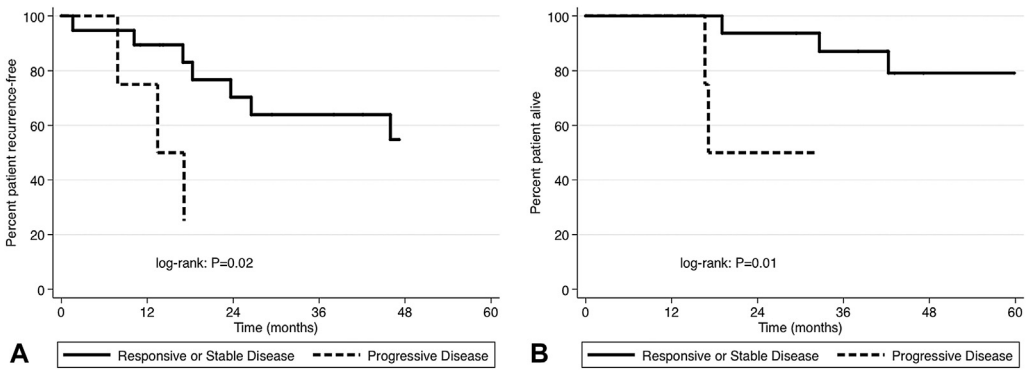

Figure 3. Recurrence-free and overall survival after surgery for patients with recurrent/metastatic gastrointestinal stromal tumors who received preoperative therapy with a tyrosine kinase inhibitor, stratified by radiographic response to the tyrosine kinase inhibitor.

therapy with imatinib. The reason for the relatively low use of neoadjuvant TKI is undoubtedly multifactorial. In large part, the underuse might be due to a "period" effect, as our study cohort included patients well before the TKI era (eg, circa 1998 to current). Of note, there was a trend observed toward increasing use of neoadjuvant TKI over time among patients with locally advanced GIST. Among those patients with locally advanced GIST who were treated with preoperative TKI, overall response was favorable. Previous investigators have noted that Response Evaluation in Solid Tumors (RECIST) criteria are not sensitive in assessing GIST response to TKI therapy, as TKI administration is often associated with decreased density of the tumor rather than changes in tumor size.[34] Choi and colleagues[31] proposed alternative criteria, which have been shown to correlate strongly with time to progression and disease-specific survival. In our cohort, all but 1 patient with locally advanced GIST who received neoadjuvant TKI (94%) had a complete/partial response or stable disease based on the Choi criteria. To date, no previous study has addressed whether administration of neoadjuvant imatinib in patients with resectable—albeit locally advanced—GIST confers a survival benefit. In the current study, we failed to find any difference in RFS when comparing patients who underwent surgery alone with patients who received neoadjuvant TKI plus surgery. Because only 1 patient had progressive disease on preoperative TKI, we were not able to assess for differences in RFS or OS comparing patients with responsive or stable disease vs those with progressive disease. These data suggest that although neoadjuvant TKI might be warranted to attempt downsizing of the tumor to facilitate resection, preoperative therapy might not be associated with an independent effect on long-term prognosis.

Treatment with a TKI is recommended as the primary therapy for all patients with metastatic GIST and surgery is generally used as an adjunct to TKI therapy in patients with stable disease.[7,17,22,27,28,35] Only 3% to 5% of patients with metastatic GIST experience a complete response after treatment with TKI therapy.[35] In fact, TKI treatment of recurrent/metastatic GIST generally results in response lasting for up to 36 months; however, TKI resistance subsequently develops in approximately 80% of patients.[36] As such, surgery has been proposed as a potential option for a subset of patients with metastatic GIST. We report on 71 patients who underwent surgical resection for recurrent/metastatic GISTs. We found that 3-year RFS and OS rates after resection were 49% and 82%, respectively. Similar long-term prognoses have been reported from past single-institution series, which noted 2-year progression-free survival after surgery for metastatic GIST to be 65% to 69%.[28,37] Factors associated with prognosis after resection of recurrent/metastatic GIST included mitotic rate, as well as receipt of adjuvant TKI therapy (Table 5). Other investigators have also noted response to preoperative TKI therapy as an important factor in long-term prognosis. In one study investigating surgical outcomes among patients with metastatic GIST, Raut and colleagues[27] reported that the 1-year progression-free survival was 80%, 33%, and 0% for patients with stable disease, limited progression, and generalized progression, respectively. Similarly, we found that patients with responsive or stable disease had significantly improved RFS and OS when compared with patients with progressive disease (Fig. 3). As such, patients with progressive metastatic disease likely derive minimal benefit from resection. Collectively, these data suggest that surgery for recurrent/metastatic disease is warranted, especially among those patients with a low-burden of disease who have demonstrated a response to preoperative TKI therapy.

Despite the relatively good long-term prognosis of patients with advanced GISTs, recurrence was fairly common. Specifically, the 3-year RFS rates among patients

with locally advanced and recurrent/metastatic disease were only 65% and 49%, respectively. Factors generally associated with an increased risk of recurrence included tumor size, high mitotic rate, male sex, as well as lack of adjuvant TKI (Tables 4 and 5). The risk factors for recurrence identified here are consistent with previously reported data.[8,17,35,38] Given the risk of recurrence among these high-risk patients, adjuvant TKI therapy might be warranted. Adjuvant therapy with imatinib for at least 3 years has been demonstrated to improve both RFS and OS among patients tumors >10 cm, a ruptured tumor, a tumor with >10 mitoses/50 HPF, as well as those patients with a tumor >5 cm that has >5 mitoses/50 HPF.[38] In our study, patients with both locally advanced and recurrent/metastatic GIST had low rates of adjuvant TKI treatment. Overall, although 82% of patients in our study were at high risk of recurrence according to modified NIH criteria or due to the fact they had recurrent/metastatic disease, only 56% of patients received adjuvant TKI therapy. In addition, no trend was seen over time for increased use of adjuvant TKI therapy. Similar to the low use of preoperative TKI therapy, part of the reason for the low use of adjuvant TKI was undoubtedly related to the fact that cohort included a number of patients treated a decade before the first trial supporting adjuvant imatinib was published.[8] Our finding that adjuvant TKI therapy was associated with improved long-term prognoses among patients with advanced GIST was consistent with prospective data noting the beneficial impact of adjuvant TKI therapy.[8,38] Together, current data support the routine use of adjuvant TKI therapy after surgical resection of all patients with high-risk GIST.

The current study had several limitations. Despite being one of largest series of advanced GIST patients to be reported in the literature, the current study still had a relatively small sample size. Collaborating with multiple institutions limited the ability to easily standardize all diagnostic and treatment criteria, although the multi-institutional study design did offer the benefits of higher statistical power and generalizability of the results. In addition, as with all other published studies on this topic, the study was retrospective in nature, which might have resulted in some limitations with regard to data selection, as well as selection bias for receipt of surgery. In turn, the data might not be representative of all patients with advanced GIST.

CONCLUSIONS

Resection of advanced GIST can be performed safely with high rates of R0 resection and low rates of tumor rupture. Patients with recurrent/metastatic GIST with responsive or stable disease on preoperative TKI therapy experienced improved RFS and OS when compared with patients with progressive disease. Predictors of recurrence among patients with locally advanced GIST after surgery were tumor size, high mitotic rate, and male sex. Risk factors for recurrence among patients with recurrent/metastatic GIST were high mitotic rate, age, and lack of postoperative therapy with a TKI. Tyrosine kinase inhibitor therapy was underused for both patients with locally advanced GIST in the adjuvant setting and patients with recurrent/metastatic GISTs. The barriers to use of TKI therapy in this population should be explored.

Author Contributions

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Final approval: Bischof, Kim, Blazer, Behman, Karanicolas, Law, Quereshy, Maithel, Gamblin, Bauer, Pawlik

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