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Identification of Preoperative Factors Associated with Outcomes Following Surgical Management of Intra-abdominal Recurrent or Metastatic GIST Following Neoadjuvant Tyrosine Kinase Inhibitor Therapy

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Abstract

Background—The role of surgical resection in the treatment of patients with metastatic/recurrent gastrointestinal stromal tumors (GIST) is unclear. The aim of this study was to identify preoperative factors associated with oncologic outcomes for recurrent/metastatic GIST after tyrosine kinase inhibitor (TKI) therapy.

Methods—We identified 107 patients with metastatic or recurrent GIST treated with TKIs and surgical resection (2002–2012). Patients that underwent palliative or incomplete resection were excluded. Complete resection was achieved in 87 patients which comprise the analytic cohort. Univariate and multivariate analyses were conducted to identify risk factors for GIST-specific survival (DSS) and time-to-recurrence (TTR).

Results—At a median follow-up of 51 months (91 months for survivors), median DSS was 74 months and TTR was 21 months. By univariate analysis, unifocal disease, duration of TKI < 365 days, and no evidence of radiographic progression were associated with improved TTR and DSS. Multivariate Cox regression demonstrated that evidence of radiographic progression was associated with shorter DSS (HR 2.53, 95% CI=1.27–5.06, P=0.008) and increased risk of recurrence (HR 3.33, 95% CI=1.91–5.82, P<0.001).

Conclusions—Patients with unifocal disease and radiographic evidence of response to TKI therapy may achieve improved oncologic outcomes when complete surgical resection is achieved following treatment with TKI.

Keywords

gastrointestinal stromal tumors; imatinib; protein kinase inhibitors; surgery

Introduction

Prior to the discovery of the c-kit driver mutation in gastrointestinal stromal tumors (GISTs) and the development of imatinib, the outcomes for patients with advanced GIST were poor, with a median survival of 19 months [1, 2]. Current level 1 data demonstrates the survival benefit of 3-years of adjuvant imatinib in patients with localized GIST following complete surgical resection [3]. However, complete pathological response to TKI therapy is rare [4], which has led to the consideration for incorporation of surgical resection in the multidisciplinary treatment of selected patients with advanced or metastatic GIST following TKI therapy. However, the benefit of surgical resection in these patients with intra-abdominal metastatic/recurrent GIST following tyrosine kinase inhibitor (TKI) therapy remains unclear and randomized control trials to answer this question have been unsuccessful due to early closure for poor accrual [5]. Over the last 15 years, a number of retrospective studies have evaluated the role of surgery in the multidisciplinary management of patients with metastatic GIST and identified prognostic factors associated with survival [4, 6–19]. In these reports, patients with progressive disease on TKI therapy did poorly. Interpretation of the outcomes of these studies is challenging because the majority of the studies included patients that underwent not only R0 or R1 resection, but also those patients who treated with palliative resection (R2 resection – not all gross disease resected) [6–14, 16–18]. In addition, the majority of studies examined both preoperative and postoperative factors associated with outcomes, making it difficult to identify which patients benefited most from surgical resection. The aim of this study was to identify preoperative factors in patients that underwent macroscopically complete surgical resection (R0/R1) of metastatic or recurrent GIST that were associated with poor oncologic outcomes, with the goal of identifying which patients were unlikely to benefit from the inclusion of surgical resection in their multidisciplinary treatment plan.

Patients & Methods

With the approval of the Institutional Review Board of The University of Texas MD Anderson Cancer Center (UTMDACC), we identified all patients that underwent surgical resection following tyrosine kinase inhibitor therapy with metastatic (n=97) or recurrent (10) GIST from 2002–2012. The diagnosis of GIST was confirmed by a UTMDACC sarcoma pathologist and in the context of multidisciplinary tumor board review. Patients that underwent resection with palliative intent (n=17) or treated with TKI for < 30 days (n=3) were excluded. Complete macroscopic resection was achieved in 87 patients and were included in the analytic cohort. A clinical database was constructed including patient, tumor, treatment, and outcome data. Clinicopathologic variables included: age at diagnosis, initial presentation (primary/metastatic; primary tumor location), duration of TKI therapy prior to surgery, overall duration of TKI therapy, radiographic response to TKI therapy (*patients were classified as having progression when either a new lesion occurred or an increase in size was observed. This includes patients with less than 20% increase in size as per RECIST*), and disease extent at the time of surgery (which was defined using two parameters: focality and number of sites). Focality was defined as the number of tumors within the same organ/cavity (i.e. number of nodules in the peritoneum or liver). Number of

sites is defined as single site (i.e. peritoneum only) vs. multisite (i.e. liver & peritoneum, etc). A subset of patients (n= 15) underwent surgical resection of metastatic disease and had residual “treated” liver metastases that remained in situ, as evidenced by cystic change with a presumed complete radiographic response and considered controlled at the time of surgery with no further intervention planned.

Statistical methods

For overall survival, an event was defined as the time from surgical resection to death due to any cause. For GIST-specific survival, an event was defined as (A) the time from surgical resection to death due to GIST & (B) the time from TKI initiation to death due to GIST. For time to recurrence, the time from surgical resection to recurrence (local or distant - which ever came first) was defined as an event. Univariate survival estimates for overall survival, GIST-specific survival and time to recurrence were calculated using Kaplan-Meier curves and significance was assessed using the log-rank test. Three percent of patients in the study died during follow-up from non-GIST related causes. Therefore, a multivariable competing risk regression analysis was used to determine the subdistribution hazard ratios (HRs). Factors included in the multivariate model include were those felt to be of clinical (age) and statistical importance ($p < 0.1$ by univariate analysis). Death due to causes other than GIST were taken into account as competing events in all analyses except for overall survival.

Results

One-hundred seven patients with metastatic/recurrent GIST who were treated with TKIs and surgical resection were identified. Of these, 17 patients underwent palliative resection only and 3 patients were treated with TKI for less than 30 days and were excluded. Complete macroscopic resection was achieved in 87 patients which comprise the analytic cohort for this study (Table 1).

The median age at the time of initial diagnosis was 55 years and 54% were male. Primary tumors were most often located in the stomach (n=33, 38%) or small bowel (n=28, 32%). At the time of initial diagnosis, 53 patients (61%) had localized disease. Prior to presentation to our institution, 19 of these patients had the primary tumor resected at the time of initial diagnosis and had metastatic disease left *in situ*. Overall, 34 patients (39%) had metastatic disease at the time of initial diagnosis, while 43 (50%) developed metachronous metastatic disease at a median of 36 months following primary resection. 10 patients developed a local recurrence at a median of 37 months.

Clinicopathologic characteristics at the time of surgical resection for recurrent or metastatic intra-abdominal GIST

Prior to surgical resection of recurrent or metastatic disease, the median duration of neoadjuvant TKI was 667 days. All patients except one were treated with imatinib preoperatively. Twenty-five patients (29%) were switched to another TKI due to progression prior to surgery. Ninety-one percent (n=79) of patients continued TKI therapy after surgery. 44 patients (51%) had a single site of disease and 49% of patients had multisite disease (Table 1) and the majority of patients had multifocal disease (n=63, 72%). Radiographically,

22 patients (25%) had evidence of tumor regression and 9 (10%) had stable disease/“no progression”. An additional 36 (41%) patients had evidence of regression followed by tumor progression prior to surgical resection and 20% of patients had progressive disease throughout treatment. These two groups were categorized as “any progression”.

Cancer-related outcomes

At a median follow-up of 51 months from surgical resection for recurrent or metastatic GIST (91 months for survivors), the median overall survival (OS) was 64.5 months (95% CI: 39.2–90.9) with a median time to recurrence of 21.3 months (95% CI: 12.7–29.2). Median disease-specific survival (DSS) was 73.5 months (95% CI: 39.9–97.7) from surgical resection. Median DSS from the time of initiation of TKI therapy was 119 months (95% CI: 72.2–142.4).

Univariate analyses for preoperative factors associated with TTR and GIST-specific survival from the time of surgery (Table 2) as well as GIST-specific survival from the time of TKI initiation (Supplementary Table 1) were performed. Unifocal/single site disease at time of resection, duration of TKI < 365 days, and no evidence of radiographic progression were associated with improved TTR and DSS. Fifty-three percent (n=46) of patients had mutation status available. We did not find an association between mutational status and outcomes in this cohort (data not shown).

By multivariable analyses (Table 3, Figure 1, Supplementary Table 2), patients with evidence of radiographic tumor progression prior to surgical resection had a significantly worse GIST-specific survival (HR 2.53, 95% CI:1.27–5.06, P=0.008) and increased risk of recurrence (HR 3.33, 95% CI:1.91–5.82, P<0.001) compared to those with preoperative radiographic stable disease or regression. Patients with multifocal disease in a single or multiple cavities also decreased GIST-specific survival (HR 2.61, 95% CI:1.12–6.06, P=0.027) compared to patients with unifocal/single site disease (Figure 2).

Discussion

Outcomes for patients with metastatic GIST have improved dramatically since the discovery of the c-kit mutation and inclusion of TKI therapy. However, the role of surgical resection in the multidisciplinary treatment for patients with metastatic GIST remains unclear. In the current study, we identified that preoperative radiographic progression of disease or multifocal disease extending beyond a single site was associated with worse prognosis following surgical resection for metastatic or recurrent GIST.

Since 2003, there have been numerous studies attempting to demonstrate an oncologic benefit associated with surgical resection in patients with metastatic GIST over TKI therapy alone. In 2009, EORTC attempted a phase III randomized study evaluating surgical resection of residual disease in patients with metastatic GIST responding to imatinib. Unfortunately, this study was terminated after accruing only 12 patients [20]. Recently, a phase III, randomized control trial comparing surgery for residual disease with imatinib treatment alone was attempted in China, but was closed early due to poor accrual [21]. The investigators reported the outcomes for 41 (of 210 planned) patients. Compared to imatinib

alone, patients that underwent surgical resection had an improved median overall survival (surgery-not reached vs. imatinib alone-49 months; $p=0.024$) and 2-year progression free-survival (surgery-88.4% - vs. imatinib alone-57.7%; $p=0.089$). Although these data are encouraging, it should be noted this trial included very strict inclusion criteria in that patients must have been treated with imatinib for 3–12 months and had either a complete response, partial response or stable disease. There were no patients included in this trial that had progressive disease on imatinib. In addition, none of the 41 patients enrolled had liver metastases. Though this trial is important for attempting to answer the question of whether incorporating metastatectomy in the treatment of patients with metastatic GIST is beneficial, like many clinical trials, this was a highly selected cohort. Many patients with metastatic or recurrent GIST would have been excluded from this trial, which mandates that clinicians extrapolate from these data and other data when making preoperative decisions. Park *et al* used propensity score matching to compare the clinical outcomes for patients ($n = 134$) from a single center of combining surgery with imatinib treatment to imatinib treatment alone in patients with recurrent or metastatic GIST who were initially responsive to imatinib [12]. Patients that underwent surgery in addition to imatinib treatment had significantly longer progression-free survival and overall survival compared to imatinib alone. The authors concluded that surgical resection of residual lesions is likely to be beneficial to patients with recurrent or metastatic GIST. Data such as these have led to the inclusion of surgery in the National Comprehensive Cancer Network guidelines as part of the treatment algorithm for patients with recurrent or metastatic GIST [22]. The guidelines suggest that patients with a favorable response or those with limited progression may be considered for surgical resection. Furthermore, future randomized trials are unlikely to be undertaken given the lack of clinical equipoise. Therefore, additional studies on existing data to determine which subset of patients with metastatic GIST are most likely to benefit are critical.

There is significant heterogeneity among patients with metastatic GIST and identifying preoperative factors associated with improved outcomes is challenging. To date, the inability to undergo a macroscopically complete resection or resection of only progressing tumors have been consistently shown to be associated with poor outcomes [4, 6, 7, 17, 18]. In the current study, only patients that successfully underwent macroscopically complete resection were included, which reflects our current clinical practice as <15% of patients that had surgery for metastatic GIST had palliative resections and were excluded from analysis.

Previous retrospective data of patients that have undergone surgery for metastatic GIST have demonstrated that patients with stable or responsive disease appear to benefit more than patients with progressive disease [7, 13, 14, 17]. However, these studies incorporated both preoperative and postoperative factors into the multivariate modeling. Preoperatively, when clinicians are attempting to decide which patients with metastatic GIST could potentially benefit from surgery, they are not able to accurately predict whether the patient will have a surgical complication or the mitotic rate of the residual disease. In the current study, evaluation of preoperative factors alone demonstrated that radiographic progression was associated with poor outcomes with a median time to recurrence of 7.8 months and median GIST-specific survival of 35 months after surgery. However, how the TTR and DSS in this group of patients compares to those treated with TKI alone is unknown. Data from the Phase II US-Finland B222 study which was the first phase II study to evaluate imatinib in patients

with metastatic GIST, sheds some light on this question.[23] At a median follow-up of 63 months, the median OS was 57 months with a median progression-free survival of 24 months. As expected, OS was related to response, in which patients with initial progression on imatinib had a median OS of 8 months compared to 63 months for patients that had a partial response, demonstrating the poor biology of patients that are unable to achieve a response with imatinib. In the current study, the median time from surgery to recurrence was 8 months for patients with progressive disease with an associated median survival of 35 months. Although patients in the current study that had surgery have better outcomes than this historical control, it should be noted that the patients in the current study represent a highly selected cohort of patients that had demonstrated a more favorable biology than most patients with metastatic GIST, making it difficult to compare. The data presented in this study suggest that although patients with progressive GIST may potentially benefit from surgical resection, the benefit is likely much smaller than for those with a response to TKI and the risks and potential morbidity of resection should be carefully weighed against the theoretic benefit before proceeding. Patients with unifocal disease fared far better than patients with multifocal disease, regardless of whether their disease was in a single cavity or in multiple sites. In addition, we found that the duration of TKI therapy was not associated with outcomes when controlling for other factors such as radiographic response and extent of disease.

These data should be evaluated in the context of their limitations. First, this was a small, non-randomized, retrospective cohort study of selected patients treated at a single institution. Despite this, we believe the data presented in this manuscript provides insight pertaining to an unanswered clinical decision-making dilemma. Inherent to the nature of retrospective studies, these data are subjective to selection bias and represent a highly selected cohort that cannot be generalized to all patients with metastatic GIST. However, the inclusion of only patients that had a macroscopically complete resection at a single institution brings uniformity in the pathologic review and treatment planning but is associated with selection bias.

Conclusions

In conclusion, our results have identified preoperative radiographic progression and multifocal disease as factors associated with poor prognosis in patients with completely resected metastatic or recurrent GIST. The management of patients with metastatic or recurrent GIST is complex and requires multidisciplinary treatment. Patients with unifocal/single site disease and radiographic evidence of tumor response to TKI therapy may achieve improved oncologic outcomes when complete surgical resection is possible following treatment with systemic TKI.

Supplementary Material

Refer to Web version on PubMed Central for supplementary material.

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Synopsis

The role of surgical resection in the multidisciplinary treatment of patients with intra-abdominal metastatic/recurrent gastrointestinal stromal tumors (GISTs) following tyrosine kinase inhibitor (TKI) therapy is unclear. The aim of this study was to identify preoperative factors that may be associated with oncologic outcomes following surgery for recurrent or metastatic GIST after TKI therapy. Patients with unifocal/single sites of disease and radiographic evidence of tumor response to TKI therapy may achieve improved oncologic outcomes when complete surgical resection is possible following treatment with systemic TKI.

Figure 1.
Adjusted Disease-Specific Survival Curves by (A) Radiographic Response and (B) Disease Extent.

Figure 2.
Adjusted Time to Recurrence Curves by (A) Radiographic Response and (B) Disease Extent

Table 1

Clinicopathologic characteristics of patients undergoing surgery for recurrent or metastatic GIST

Clinical factor	Total
N	87
Gender, n (%)	
Male	47 (54)
Female	40 (46)
Age, median (range), y	55 (22–75)
55, n (%)	43 (49)
>55, n (%)	44 (51)
Location, n (%)	
Stomach	33 (38)
Duodenum/Small Bowel	38 (43)
Colon/Rectum	10 (12)
Other	6 (7)
Stage at Initial Diagnosis, n (%)	
Localized	54 (62)
Metastatic	33 (38)
Disease State, n (%)	
Local Recurrence	10 (12)
Synchronous metastases, prior resection of primary	19 (22)
Synchronous metastases, simultaneous resection	15 (17)
Metachronous metastases	43 (49)
Extension of Disease, n (%)	
Single Site	44 (51)
<i>Peritoneum only</i>	19
<i>Liver only</i>	15
<i>Local</i>	10
Multiple sites	43 (49)
Primary & metastasis	13
<i>Liver</i>	8
<i>Peritoneum</i>	2
<i>Liver & Peritoneum</i>	3
Local Recurrence & Metastasis	7
<i>Liver</i>	4
<i>Peritoneum</i>	3
Liver & Peritoneum	19
Other	4
Disease Spread, n (%)	
Unifocal	24 (28)

Clinical factor	Total
Multifocal	63 (72)
Mutational status, n (%)	
Exon 11	22 (25)
Wild-type	8 (9)
Exon 2	6 (7)
Exon 9	4 (5)
Other	6 (7)
Unavailable	41 (47)
“Treated” Liver metastasis not resected, n (%)	
Yes	15 (17)
<i>Liver only</i>	<i>2</i>
<i>Liver & Peritoneum</i>	<i>8</i>
<i>Primary & Liver</i>	<i>5</i>
No	72 (83)
Duration of pre-operative TKI therapy	
Median, days (range)	667 (43 - 3257)
365 days	26 (30)
>365 days	61 (70)
Response to TKI therapy	
Stable	9 (10)
Progression only	17 (20)
Regression only	22 (25)
Regression & progression	36 (41)

Table 2

Univariate analysis of factors associated with Time to Recurrence and GIST-Specific Survival

	Time to Recurrence		GIST-Specific Survival- From time of surgery	
	Median Time to Recurrence; months (95% CI)	p-value	Median GIST-Specific Survival; months (95 % CI)	p-value
Gender				
Male	25.1 (12.7–33.7)	0.491	90.8 (39.9-NR)	0.162
Female	17.1 (7.8–30.8)		73.6 (34.5–90.9)	
Primary Tumor Location				
Stomach	18.2 (7.2–40.5)	0.152	82.9 (25.2-NR)	0.378
Small Bowel			59.6 (34.7–93.5)	
Colorectal	30.1 (5.07-NR)		NR	
Other	7.8 (3.83-NR)		38.9 (22.3-NR)	
Stage at Diagnosis				
Localized	23.7 (12.7–32.5)	0.723	88.6 (39.9–105.6)	0.854
Metastatic	17.9 (7.8–27.3)		48.8 (34.47-.)	
Disease spread				
Unifocal, single site	40.5 (17.3–90.5)	0.019	105.6 (90.8-NR)	0.021
All others	14.7 (7.8–23.7)		50.8 (34.6–82.9)	
Duration of pre-operative TKI				
365 days	33.7 (17.9–72.1)	0.028	NR	0.012
>365 days	14.2 (7.8–23.7)		59.6 (34.7–90.8)	
Radiographic Response to TKI				
No Progression	62.4 (28.6–136.7)	<0.001	NR	<0.001
Any Progression	7.8 (5.7–17.2)		34.7 (25.2–61.4)	
“Treated” liver metastases				
Yes	7.8 (4.1–17.9)	<0.001	48.8 (20.7–73.6)	0.037
No	25.1 (14.7–33.1)		90.8 (42.7–130.1)	

Table 3

Univariate analysis and Multivariate Competing Risk Regression evaluating preoperative factors associated with GIST-Specific Survival from TKI initiation

	Time to Recurrence		GIST-Specific Survival from time of surgery	
	HR (95% CI)	p-value	HR (95% CI)	p-value
Age (per 1-year increase)	1.01 (0.99–10.3)	0.305	1.34 (1.01–1.07)	0.007
Disease extent				
Unifocal, single site	1	0.055	1	0.027
All others	1.89 (0.99–3.63)		2.61 (1.12–6.06)	
Radiographic Response to TKI				
No Progression	1	<0.001	1	0.008
Any Progression	3.33 (1.91–5.82)		2.53 (1.27–5.06)	
TKI Time				
365 days	1		1	
>365	1.12 (0.63–1.99)	0.696	1.68 (0.75–3.79)	0.209
“Treated” Liver metastasis				
No	1	0.765	1	0.302
Yes	1.11 (0.55–2.23)		0.69 (0.33–1.4)	