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Cytoreductive Surgery for Metastatic Gastrointestinal Stromal Tumors Treated with Tyrosine Kinase Inhibitors: A Two Institutional Analysis

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Abstract

Objective: To refine treatment recommendations for patients with metastatic gastrointestinal stromal tumors (GISTs) treated with tyrosine kinase inhibitors (TKIs) and surgery.

Background: Early reports suggested that patients with metastatic GIST responding to TKIs treated with surgery may have favorable outcomes. However, identification of prognostic factors was limited by small cohorts.

Methods: Progression-free survival (PFS) and overall survival (OS) from time of surgery and from start of initial TKI was determined. Multivariate analysis was conducted on all patients undergoing GIST metastasectomy between 2001 and 2014 at two institutions.

Results: We performed 400 operations on 323 patients with metastatic GIST on TKIs. Radiographic response at time of surgery was classified as responsive disease (RD, n=64, 16%), stable disease (SD, n=100, 25%), unifocal progressive disease (UPD, n=132, 33%), and multifocal progressive disease (MPD, n=104, 26%). For patients on imatinib prior to surgery, radiographic response was predictive of PFS from time of surgery (RD 36 mo, SD 30 mo, UPD 11 mo, MPD 6 mo, $P<0.001$) and from imatinib initiation (RD 71 mo, SD 51 mo, UPD 47 mo, MPD 33 mo, $P<0.001$). Radiographic response was predictive of OS from time of surgery (RD not reached, SD 110 mo, UPD 59 mo, MPD 24 mo, $P<0.001$) and from imatinib initiation (RD not reached, SD

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Study description: Retrospective two institutional case series

144 months, UPD 105 mo, MPD 66 mo, $P=0.005$). Radiographic response was not predictive of PFS/OS for patients on sunitinib. Metastatic mitotic index 5/50 HPF, MPD, and R2 resection were prognostic of worse PFS/OS; primary mutation was not.

Conclusions: Surgery in metastatic GIST patients in the absence of MPD on imatinib is associated with outcomes at least comparable to second-line sunitinib and may be considered in select patients.

MINI-ABSTRACT

To our knowledge, we report the largest series of patients with metastatic gastrointestinal stromal tumors (GISTs) treated with tyrosine kinase inhibitor (TKI) therapy and cytoreductive surgery. Radiographic response to TKI therapy at the time of surgery, resection margins, and the metastatic mitotic index are significant independent predictors of outcomes.

INTRODUCTION

Gastrointestinal stromal tumors (GISTs) are rare tumors of mesenchymal origin arising from the visceral interstitial cells of Cajal. GIST is the most common sarcoma with 3,000–5,000 new cases per year in the United States. GISTs typically metastasize to the liver and peritoneum. Metastatic disease is present in up to 50% of patients at initial presentation, and nearly one-third of patients who undergo a macroscopically complete resection of a primary GIST will recur at 3 years in the absence of adjuvant therapy.

In 1998, Hirota and colleagues demonstrated that GISTs harbor gain-of-function mutations in the receptor tyrosine kinase encoded by the proto-oncogene *KIT*. Subsequently, several clinical trials demonstrated the efficacy of targeting the mutant KIT oncoprotein in patients with metastatic GIST with the tyrosine kinase inhibitor (TKI) imatinib mesylate (Gleevec, Novartis, Basel, Switzerland). Patients treated with imatinib experienced durable periods of disease control, with a median progression-free survival (PFS) of 2 years, and median overall survival (OS) of 5 years, compared to historical median OS of 9 months. Sunitinib malate (Sutent, Pfizer, New York, NY) and regorafenib (Stivarga, Bayer, Leverkusen, Germany) have since been approved as second- and third-line TKIs for metastatic GIST.

Despite its efficacy, fewer than 2% of patients with metastatic GIST treated with imatinib experience a pathologic complete response. Furthermore, response to imatinib and subsequent-line TKIs is limited by most patients developing drug resistance; median time to progression is 24 months for imatinib, 6.8 months for sunitinib, and 4.8 months for regorafenib.

Multiple American, European, and Asian retrospective studies (mostly single-institution) have demonstrated that cytoreductive surgery in patients with metastatic GIST is feasible, with greatest benefit in PFS and overall survival (OS) observed in patients with responsive, stable, or limited disease progression on TKI therapy. The goal of such cytoreductive surgery is to prolong the time the disease is controlled by each TKI and potentially, in select cases, offer a curative option. Unfortunately, phase III clinical trials designed to address this hypothesis closed early due to poor accrual. Lacking data from prospective trials, we

combined the experience from our two large sarcoma centers to identify additional potential prognostic factors and further refine guidelines for cytoreductive surgery in this rare disease.

METHODS

Patient Selection and Preoperative Management

Following Institutional Review Board approval at both institutions, records of all patients with metastatic GIST undergoing cytoreductive surgery at the Brigham and Women's Hospital/Dana-Farber Cancer Institute (BWH/DFCI) (Boston, MA) and Memorial Sloan Kettering Cancer Center (MSKCC) (New York, NY) were retrieved from each institution's prospective registries and retrospectively reviewed. Patients who had metastatic disease at presentation or recurrence after prior resection of primary GIST were included. All patients underwent evaluation by medical and surgical oncologists to determine if surgery or change in TKI therapy was appropriate. Pathologic diagnosis of GIST was confirmed with immunostaining for KIT (CD117) +/- DOG-1.

Based on analysis of serial preoperative imaging using either RECIST or, more recently, Choi criteria, radiographic response at time of surgery was categorized as responsive disease (RD), stable disease (SD), unifocal progressive disease (UPD, progression at single site of disease with all other sites responsive or stable), and multifocal progressive disease (MPD, progression at more than one site). Location of metastasis was defined as liver only, peritoneum only, both liver and peritoneum, or other location.

Conduct of Surgery and Postoperative Management

All operations were performed at either BWH/DFCI or MSKCC. All patients were on TKI therapy at time of surgery. TKIs were discontinued 1 to 14 days preoperatively depending on the type of TKI or protocol. The goal of resection was to remove all visible disease in patients with RD and SD and at minimum areas of progressive disease in patients with UPD or MPD, in addition to any remaining disease when feasible. Extent of resection was defined as macroscopically complete with a negative microscopic margin (R0), macroscopically complete with a positive microscopic margin (R1), or macroscopically incomplete (R2). Postoperative complications were categorized using the Clavien-Dindo classification system. Patients generally resumed the same TKI agent either upon discharge or after their first postoperative visit.

Pathology

Mutation analysis was performed on resected primary tumors or metastases as previously described. Testing was performed for mutation sites of KIT (exon 9, 11, 13, 14, and 17) and PDGFRA (exons 12 and 18). Primary mutations were included in the analysis; secondary mutations were not. The metastatic mitotic index was defined as the number of mitoses per 50 high power fields (HPF) in the resected metastatic specimen.

Statistical Analysis

PFS and OS were estimated by the Kaplan-Meier method. PFS was calculated from both date of metastasectomy and start date of TKI to date of documented radiographic disease

recurrence. OS was calculated from both date of metastasectomy and date of TKI initiation to date of death or last follow-up. Regional recurrence (RR) was defined as those occurring within the pelvis, peritoneum (excluding the liver), or retroperitoneum and distant metastasis (DM) was defined as those occurring outside these regions (ie. lung, liver, abdominal wall). The log-rank test was used to determine statistical differences in OS and PFS. Univariate and multivariate regression analysis was performed using a Cox proportional hazards model. Variables that were statistically significant on univariate analysis were included in the corresponding multivariate analyses. A *P* value of less than 0.05 was considered statistically significant, and statistical calculations and data analysis were performed using Stata version 11.2 software (College Station, Texas).

RESULTS

Between January 2001 and December 2014, 323 patients with metastatic GIST undergoing treatment with TKIs underwent 400 operations between our two centers. Clinicopathologic characteristics are detailed in Table 1. Median primary tumor size was 11 cm (range 2–55 cm) and median size of resected metastases was 9 cm (range 1–94 cm in aggregate). The most common primary tumor sites were small bowel (n=139, 43%) and stomach (n=131, 41%). Recurrences were identified in peritoneum alone (n=180, 45%), liver alone (n=94, 24%), or synchronously in the peritoneum and liver (n=110, 28%). TKI therapy at time of surgery was imatinib (n=234, 59%), sunitinib (n=93, 23%), or regorafenib or an alternative/clinical trial agent (n=73, 18%). Median time from start of TKI to surgery for the entire cohort was 20 mo (16 mo for imatinib, 25 mo for sunitinib).

Radiographic response at time of surgery was RD in 64 patients (16%), SD in 100 patients (25%), UPD in 132 patients (33%), and MPD in 104 patients (26%). Resections were macroscopically complete (R0/R1) in 275 patients (69%) and incomplete (R2) in 125 patients (31%). The primary mutational genotype of metastasis was available for 185 patients (46%) with exon 11 being the most common site of mutation, either in the form of a deletion (n=79, 43%) or point mutation (n=32, 17%). Median follow-up for the entire cohort was 33.6 mo (interquartile range, 9.5–45.9 mo) from the time of surgery and 69.0 mo (interquartile range, 41.6–104.4 mo) from start of TKI therapy.

Progression-Free Survival

Median PFS for the entire cohort was 11 mo from date of metastasectomy and 43 mo from start of initial TKI therapy. Radiographic response at time of surgery significantly influenced PFS, measured from date of metastasectomy: RD median 31 mo, SD 19 mo, UPD 10 mo, and MPD 5 mo ($P<0.001$) (Figure 1A). Not surprisingly, patients on imatinib at the time of metastasectomy had a significantly longer median PFS (from date of metastasectomy and start of TKI) compared to patients on sunitinib (from date of metastasectomy, 16 mo vs. 7 mo, $P<0.001$, Figure 1B; from start of TKI therapy, 47 mo vs. 40 mo, $P=0.001$, Supplemental Figure 1A). Amongst patients on imatinib at the time of metastasectomy (n=234), the influence of radiographic response on PFS remained significant when measured both from date of metastasectomy (RD median 36 mo, SD 30 mo, UPD 11 mo, MPD 6 mo, $P<0.001$, Figure 1C) and from start of imatinib (RD median 71 mo, SD 51 mo, UPD 47 mo,

MPD 33 mo, $P < 0.001$, Figure 1D). The radiographic response at time of surgery did not influence the median time to progression for patients on sunitinib (from date of metastasectomy, Figure 1E, $P = 0.093$; from start of sunitinib, $P = 0.12$, Figure 1F).

Overall Survival

The median OS for all patients was 81 months from time of metastasectomy and 124 months from start of initial TKI therapy. Radiographic response at the time of surgery was significantly associated with median OS measured from date of metastasectomy (RD not reached, SD 110 mo, UPD 54 mo, MPD 26 mo, $P < 0.001$, Figure 2A). As was the case with PFS, the type of TKI influenced median OS with patients on imatinib at time of surgery having a median OS of 105 mo and those on sunitinib 48 mo measured from date of metastasectomy (Figure 2B, $P = 0.001$) and 124 mo and 91 mo for patients on imatinib and sunitinib, respectively, measured from start of TKI therapy (Supplemental Figure 1B). For patients on imatinib at the time of metastasectomy, radiographic response again significantly influenced the median OS when measured from both date of metastasectomy (RD not reached, SD 110 mo, UPD 59 mo, MPD 24 mo, $P < 0.001$, Figure 2C) and from start of imatinib (RD not reached, SD 144 months, UPD 105 mo, MPD 66 months, $P = 0.005$, Figure 2D). Radiographic response did not correlate with median OS in patients on sunitinib (Figure 2E and F).

Prognostic Factors: PFS

On univariate analysis, duration of preoperative TKI use, radiographic response at time of metastasectomy, location of metastasis, metastatic mitotic index, extent of resection, and number of metastases were predictive of PFS both for the entire cohort and for patients undergoing surgery on imatinib (Supplemental Table 1 and 2). Pattern of recurrence was a significant prognostic factor of PFS for the entire cohort but not for the imatinib patient subset. Notably, primary mutation was not a significant prognostic factor for PFS in either the entire cohort or the imatinib subset. For patients on sunitinib, primary mutation was a significant prognostic factor for PFS, in addition to metastatic mitotic index and number of metastases (Supplemental Table 3).

On multivariate analysis for the entire cohort, MPD (hazard ratio (HR) 1.85, $P = 0.004$), metastatic mitotic index 5/50 HPF (HR 3.28, $P < 0.001$), and R2 resection (HR 1.85, $P = 0.006$) were independent prognosticators of worse PFS (Table 2). For the subset of patients on imatinib at the time of metastasectomy, the same three factors were independently prognostic of worse PFS: MPD (HR 3.08, $P = 0.001$), metastatic mitotic index 5/50 HPF (HR 2.55, $P = 0.003$), and R2 resection (HR 1.90, $P = 0.044$; Table 3). For patients on sunitinib at time of surgery, metastatic mitotic index 5/50 HPF (HR 10.74, $P = 0.029$) was the only independent factor associated with decreased PFS (Supplemental Table 4).

Prognostic Factors: OS

On univariate analysis of OS, radiographic response, metastatic mitotic index, and extent of resection were significant prognostic factors for both the entire cohort and patients using imatinib (Supplemental Table 1 and 2). Duration of preoperative TKI use was a significant prognostic factor for OS for imatinib patients but was not significant for the entire cohort.

Extent of resection was the only significant prognostic factor for OS for patients using sunitinib (Supplemental Table 3).

On multivariate analysis, MPD (HR 2.81, $P=0.003$), metastatic mitotic index $\geq 5/50$ HPF (HR 6.46, $P=0.001$), and R2 resection (HR 1.72, $P=0.039$) independently predicted worse OS (Table 2). Multifocal progressive disease (HR 5.84, $P=0.005$) and metastatic mitotic index $\geq 5/50$ HPF (HR 4.72, $P=0.022$) were associated with worse OS for patients on imatinib (Table 3). For patients on sunitinib, no variables were independently prognostic of OS (Supplemental Table 4).

Morbidity and Mortality

One-hundred and five patients developed 131 postoperative complications following 110/400 operations (28%). List of complications and management are detailed in Table 4. Significant grade III or higher complications were noted after 70 operations (18%). There were 7 perioperative deaths (1.8%), three secondary to multi-system organ failure, two from pneumonia, and two due to intra-abdominal hemorrhage.

DISCUSSION

To the best of our knowledge, this is the largest series of patients with metastatic GIST treated with TKI undergoing surgical resection. The goal of metastasectomy is to remove disease before secondary resistance develops and to stop disease progression by eliminating resistant clones. The critical question in considering metastasectomy for GIST is determining whether surgery (as the “adjuvant therapy”) provides any additional benefit over remaining on standard-of-care TKI therapy alone. Phase III trials designed to compare metastasectomy plus imatinib to remaining on imatinib alone were attempted, but were closed due to poor accrual. Limited data from one of the two trials have been reported. While only enrolling 41 of a planned 210 patients, Du et al. reported that the 2-year PFS was 88% for patients undergoing surgery while on imatinib compared to 58% for those on imatinib alone (no surgery) ($P=0.089$). There was a significant difference in median OS favoring patients undergoing surgery (not reached v. 49 months, $P=0.024$), though this was not a primary endpoint. While underpowered, this study did suggest a potential benefit for metastasectomy and highlighted the need for further investigation.

In the present study, patients with RD and SD treated with TKI therapy and metastasectomy showed significantly prolonged PFS and OS compared to those with progressive disease. Amongst patients with progressive disease, those patients with UPD were found to have a significantly longer PFS compared to patients with MPD. While a median PFS of 11 months from date of surgery for the highly selected subset of patients with UPD on imatinib undergoing surgery is less than ideal, it is important to note that these patients would otherwise change to second-line sunitinib, with a median time to progression of 6.8 months (all patients). Our results indicate that metastasectomy should be considered in patients on imatinib with RD (median PFS 71 mo and median OS not reached but >12 yrs from start of imatinib) and SD (median PFS 51 mo and median OS 144 mo from start of imatinib) while the disease is under control and may also be beneficial for those with UPD to delay switching to sunitinib, reflecting our current practice. Due to probable selection bias, it is

difficult to determine which patients on sunitinib will benefit from metastasectomy. Outcomes for patients with MPD are worse, and these individuals are unlikely to benefit from metastasectomy in terms of prolonged PFS or OS.

Bauer et al. reported results from a 2014 multi-institutional study supporting resection in patients with RD or SD only when a macroscopically complete (R0/R1) resection can be achieved. Although we also found that R2 resection predicts worse outcome, this variable is complex. There may be a difference in the outcome in leaving behind stable bilobar liver disease versus leaving behind an unresectable progressing metastasis, although both are R2 resections. The primary goal of metastasectomy should be to remove all progressing disease and, when feasible, non-progressing macroscopic disease.

The metastatic mitotic index also predicted worse PFS and OS for the entire cohort and for imatinib patients and worse PFS for patients on sunitinib. Mitotic index is a marker of tumor biology and reflects disease aggressiveness. While the mitotic count of the primary tumor is included as a significant prognostic factor in multiple risk stratification systems and nomograms predicting risk of recurrence following primary resection, the mitotic count of metastatic disease has not been previously identified as an independent prognostic factor for patients with metastatic disease.

Consistent with previous reports, primary mutation was not a significant prognostic factor. Mutations involving KIT exon 11 have been associated with a higher rate of disease recurrence and worse prognosis in patients with primary GIST.⁷ With mutation data available on approximately half of patients (n=185, 46%), the majority of our patients had exon 11 mutations (n=111, 60%). Only 28 patients had an exon 9 mutation, 12 had PDGFRA mutations and 29 patients were wild-type tumors, making it difficult to draw definitive conclusions for patients with these metastatic genotypes.

Postoperative complications of any grade were observed following less than one-third of operations in our study. Previous studies have reported complication rates ranging from <10% up to 58%, with majority of complications being either grade 1 or 2.¹¹ Seven perioperative deaths were observed that occurred in the setting of multi-system organ failure (3 patients), pneumonia (2 patients) and intra-abdominal hemorrhage (2 patients). Major complications (grade III or higher) were observed following 70 operations (18%). Metastasectomy for GIST has an inherent morbidity due to their typically large size and multi-organ involvement. Morbidity rates reported here, while significant, are similar to morbidity rates reported for retroperitoneal sarcomas.¹²

There are several points supporting the validity of our results. First, this represents a large series of consecutively managed patients. In addition, treatment and outcomes data reflect established procedures at two major sarcoma centers. Although not a randomized trial, this brings some degree of uniformity to important variables, such as histopathology review, radiographic evaluation, and decisions concerning timing of surgery or switch to new TKI treatment. Metastasectomy cannot be definitively proven to significantly improve outcomes due to the inherent selection bias in our study. Our data does facilitate the identification of patients who may potentially benefit from surgery. Additionally, while patients with MPD at

the time of surgery have worse outcomes, 10 patients (9.6%) underwent surgery in an urgent/emergent setting due to bleeding, perforation, or obstruction. Our study is also limited by lead-time bias, especially when comparing imatinib and sunitinib results.

In summary, our results demonstrate that radiographic response to TKI treatment and metastatic mitotic counts predict clinical outcome for patients undergoing surgery for metastatic GIST. The goal of resection for those patients undergoing metastasectomy is a macroscopically complete resection as a R2 resection is associated with worse outcomes. Patients with RD and SD treated with imatinib and metastasectomy have prolonged PFS and OS compared to historical metastatic GIST patients treated with imatinib alone. In addition, patients with UPD on imatinib may also benefit from metastasectomy by prolonging the time to progression and subsequent switch to an alternative TKI. Patients with MPD have worse outcomes and do not demonstrate benefit from metastasectomy. The median OS rates for patients with RD, SD, and UPD are promising; however, it is difficult to assess the direct impact of surgery due to additional treatments received during the course of the disease. Likewise, the benefit of metastasectomy for patients on sunitinib is difficult to assess due to bias in patient selection and patients must be selected carefully. Although ideal, recent experience shows that it is not feasible to conduct a randomized trial to confirm a benefit for surgery in patients with metastatic GIST.

Supplementary Material

Refer to Web version on PubMed Central for supplementary material.

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(A)

(B)

(C)

(D)

(E)

(F)

Figure 1.

Progression-free survival from date of metastasectomy by (A) radiographic response at time of surgery on any tyrosine kinase inhibitor (TKI) and (B) individual TKI at surgery, and radiographic response at surgery for patients on (C) imatinib. (D) Progression-free survival from date of TKI initiation by radiographic response at surgery for patients on imatinib. Progression-free survival by radiographic response at time of surgery for patients on sunitinib from (E) date of metastasectomy and from (F) date of TKI initiation.

(A)

(B)

(C)

(D)

(E)

(F)

Figure 2.

Overall survival from date of metastasectomy by (A) radiographic response at time of surgery on any tyrosine kinase inhibitor (TKI), (B) individual TKI at surgery, and radiographic response at surgery for patients on (C) imatinib. (D) Overall survival from date of TKI initiation by radiographic response at surgery for patients on imatinib. Overall survival by radiographic response at time of surgery for patients on sunitinib from (E) date of metastasectomy and from (F) date of TKI initiation.

Table 1.

Clinicopathologic characteristics for patients (n=323) with metastatic GIST treated with TKI followed by metastasectomy (n=400).

Clinicopathologic characteristics	Number of patients
Median tumor size, cm (range)	
Primary tumor	11 (2–55)
Metastatic disease *	9 (1–94)
Location of primary tumor (n=323)	
Gastric	131 (41%)
Small bowel	139 (43%)
Duodenum	14 (4%)
Other	39 (12%)
Location of metastasis	
Liver	94 (24%)
Peritoneum	180 (45%)
Both	110 (28%)
Other	16 (4%)
TKI at time of surgery	
Imatinib	234 (59%)
Sunitinib	93 (23%)
Other	73 (18%)
Median duration pre-op TKI, mos (IQR range)	
Overall	20 (8–39)
Imatinib	16 (7–36)
Sunitinib	25 (12–39)
Other	30 (13–54)
Radiographic response at time of surgery	
Responsive	64 (16%)
Stable	100 (25%)
Unifocal progression	132 (33%)
Multifocal progression	104 (26%)
Margin of resection	
R0	134 (34%)
R1	141 (35%)
R2	125 (31%)
Primary genotype of metastasis [#]	
<i>KIT</i> exon 11 deletion	79 (43%)
<i>KIT</i> exon 11 point mutation	32 (17%)
<i>KIT</i> exon 9	28 (15%)
<i>KIT</i> exon 17	19 (10%)
<i>KIT</i> exon 14	2 (1%)
PDGFRA	12 (6%)

Clinicopathologic characteristics	Number of patients
Wild-type	29 (16%)

Abbreviations: TKI, tyrosine kinase inhibitor; IQR, interquartile range.

* Aggregate size of metastatic lesions resected

Available for 185 patients (46%)

Table 2.

Multivariate analysis of treatment and tumor variables on progression-free survival and overall survival for all patients with gastrointestinal stromal tumor treated with TKI at time of metastasectomy (n = 400).

Variables	Progression-free survival		Overall survival	
	Hazard Ratio (CI)	P-value	Hazard Ratio (CI)	P-value
Duration of preoperative TKI			-	-
24 mo	Ref	-		
>24 mo	0.84 (0.63 – 1.11)	0.225		
Radiographic response				
Stable	Ref	-	Ref	-
Responsive	0.54 (0.30 – 0.95)	0.034	1.30 (0.55 – 3.12)	0.550
Unifocal progression	1.12 (0.75 – 1.67)	0.593	1.47 (0.74 – 2.92)	0.265
Multifocal progression	1.85 (1.21 – 2.81)	0.004	2.81 (1.43 – 5.50)	0.003
Location of disease			-	-
Liver only	Ref	-		
Peritoneum only	0.97 (0.61 – 1.54)	0.886		
Both	1.15 (0.71 – 1.85)	0.575		
Other	1.36 (0.61 – 3.03)	0.454		
Metastatic mitotic index				
<5/50 HPF	Ref	-	Ref	-
5/50 HPF	3.28 (1.90 – 5.67)	<0.001	6.46 (2.22 – 18.77)	0.001
Extent of resection				
R0	Ref	-	Ref	-
R1	1.04 (0.68 – 1.57)	0.869	0.54 (0.30 – 0.96)	0.035
R2	1.85 (1.19 – 2.87)	0.006	1.72 (1.03 – 2.87)	0.039
Number of metastases			-	-
5	Ref	-		
>5	1.25 (0.92 – 1.71)	0.155		
Recurrence pattern			-	-
Local	Ref	-		
Distant	1.18 (0.75 – 1.85)	0.470		
Local and distant	1.11 (0.72 – 1.72)	0.637		

Abbreviations: CI, 95% confidence interval; TKI, tyrosine kinase inhibitor; Ref, reference; HPF, high-power field.

Table 3.

Multivariate analysis of treatment and tumor variables on progression-free survival and overall survival for all patients with gastrointestinal stromal tumor treated with imatinib at time of metastasectomy (n = 234).

Variables	Progression-free survival		Overall survival	
	Hazard Ratio (CI)	P-value	Hazard Ratio (CI)	P-value
Duration of preoperative TKI			-	-
24 mo	Ref	-	Ref	-
>24 mo	0.89 (0.59 – 1.36)	0.599	1.31 (0.69 – 2.47)	0.410
Radiographic response				
Stable	Ref	-	Ref	-
Responsive	0.74 (0.37 – 1.47)	0.388	1.46 (0.38 – 5.61)	0.581
Unifocal progression	1.73 (0.91 – 3.29)	0.092	2.62 (0.81 – 8.46)	0.107
Multifocal progression	3.08 (1.54 – 6.16)	0.001	5.84 (1.68 – 20.32)	0.005
Location of disease			-	-
LoLiver only	Ref	-		
Peritoneum only	0.83 (0.48 – 1.43)	0.502		
Both	0.90 (0.47 – 1.72)	0.748		
Other	1.45 (0.57 – 3.70)	0.433		
Metastatic mitotic index				
<5/50 HPF	Ref	-	Ref	-
5/50 HPF	2.55 (1.37 – 4.76)	0.003	4.72 (1.25 – 17.84)	0.022
Extent of resection				
R0	Ref	-	Ref	-
R1	1.23 (0.74 – 2.04)	0.427	0.45 (0.19 – 1.02)	0.056
R2	1.90 (1.02 – 3.54)	0.044	1.44 (0.71 – 2.94)	0.312
Number of metastases			-	-
5	Ref	-		
>5	1.34 (0.83 – 2.15)	0.232		

Abbreviations: CI, 95% confidence interval; TKI, tyrosine kinase inhibitor; Ref, reference; HPF, high-power field

TABLE 4.

Types and management of 131 complication following 110/400 operations (28%).

Complication	n
Abscess	
Antibiotics treatment (II)	2
IR or operative intervention (III)	31
Bleeding (non-gastrointestinal)	
Transfusion (II)	3
IR or operative intervention (III)	3
ICU admission (IV)	7
Death (V)	2
Gastrointestinal bleed	
Endoscopic intervention (III)	1
ICU admission (IV)	2
Wound infection	
Bedside wound care (I)	5
Antibiotic treatment (II)	17
IR or operative intervention (III)	2
Ileus/bowel obstruction	
No intervention (I)	3
Total parental nutrition (II)	11
DVT/PE	
Systemic anticoagulation (II)	9
Pleural effusion	
IR or operative intervention (III)	9
ICU admission (IV)	1
Anastomotic leak	
Operative intervention (III)	2
Multi-system organ failure	
Death (V)	3
Pneumonia	
Antibiotic treatment (II)	2
Death (V)	2
Other	
No intervention (I)	1
Medical management(II)	8
IR or operative intervention (III)	5

Abbreviations: IR, interventional radiology; ICU, intensive care unit; DVT, deep venous thrombosis; PE, pulmonary embolus.