Journal of Gastrointestinal Cancer (2019) 50:750–758
https://doi.org/10.1007/s12029-018-0137-9

ORIGINAL RESEARCH

Outcomes After Surgical Resection Differ by Primary Tumor Location for Metastatic Gastrointestinal Stromal Tumors (GISTs): a Propensity Score Matching Population Study

Apostolos Gaitanidis[1] · Michail Alevizakos[2] · Alexandra Tsaroucha[1] · Michail Pitiakoudis[1]

Published online: 23 July 2018

Abstract

Purpose Primary tumor location has been identified as an important prognostic factor among patients with gastrointestinal stromal tumors (GISTs). The purpose of this study is to identify how primary tumor location may affect outcomes after resection for patients with metastatic GISTs.

Methods Patients with GISTs and distant metastases at diagnosis were identified in the Surveillance Epidemiology and End Results (SEER) database. Patients that underwent surgery were matched to patients that did not undergo surgery using propensity score matching (PSM) analysis.

Results After PSM, 570 patients were identified (males 334 [58.6%], females 236 [41.4%], age 62 ± 13.9 years). Gastric tumors constituted the majority (325 [57%]), followed by small intestinal (136 [23.9%]), colorectal (19 [3.3%]), and retroperitoneal/peritoneal tumors (23 [4%]). Median follow-up was 25.5 months (95% CI 23–29 months). Undergoing surgery was associated with improved disease-specific survival (DSS) on both univariate (median not reached vs. 51 months, $p < 0.001$) and multivariate analyses (HR 4.98, 95% CI 2.23–11.12, $p < 0.001$). A sub-analysis of patients with gastric GISTs showed that undergoing surgery was the only significant factor associated with improved DSS (median not reached vs. 39 months, $p < 0.001$, HR 2.95, 95% CI 1.92–4.53). In contrast, undergoing surgery was not associated with improved survival for small intestinal, colorectal, or retroperitoneal/peritoneal tumors.

Conclusions Surgery for gastric metastatic GISTs is associated with improved survival. No discernible benefit after surgical resection was identified for patients with small intestinal, colorectal, retroperitoneal, or peritoneal metastatic GISTs.

Keywords Gastrointestinal stromal tumors · GIST · Sarcoma · Metastases

Introduction

Gastrointestinal stromal tumors (GISTs) are the most frequent digestive tumors of mesenchymal origin, with an estimated incidence of 7.8 cases per million persons per year [1]. The most common location for these tumors is the stomach (40–51%), followed by the small intestine (20–40%), while men are affected more often than women [2, 3]. Metastatic disease at the time of diagnosis is quite common and is found in 15–50% of patients with GISTs [3, 4]. Major advances have been recorded during the past decades in unraveling the pathogenesis of these tumors and several associated sporadic and germline mutations have been described. The most frequent sporadic mutation is a gain-of-function mutation in *c-KIT*, which is found in 70–80% of all GISTs and may be detected in tissue samples through immunohistochemistry for CD117 [5, 6]. Mutations in the *PDGFRA* gene, which encodes for the platelet-derived growth factor receptor A, are the second most common sporadic mutations and are encountered in 30–40% of patients with *KIT*-negative GISTs [5, 7].

Recommendations for surgical management suggest the resection of primary tumors > 2 cm, due to an elevated risk of malignancy, but the risk of recurrence after surgical resection is 40–50% [8, 9]. Imatinib mesylate, a tyrosine kinase

✉ Apostolos Gaitanidis
agaitanidis@gmail.com

[1] Second Department of Surgery, University General Hospital of Alexandroupoli, Democritus University of Thrace Medical School, 68100 Alexandroupoli, Greece

[2] Department of Medicine, University of Pittsburgh Medical Center, Pittsburgh, PA, USA

inhibitor (TKI), was granted approval by the United States Food and Drug Administration (FDA) for metastatic or unresectable GISTs in 2001 [10]. This drug inhibits signaling through the pathways involving the proteins coded by the *c-KIT* and *PDGFRA* genes and when given in an adjuvant fashion may prolong the recurrence-free and overall survival of patients with GISTs [11–13]. These advances in targeted treatments have placed surgical treatment of patients with advanced disease into question. However, several retrospective series have suggested that surgical treatment may still hold a therapeutic role in the era of TKIs, although not all patients benefit from it and hence careful selection of patients for surgical treatment (e.g., stable disease or limited progression, imatinib-responsive disease) is mandatory [14–22]. Based on these findings, National Comprehensive Cancer Network (NCCN) and European Society for Medical Oncology (ESMO) guidelines currently recommend surgical resection for imatinib-responsive cases where complete resection may be achieved or imatinib-refractory disease with limited progression [23, 24].

Primary tumor location has previously been identified as an important prognostic factor and nongastric GISTs tend to be associated with higher rates of recurrence after resection, as well as more aggressive overall clinical course [25–29]. The purpose of this study is to examine whether primary tumor location may impact survival after resection for patients with metastatic GISTs and thus contribute towards improved patient selection for surgery.

Methods

A retrospective search of the Surveillance Epidemiology and End Results (SEER) database was performed for cases diagnosed during years 2004–2013. The SEER database collects data on multiple clinical and pathologic aspects associated with cancer management and encompasses approximately 28% of the US population [30]. GISTs were identified based on the ICD-O-3 code 8936. Distant metastases at diagnosis were identified based on the variable "CS mets at dx (2004+)" and codes 40, 45, 50, and 60. No included patient had metachronous metastatic disease. Cases without microscopic diagnosis, unavailable survival information, or unavailable information regarding surgical management were excluded. Surgery refers to at least primary tumor resection with curative intent, while information regarding resection of distant sites was not available for the majority of patients. AJCC T stages were coded based on the seventh edition system. N stage was derived from variables "SEER historic stage A," "Regional nodes positive (1988+)," and AJCC stage. The study was exempted from Institutional Review Board approval, due to SEER's inclusion of unidentifiable patient information.

Statistical Analysis

Propensity score matching (PSM) was employed to limit confounders between patients that underwent curative surgery and those that did not in order to allow their comparison. Propensity scores were calculated using a logistic regression model after consideration of all clinically relevant parameters (age, sex, race, primary tumor location, tumor grade, mitotic count, AJCC T and N stages). Initial comparison between patients undergoing and those not undergoing curative surgery was performed with Pearson's correlation coefficient and all significant variables were included in the logistic regression model. Cases were matched with a 1:1 ratio using the nearest-neighbor method.

Survival univariate analysis with the log-rank test and multivariate analysis using Cox proportional hazards model were performed. The primary end-points were disease-specific survival (DSS) and overall survival (OS). Cases with missing values were excluded from multivariate analysis. Only variables significant on univariate analysis were included in multivariate analysis. Statistical tests employed two-tailed p values and 0.05 was used as a threshold for significance. All statistical analyses were performed on SPSS v.24 (IBM Corp., Armonk, NY).

Results

Prior to PSM, 1130 patients were identified, of which 514 underwent surgery and 616 did not. The median age for the cohort was 64 years (range 14–96 years, IQR, 21.3 years), while male and female patients constituted 58.8 and 41.2% of the cohort, respectively. Demographic, clinical, and pathologic characteristics for the entire cohort are displayed in Table 1.

Among the 514 patients that underwent surgical resection with curative intent (median follow-up 33 months [95% CI 30–36 months]), age > 64 years ($p = 0.021$) and primary tumor location ($p < 0.001$) were associated with worse DSS. On multivariate analysis, colorectal (HR 4.9, 95% CI 2.32–10.33, $p < 0.001$) and retroperitoneal/peritoneal primary tumor location (HR 2.99, 95% CI 1.33–6.71, $p = 0.008$), as well as age > 64 years (HR 1.6, 95% CI 1.1–2.33, $p = 0.014$), were independent prognostic factors of worse DSS. In the same group of patients, age > 64 years ($p < 0.001$), primary tumor location ($p = 0.004$), and presence of nodal metastasis ($p = 0.04$) were associated with worse OS in univariate analysis. Multivariate analysis identified colorectal (HR 4.54, 95% CI 2.12–9.72, $p < 0.001$) and retroperitoneal/peritoneal primary tumor location (HR 2.69, 95% CI 1.32–5.49, $p = 0.007$), as well as age > 64 years (HR 2.72, 95% CI 1.77–4.19, $p < 0.001$), were independent prognostic factors of worse OS (Table 2).

After PSM, 570 patients were identified (males 334 [58.6%], females 236 [41.4%]). The median age of the cohort

Table 1 Patient characteristics before and after propensity score matching

	Initial cohort ($n = 1130$)				After PSM ($n = 570$)			
	Surgery ($n = 514$)	No surgery ($n = 616$)	*P* value	Standardized difference	Surgery ($n = 285$)	No surgery (n = 285)	*P* value	Standardized difference
Age (years)	61.5 ± 14.6	64.9 ± 13.9	< 0.001	− 0.239	61.1 ± 14.1	63 ± 13.6	0.111	− 0.137
≤ 64 years	291 (56.6%)	303 (49.2%)		0.149	158 (55.4%)	165 (57.9%)		− 0.050
> 64 years	223 (43.4%)	313 (50.8%)		− 0.149	127 (44.6%)	120 (42.1%)		0.050
Sex			0.008				0.932	
Male	280 (54.5%)	385 (62.5%)		− 0.163	166 (58.2%)	168 (58.9%)		− 0.014
Female	234 (45.5%)	231 (37.5%)		0.163	119 (41.8%)	117 (41.1%)		0.014
Race			0.034				0.53	
White	376 (73.2%)	409 (66.4%)		0.149	194 (68.1%)	188 (66%)		0.045
Black	79 (15.4%)	116 (18.8%)		− 0.09	59 (20.7%)	58 (20.4%)		0.007
Other	56 (10.9%)	90 (14.6%)		− 0.111	30 (10.5%)	39 (13.7%)		− 0.098
Primary tumor location			< 0.001				0.141	
Stomach	209 (40.7%)	318 (51.6%)		− 0.220	164 (57.5%)	161 (56.5%)		0.020
Small intestine	237 (46.1%)	78 (12.7%)		0.788	71 (24.9%)	65 (22.8%)		0.049
Colon/rectum	16 (3.1%)	30 (4.9%)		− 0.092	8 (2.8%)	11 (3.9%)		− 0.061
Retroperitoneum/ peritoneum	18 (3.5%)	30 (4.9%)		− 0.070	17 (6%)	6 (2.1%)		0.199
Other	34 (6.6%)	160 (26%)		− 0.544	25 (8.8%)	42 (14.7%)		− 0.184
Histologic grade			0.162				0.019	
WD	18 (3.5%)	11 (1.8%)		0.106	7 (2.5%)	8 (2.8%)		− 0.019
MD	36 (7%)	8 (1.3%)		0.289	21 (7.4%)	4 (1.4%)		0.296
PD/UD	108 (21%)	45 (7.3%)		0.401	67 (23.5%)	19 (6.7%)		0.483
Mitotic count			0.07				0.106	
≤ 5/50 HPF	85 (16.5%)	32 (5.2%)		0.369	46 (16.1%)	17 (6%)		0.326
> 5/50 HPF	81 (15.8%)	16 (2.6%)		0.469	45 (15.8%)	7 (2.5%)		0.474
AJCC T Stage			< 0.001				0.001	
T1/T2	65 (12.6%)	47 (7.6%)		0.167	30 (10.5%)	30 (10.5%)		0.000
T3	125 (24.3%)	81 (13.1%)		0.290	66 (23.2%)	45 (15.8%)		0.188
T4	221 (43%)	74 (12%)		0.740	128 (44.9%)	44 (15.4%)		0.679
AJCC N Stage			0.652				0.612	
N0	253 (49.2%)	175 (28.4%)		0.437	141 (49.5%)	93 (32.6%)		0.349
N1	56 (10.9%)	43 (7%)		0.137	28 (9.8%)	15 (5.3%)		0.171

PSM propensity score matching, *WD* well-differentiated, *MD* moderately differentiated, *PD* poorly differentiated, *UD* undifferentiated, *HPF* high-power field, *AJCC* American Joint Committee on Cancer

after PSM was 63 years (range 18–94 years, IQR 19 years) and mean age was 62 ± 13.9 years. Most primary tumors were located in the stomach (325 [57%]), followed by the small intestine (136 [23.9%]), colon/rectum (19 [3.3%]), and retroperitoneum/peritoneum (23 [4%]). Median survival was 79 months for gastric tumors, 107 months for small intestinal tumors, 24 months for colorectal tumors, and 31 months for retroperitoneal/peritoneal tumors. Median follow-up for the cohort after PSM was 25.5 months (95% CI 23–29 months, range 1–119 months). Univariate survival analysis in the cohort after PSM showed that primary tumor location ($p = 0.001$), higher tumor grade ($p = 0.027$), and not undergoing surgery (51 months vs. median not reached, $p < 0.001$, Fig. 1) were significantly associated with worse DSS. On multivariate analysis for DSS, not undergoing surgery was independently associated with worse DSS (HR 4.98, 95% CI 2.23–11.12, $p < 0.001$), along with tumor location ($p = 0.002$, small intestine: HR 0.54, 95% CI 0.21–1.43, $p = 0.216$, colon/rectum: HR 12.4, 95% CI 3.07–49.9, $p < 0.001$, retroperitoneum/peritoneum: HR 1.66, 95% CI 0.46–6, $p = 0.441$) and tumor grade ($p = 0.049$, MD: HR 3.12, 95% CI 0.31–31.26, $p = 0.334$, PD/UD: HR 8.04, 95% CI 1.05–61.4, $p = 0.045$). Univariate analysis for OS, age > 64 years ($p < 0.001$), primary tumor location ($p = 0.011$), higher tumor

Table 2 Survival analysis for patients that underwent surgical resection

	P value univariate	Adjusted HR (95% CI)	*P* value multivariate
DSS			
Age > 64 years	0.021	1.6 (1.1–2.33)	0.014
Sex	0.768		
Race	0.4		
Primary tumor location	< 0.001		< 0.001
Stomach		Reference	
Small intestine		1.36 (0.91–2.04)	0.132
Colon/rectum		4.9 (2.32–10.33)	< 0.001
Retroperitoneum/peritoneum		2.99 (1.33–6.71)	0.008
Histologic grade	0.234		
Mitotic count	0.464		
AJCC T stage	0.15		
Nodal metastases	0.107		
OS			
Age > 64 years	< 0.001	2.72 (1.77–4.19)	< 0.001
Sex	0.788		
Race	0.664		
Primary tumor location	0.004		< 0.001
Stomach		Reference	
Small intestine		1.09 (0.68–1.74)	0.722
Colon/rectum		4.54 (2.12–9.72)	< 0.001
Retroperitoneum/peritoneum		2.69 (1.32–5.49)	0.007
Histologic grade	0.069		
Mitotic count	0.546		
AJCC T stage	0.163		
Nodal metastases	0.04	1.58 (0.99–2.52)	0.055

HR hazard ratio, *CI* confidence interval, *DSS* disease-specific survival, *WD* well-differentiated, *MD* moderately differentiated, *PD* poorly differentiated, *UD* undifferentiated, *AJCC* American Joint Committee on Cancer, *OS* overall survival

grade ($p = 0.022$), and not undergoing surgery (median 32 vs. 74 months, $p < 0.001$) were significantly associated with worse survival. Multivariate analysis for OS identified primary tumor location ($p = 0.01$, small intestine: HR 0.73, 95% CI 0.36–1.47, $p = 0.376$, colon/rectum: HR 6.66, 95% CI 1.86–23.76, $p = 0.004$, retroperitoneum/peritoneum: HR 1.89, 95% CI 0.76–4.74, $p = 0.173$), higher tumor grade ($p = 0.021$, moderately differentiated [MD]: HR 1.17, 95% CI 0.3–0.63, $p = 0.824$, poorly differentiated [PD]/undifferentiated [UD]: HR 3.33, 95% CI 1.06–10.45, $p = 0.039$) and not undergoing surgery (HR 3.37, 95% CI 1.75–6.5, $p < 0.001$) to be independent predictors of worse survival (Table 3).

Sub-Analysis of Patients with Gastric Tumors

A sub-analysis of 325 patients with gastric tumors was then performed, of which 164 patients underwent surgery and 161 did not. Demographic, clinical, and pathologic characteristics are displayed in Table 4. Survival analysis for these patients showed that not undergoing curative surgery was the only variable associated with worse DSS among all variables examined (39 months vs. median not reached, $p < 0.001$, HR 2.95, 95% CI 1.92–4.53). On univariate analysis for OS, higher tumor grade ($p = 0.02$) and not undergoing surgery (median 30 months vs. 76 months, $p < 0.001$) were associated with worse survival. On multivariate analysis for OS, higher tumor grade ($p = 0.027$, MD: HR 1.12, 95% CI 0.18–7.18, $p = 0.903$, PD/UD: HR 3.98, 95% CI 0.91–17.41, $p = 0.067$) and not undergoing surgery were independent predictors of worse survival (HR 2.4, 95% CI 1.12–5.15, $p = 0.025$, Table 5).

Sub-Analysis of Patients with Small Intestinal Tumors

Next, a sub-analysis of 136 patients with small intestinal tumors was performed. Demographic, clinical, and pathologic characteristics are displayed in Table 4. Undergoing surgery was not associated with either improved DSS (median not

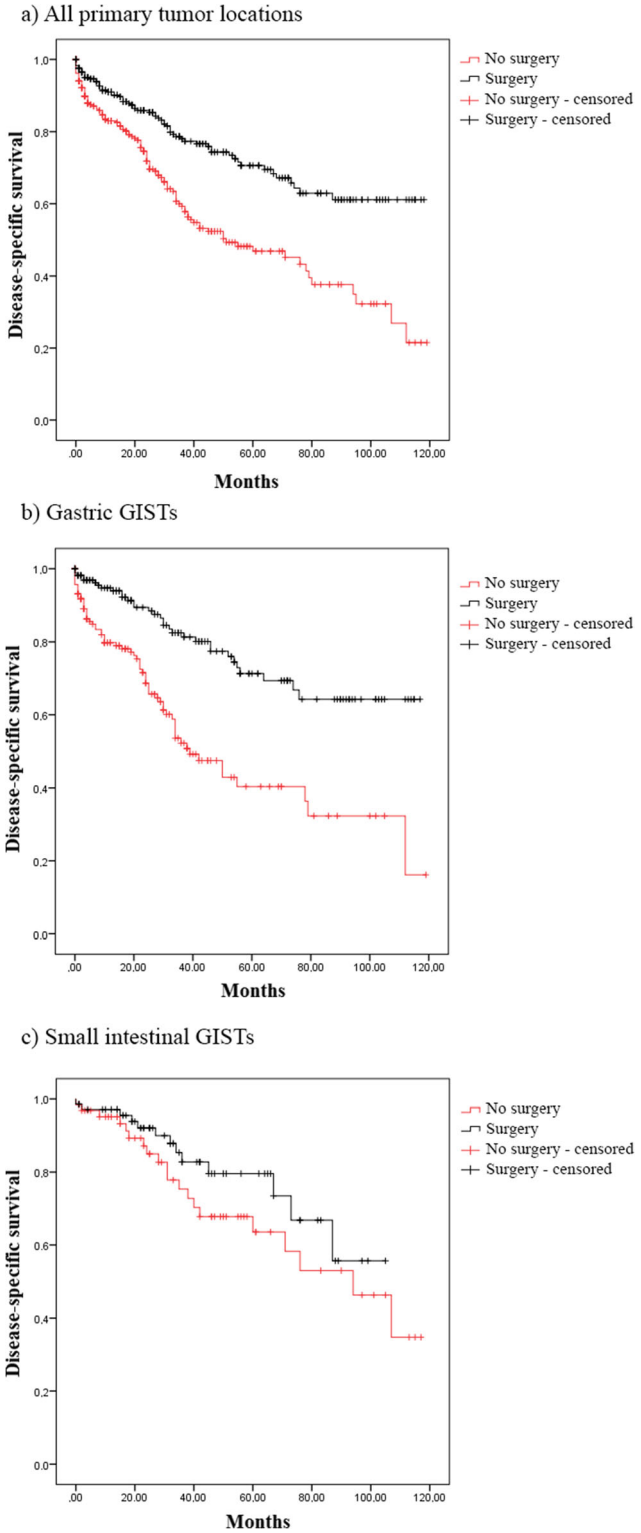

Fig. 1 Kaplan-Meier curves for undergoing curative surgery. **a** All primary tumor locations ($p < 0.001$, HR 4.98; 95% CI 2.23–11.12). **b** Gastric GISTs ($p < 0.001$, HR 2.95, 95% CI 1.92–4.53). **c** Small intestinal GISTs ($p = 0.206$, HR 1.56, 95% CI 0.77–3.2)

reached vs. 94 months, $p = 0.206$) or OS (median 87 vs. 57 months, $p = 0.062$) for these patients.

Sub-Analysis of Patients with Colorectal and Retroperitoneal/Peritoneal Tumors

Sub-analyses were then performed for 19 patients with colorectal tumors and 23 patients with retroperitoneal/peritoneal tumors were performed. Undergoing curative resection was not associated with either improved DSS or OS for both colorectal (DSS: median 24 months vs. 13 months, $p = 0.647$, OS: median 24 months vs. 13 months, $p = 0.924$) or retroperitoneal/peritoneal tumors (DSS: median not reached vs. 25 months, $p = 0.67$, OS: median 26 months vs. 22 months, $p = 0.738$).

Discussion

The results of this study show that outcomes after surgical resection differ among different primary tumor locations in patients with metastatic GISTs. Among all patients that underwent curative resection, primary tumor location was an independent prognostic factor of both worse DSS and OS, as colorectal and retroperitoneal/peritoneal tumors had significantly worse prognosis. In addition, there was a significant survival benefit for patients with gastric GISTs undergoing surgical resection. In contrast, no benefit after surgical resection was identified for patients with small intestinal metastatic GISTs. Finally, no benefit after resection was found for colorectal, retroperitoneal, and peritoneal tumors, but the low numbers of cases in these sub-analyses may limit the generalizability of these conclusions.

Gastrointestinal stromal tumors represent the most frequent gastrointestinal malignancies of mesenchymal origin, comprising 0.2% of all gastrointestinal malignancies [31]. Distant metastatic disease at diagnosis is fairly common, since 15–50% of all patients present with metastatic disease [3, 4]. Administration of imatinib is a dominant treatment approach for metastatic GISTs and its use has increased 2-year overall survival rates from 41 to 72% [5, 32]. Newer agents, such as sunitinib and regorafenib, can also be employed as second- and third-line agents, respectively, when resistance to imatinib develops [33]. Notably, continuing therapy with a TKI even after disease progression has been found to lead to better OS rates than stopping systemic treatment altogether [34]. Several retrospective studies have demonstrated a survival benefit in selected patients with metastatic GISTs after undergoing curative surgery [14–22] and subsequent NCCN and ESMO guidelines recommend surgery for patients with imatinib-responsive tumors where complete resection may be achieved or imatinib-refractory tumors with limited disease progression [23, 24]. Interestingly, in our analysis, we identified that primary tumor location had a significant impact on outcomes after resection, as gastric metastatic GISTs portended a more pronounced benefit after resection when compared to small intestinal, colorectal, retroperitoneal, or peritoneal metastatic

Table 3 Results of univariate and multivariate survival analyses for all primary tumor locations

	P value univariate	Adjusted HR (95% CI)	*P* value multivariate
DSS			
Age > 64 years	0.094		
Sex	0.694		
Race	0.439		
Primary tumor location	0.001		0.002
Stomach		Reference	
Small intestine		0.54 (0.21–1.43)	0.216
Colon/rectum		12.4 (3.07–49.9)	< 0.001
Retroperitoneum/peritoneum		1.66 (0.46–6)	0.441
Histologic grade	0.027		0.049
WD		Reference	
MD		3.12 (0.31–31.26)	0.334
PD/UD		8.04 (1.05–61.4)	0.045
Mitotic count	0.86		
AJCC T stage	0.542		
Nodal metastases	0.114		
Surgery not performed	< 0.001	4.98 (2.23–11.12)	< 0.001
OS			
Age > 64 years	< 0.001	1.79 (0.97–3.3)	0.061
Sex	0.948		
Race	0.481		
Primary tumor location	0.011		0.01
Stomach		Reference	
Small intestine		0.73 (0.36–1.47)	0.376
Colon/rectum		6.66 (1.86–23.76)	0.004
Retroperitoneum/peritoneum		1.89 (0.76–4.74)	0.173
Histologic grade	0.022		0.021
WD		Reference	
MD		1.17 (0.3–.63)	0.824
PD/UD		3.33 (1.06–10.45)	0.039
Mitotic count	0.439		
AJCC T stage	0.269		
Nodal metastases	0.233		
Surgery not performed	< 0.001	3.37 (1.75–6.5)	< 0.001

HR hazard ratio, *CI* confidence interval, *DSS* disease-specific survival, *WD* well-differentiated, *MD* moderately differentiated, *PD* poorly differentiated, *UD* undifferentiated, *AJCC* American Joint Committee on Cancer, *OS* overall survival

GISTs. This finding is in accord with previous reports of similar findings [25–29]. This difference in survival outcomes may be traced to the different histologic findings between gastric and small intestinal GISTs [26], as well as the limited malignant potential of microscopic gastric GISTs [25]. Additionally, nongastric GISTs have higher recurrence rates, both after surgery [28, 29] and treatment with imatinib [35]. Furthermore, mutational patterns also differ between different tumor locations, with exon 9 and 17 mutations being more commonly identified in small intestinal tumors [36–38]. As such, tumor site is now implemented as a major independent predictor of recurrence in pertinent GIST nomograms [39]. In this way, higher recurrence rates after resection as well as underlying differences in disease behavior may explain why surgery exerted a beneficial effect for gastric GISTs but failed to do so for tumors in other locations.

One of the proposed ways in which operative management may assist in prolonging survival is the reduction of tumor bulk in order for imatinib to act more efficiently in the remaining cells. At the same time, surgery may also potentially remove clones that have developed resistance to TKI treatment or at least reduce the speed of the inevitable development of resistant clones [5]. In this way, commencement of second-line agents, such as sunitinib and regorafenib, and eventual

Table 4 Characteristics of patients with gastric and small intestinal tumors

	Gastric ($n = 325$)			Small intestinal ($n = 136$)		
	Surgery ($n = 164$)	No surgery ($n = 161$)	p value	Surgery ($n = 71$)	No surgery ($n = 65$)	p value
Age (years)			0.505			1.00
≤ 64 years	84 (51.2%)	89 (55.3%)		40 (56.3%)	36 (55.4%)	
> 64 years	80 (48.8%)	72 (44.7%)		31 (43.7%)	29 (44.6%)	
Sex			0.649			0.598
Male	98 (59.8%)	101 (62.7%)		46 (64.8%)	39 (60%)	
Female	66 (40.2%)	60 (37.3%)		25 (35.2%)	26 (40%)	
Race			0.436			0.913
White	107 (65.2%)	102 (63.4%)		53 (74.6%)	50 (76.9%)	
Black	46 (28%)	44 (27.3%)		4 (5.6%)	4 (6.2%)	
Other	9 (5.5%)	15 (9.3%)		14 (19.7%)	11 (16.9%)	
Histologic grade			0.03			0.466
WD	4 (2.4%)	7 (4.3%)		1 (1.4%)	1 (1.5%)	
MD	15 (9.1%)	3 (1.9%)		5 (7%)	1 (1.5%)	
PD/UD	34 (20.7%)	15 (9.3%)		17 (23.9%)	3 (4.6%)	
Mitotic count			0.429			0.288
≤ 5/50 HPF	33 (20.1%)	14 (8.7%)		11 (15.5%)	3 (4.6%)	
> 5/50 HPF	24 (14.6%)	6 (3.7%)		18 (25.4%)	1 (1.5%)	
AJCC T stage			0.022			0.027
T1/T2	19 (11.6%)	21 (13%)		8 (11.3%)	7 (10.8%)	
T3	44 (26.8%)	31 (19.3%)		19 (26.8%)	13 (20%)	
T4	80 (48.8%)	33 (20.5%)		35 (49.3%)	7 (10.8%)	
AJCC N stage			0.52			1.00
N0	86 (52.4%)	67 (41.6%)		33 (46.5%)	18 (27.7%)	
N1	17 (10.4%)	9 (5.6%)		7 (9.9%)	4 (6.2%)	

WD well-differentiated, *MD* moderately differentiated, *PD* poorly differentiated, *UD* undifferentiated, *HPF* high-power field, *AJCC* American Joint Committee on Cancer

tumor resistance towards them would be delayed. Based on these mechanisms, cytoreductive surgery has also been advocated for selected patients with metastatic GISTs and favorable outcomes have been reported, which are superior to those of non-operative management [40, 41]. In addition, while for many types of tumors, generalized progression is the typical form of disease progression, GISTs demonstrate a slower growth pattern with either progressive imatinib-responsive tumor growth in distant locations or generalized disease that is stable on TKI treatment, which renders patients with metastatic GISTs candidates for surgical intervention more often compared to patients with other malignancies [5, 14].

This study is limited by its retrospective design and the use of a multi-institutional database, since such registries are subject to potential non-uniform practice. Importantly, there is no information in SEER concerning the resistance or duration of TKI regimens, whether an R0/R1 or cytoreductive resection was performed and whether there was progressive or stable metastatic disease. However, since cytoreductive surgery has been advocated by some authors for selected patients with metastatic GISTs and favorable outcomes have been reported [40, 41], the individualized performance of cytoreductive—and not R0/R1 surgery—would be justified in selected patients. Information regarding specific TKI regimens is also lacking, but different response rates among different primary tumor locations [35] may partly explain the findings of this study. In addition, several variables, such as tumor grade and mitotic count, were not available for the majority of the cohort, but this did not have an impact on the major findings of this study, since only tumor grade was included in one multivariate analysis (i.e., for all primary tumor locations) and did not affect the results of the sub-analyses by primary tumor location. As previously stated, the low number of patients with colorectal, peritoneal, and retroperitoneal tumors may also limit proper conclusions for these patient groups, but that is to be expected due to their relative rarity. Additionally, this study is based on results reported from multiple different pathology laboratories, per participating institutions, rendering the data prone to tumor

Table 5 Results of univariate and multivariate survival analyses for patients with gastric primary tumors

	p value univariate	Adjusted HR (95% CI)	*p* value multivariate
DSS			
Age > 64 years	0.525		
Sex	0.745		
Race	0.875		
Histologic grade	0.074		
Mitotic count	0.177		
AJCC T stage	0.558		
Nodal metastases	0.926		
Surgery not performed	< 0.001	2.95 (1.92–4.53)	
OS			
Age > 64 years	0.081		
Sex	0.494		
Race	0.636		
Histologic grade	0.02		0.027
WD		Reference	
MD		1.12 (0.18–7.18)	0.903
PD/UD		3.98 (0.91–17.41)	0.067
Mitotic count	0.376		
AJCC T stage	0.41		
Nodal metastases	0.577		
Surgery not performed	< 0.001	2.4 (1.12–5.15)	0.025

HR hazard ratio, *CI* confidence interval, *DSS* disease-specific survival, *WD* well-differentiated, *MD* moderately differentiated, *PD* poorly differentiated, *UD* undifferentiated, *AJCC* American Joint Committee on Cancer, *OS* overall survival

misclassifications. Unfortunately, since randomized control trials are currently lacking in this patient population and small retrospective studies often do not have enough statistical power to yield certain conclusions, large cancer databases may be the best available sources for answering several questions. Despite these limitations, the results of this study suggest that some patients may not receive considerable benefit from surgical resection, which suggests that improved case selection is needed to improve outcomes in the population.

In conclusion, primary tumor location is an independent prognostic factor among patients that underwent curative resection, with colorectal, peritoneal, and retroperitoneal tumors being associated with worse prognosis. Patients with metastatic gastric GISTs have a significant benefit from surgical resection. In contrast, there is no discernible survival benefit after surgical resection for patients with small intestinal, colorectal, retroperitoneal, or peritoneal metastatic GISTs. These differences may be explained by the distinct mutational patterns, different disease behaviors, and higher recurrence rates among primary tumors of different sites. Primary tumor location should be taken into consideration in the design of future randomized trials, which are needed to improve patient selection for surgical treatment.

Acknowledgments All the authors that contributed in the preparation of this manuscript have been mentioned.

Compliance with Ethical Standards

Conflict of Interest The authors have nothing to disclose.

References

1. Ma GL, Murphy JD, Martinez ME, Sicklick JK. Epidemiology of gastrointestinal stromal tumors in the era of histology codes: results of a population-based study. Cancer Epidemiol Biomark Prev. 2015;24:298–302.
2. Tran T, Davila JA, El-Serag HB. The epidemiology of malignant gastrointestinal stromal tumors: an analysis of 1,458 cases from 1992 to 2000. Am J Gastroenterol. 2005;100:162–8.
3. Nilsson B, Bümming P, Meis-Kindblom JM, Odén A, Dortok A, Gustavsson B, et al. Gastrointestinal stromal tumors: the incidence, prevalence, clinical course, and prognostication in the preimatinib mesylate era. Cancer. Wiley Subscription Services, Inc., A Wiley Company. 2005;103:821–9.
4. Roberts PJ, Eisenberg B. Clinical presentation of gastrointestinal stromal tumors and treatment of operable disease. Eur J Cancer. 2002;38:S37–8.
5. Ford SJ, Gronchi A. Indications for surgery in advanced/metastatic GIST. Eur J Cancer. 2016;63:154–67.
6. Fletcher CDM, Berman JJ, Corless C, Gorstein F, Lasota J, Longley BJ, et al. Diagnosis of gastrointestinal stromal tumors: a consensus approach. Int J Surg Pathol.Sage Publications Sage CA: Thousand Oaks. 2002;10:81–9.

7. Lasota J, Miettinen M. KIT and PDGFRA mutations in gastrointestinal stromal tumors (GISTs). Semin Diagn Pathol. 2006;23:91–102.
8. Demetri GD, von Mehren M, Antonescu CR, DeMatteo RP, Ganjoo KN, Maki RG, et al. NCCN Task Force report: update on the management of patients with gastrointestinal stromal tumors. J Natl Compr Cancer Netw. NIH Public Access. 2010;Suppl 2:S1–41.
9. Frankel TL, Chang AE, Wong SL. Surgical options for localized and advanced gastrointestinal stromal tumors. J Surg Oncol. 2011;104:882–7.
10. Dagher R, Cohen M, Williams G, Rothmann M, Gobburu J, Robbie G, et al. Approval summary: imatinib mesylate in the treatment of metastatic and/or unresectable malignant gastrointestinal stromal tumors. Clin Cancer Res. 2002;8:3034–8.
11. DeMatteo RP, Ballman KV, Antonescu CR, Corless C, Kolesnikova V, von Mehren M, et al. Long-term results of adjuvant imatinib mesylate in localized, high-risk, primary gastrointestinal stromal tumor. Ann Surg. 2013;258:422–9.
12. Joensuu H, Eriksson M, Sundby Hall K, Hartmann JT, Pink D, Schütte J, et al. One vs three years of adjuvant imatinib for operable gastrointestinal stromal tumor. JAMA. 2012;307:1265–72.
13. Joensuu H, Eriksson M, Sundby Hall K, Reichardt A, Hartmann JT, Pink D, et al. Adjuvant imatinib for high-risk GI stromal tumor: analysis of a randomized trial. J Clin Oncol. American Society of Clinical Oncology. 2016;34:244–50.
14. Raut CP, Posner M, Desai J, Morgan JA, George S, Zahrieh D, et al. Surgical management of advanced gastrointestinal stromal tumors after treatment with targeted systemic therapy using kinase inhibitors. J Clin Oncol. American Society of Clinical Oncology. 2006;24:2325–31.
15. Andtbacka RHI, Ng CS, Scaife CL, Cormier JN, Hunt KK, Pisters PWT, et al. Surgical resection of gastrointestinal stromal tumors after treatment with imatinib. Ann Surg Oncol. 2006;14:14–24.
16. Rutkowski P, Nowecki Z, Nyckowski P, Dziewirski W, Grzesiakowska U, Nasierowska-Guttmejer A, et al. Surgical treatment of patients with initially inoperable and/or metastatic gastrointestinal stromal tumors (GIST) during therapy with imatinib mesylate. J Surg Oncol. Wiley Subscription Services, Inc., A Wiley Company. 2006;93:304–11.
17. DeMatteo RP, Maki RG, Singer S, Gonen M, Brennan MF, Antonescu CR. Results of tyrosine kinase inhibitor therapy followed by surgical resection for metastatic gastrointestinal stromal tumor. Ann Surg. 2007;245:347–52.
18. Colombo C, Ronellenfitsch U, Yuxin Z, Rutkowski P, Miceli R, Bylina E, et al. Clinical, pathological and surgical characteristics of duodenal gastrointestinal stromal tumor and their influence on survival: a multi-center study. Ann Surg Oncol. Springer-Verlag. 2012;19:3361–7.
19. Gronchi A, Fiore M, Miselli F, Lagonigro MS, Coco P, Messina A, et al. Surgery of residual disease following molecular-targeted therapy with imatinib mesylate in advanced/metastatic GIST. Ann Surg. 2007;245:341–6.
20. Mussi C, Ronellenfitsch U, Jakob J, Tamborini E, Reichardt P, Casali PG, et al. Post-imatinib surgery in advanced/metastatic GIST: is it worthwhile in all patients? Ann Oncol. Oxford University Press. 2010;21:403–8.
21. Sym SJ, Ryu M, Lee J, Chang HM, Kim T, Kim HC, et al. Surgical intervention following imatinib treatment in patients with advanced gastrointestinal stromal tumors (GISTs). J Surg Oncol. Wiley Subscription Services, Inc., A Wiley Company. 2008;98:27–33.
22. Rubió-Casadevall J, Martinez-Trufero J, Garcia-Albeniz X, Calabuig S, Lopez-Pousa A, del Muro JG, et al. Role of surgery in patients with recurrent, metastatic, or unresectable locally advanced gastrointestinal stromal tumors sensitive to Imatinib: a retrospective analysis of the Spanish Group for Research on Sarcoma (GEIS). Ann Surg Oncol. 2015;22:2948–57.
23. von Mehren M, Randall RL, Benjamin RS, Boles S, Bui MM, Conrad EU, et al. Soft tissue sarcoma, version 2.2017, NCCN clinical practice guidelines in oncology. J Natl Compr Cancer Netw. 2017;14:758.
24. ESMO/European Sarcoma Network Working Group. Gastrointestinal stromal tumours: ESMO clinical practice guidelines for diagnosis, treatment and follow-up. Ann Oncol. 2014;25:iii21–6.
25. Joensuu H. Risk stratification of patients diagnosed with gastrointestinal stromal tumor. Hum Pathol. 2008;39:1411–9.
26. Miettinen M, Lasota J. Gastrointestinal stromal tumors: pathology and prognosis at different sites. Semin Diagn Pathol. 2006;23:70–83.
27. Mrowiec S, Jabłońska B, Liszka Ł, Pająk J, Leidgens M, Szydło R, et al. Prognostic factors for survival post surgery for patients with gastrointestinal stromal tumors. Eur Surg Res. 2012;48:3–9.
28. Joensuu H, Vehtari A, Riihimäki J, Nishida T, Steigen SE, Brabec P, et al. Risk of recurrence of gastrointestinal stromal tumour after surgery: an analysis of pooled population-based cohorts. Lancet Oncol. 2012;13:265–74.
29. DeMatteo RP, Gold JS, Saran L, Gönen M, Liau KH, Maki RG, et al. Tumor mitotic rate, size, and location independently predict recurrence after resection of primary gastrointestinal stromal tumor (GIST). Cancer. 2008;112:608–15.
30. National Cancer Institute. Overview of the SEER Program. 2013
31. Blay J-Y, Bonvalot S, Casali P, Choi H, Debiec-Richter M, Dei Tos AP, et al. Consensus meeting for the management of gastrointestinal stromal tumors: report of the GIST Consensus Conference of 20-21 March 2004, under the auspices of ESMO. Ann Oncol. 2005;16:566–78.
32. Verweij J, Casali PG, Zalcberg J, LeCesne A, Reichardt P, Blay J-Y, et al. Progression-free survival in gastrointestinal stromal tumours with high-dose imatinib: randomised trial. Lancet. 2004;364:1127–34.
33. Maki RG, Blay J-Y, Demetri GD, Fletcher JA, Joensuu H, Martin-Broto J, et al. Key issues in the clinical management of gastrointestinal stromal tumors: an expert discussion. Oncologist. 2015;20:823–30.
34. Kang Y-K, Ryu M-H, Yoo C, Ryoo B-Y, Kim HJ, Lee JJ, et al. Resumption of imatinib to control metastatic or unresectable gastrointestinal stromal tumours after failure of imatinib and sunitinib (RIGHT): a randomised, placebo-controlled, phase 3 trial. Lancet Oncol. 2013;14:1175–82.
35. Joensuu H, Eriksson M, Hall KS, Hartmann JT, Pink D, Schütte J, et al. Risk factors for gastrointestinal stromal tumor recurrence in patients treated with adjuvant imatinib. Cancer. 2014;120:2325–33.
36. Lasota J, Wozniak A, Sarlomo-Rikala M, Rys J, Kordek R, Nassar A, et al. Mutations in exons 9 and 13 of KIT gene are rare events in gastrointestinal stromal tumors. Am J Pathol. 2000;157:1091–5.
37. Antonescu CR, Sommer G, Sarran L, Tschernyavsky SJ, Riedel E, Woodruff JM, et al. Association of KIT exon 9 mutations with nongastric primary site and aggressive behavior: KIT mutation analysis and clinical correlates of 120 gastrointestinal stromal tumors. Clin Cancer Res. American Association for Cancer Research. 2003;9:3329–37.
38. Lasota J, Corless CL, Heinrich MC, Debiec-Rychter M, Sciot R, Wardelmann E, et al. Clinicopathologic profile of gastrointestinal stromal tumors (GISTs) with primary KIT exon 13 or exon 17 mutations: a multicenter study on 54 cases. Mod Pathol. 2008;21:476–84.
39. Bischof DA, Kim Y, Behman R, Karanicolas PJ, Quereshy FA, Blazer DG, et al. A nomogram to predict disease-free survival after surgical resection of GIST. J Gastrointest Surg. 2014;18:2123–9.
40. Xia L, Zhang M-M, Ji L, Li X, Wu X-T. Resection combined with imatinib therapy for liver metastases of gastrointestinal stromal tumors. Surg Today. 2010;40:936–42.
41. Bauer S, Rutkowski P, Hohenberger P, Miceli R, Fumagalli E, Siedlecki JA, et al. Long-term follow-up of patients with GIST undergoing metastasectomy in the era of imatinib? Analysis of prognostic factors (EORTC-STBSG collaborative study). Eur J Surg Oncol. 2014;40:412–9.