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ORIGINAL ARTICLE – SARCOMA

Ten-Year Survivorship in Patients with Metastatic Gastrointestinal Stromal Tumors

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ABSTRACT

Introduction. Patients developing metastatic gastrointestinal stromal tumors (mGIST) have heterogenous disease biology and oncologic outcomes; prognostic factors are incompletely characterized. We sought to evaluate predictors of 10-year metastatic survivorship in the era of tyrosine kinase inhibitor (TKI) therapy.

Methods. We reviewed patients with mGIST treated at our Comprehensive Cancer Center from 2003 to 2019, including only patients with either mortality or 10 years of follow-up. Ten-year survivorship was evaluated with logistic regression.

Results. We identified 109 patients with a median age of 57 years at mGIST diagnosis. Synchronous disease was present in 57% (n = 62) of patients; liver (n = 48, 44%), peritoneum (n = 40, 37%), and liver + peritoneum (n = 18, 17%) were the most common sites. Forty-six (42%) patients were 10-year mGIST survivors. Following mGIST diagnosis, radiographic progression occurred within 2 years in 53% (n = 58) of patients, 2–5 years in 16% (n = 17), and 5–10 years in 16% (n = 17), with median survival of 32, 76, and 173 months, respectively. Seventeen (16%) patients had not progressed by 10 years. Fifty-two (47%) patients underwent metastasectomy, which was associated with improved progression-free survival (hazard ratio 0.63, p = 0.04). In patients experiencing progression, factors independently associated with 10-year survivorship were age (odds ratio [OR] 0.96, p = 0.03) and time to progression (OR 1.71/year, $p < 0.001$).

Conclusions. Ten-year survivorship is achievable in mGIST in the era of TKIs and is associated with younger age and longer time to first progression, while metastasectomy is associated with longer time to first progression. The role of metastasectomy in the management of patients with disease progression receiving TKI therapy merits further study.

Keywords Gastrointestinal stromal tumor · Time to progression · Imatinib · Tyrosine kinase inhibitor · Metastatic · Survivorship

INTRODUCTION

Gastrointestinal stromal tumors (GIST) are mesenchymal neoplasms that originate from the interstitial cells of Cajal.[1] Upwards of 85% are driven by oncogenic mutations in *KIT* and *PDGFRA,* for which multiple lines of tyrosine kinase inhibitor (TKI) therapy are now available.[2] While approximately 90% of patients with GIST are non-metastatic at diagnosis, up to 10% can present with synchronous primary and metastatic disease, with the liver and peritoneum being the most common sites of GIST metastasis.[3,4] Additionally, upwards of 50% of patients with high-risk resected GIST will develop metastatic disease, making metastasis a common scenario.[5]

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Before the advent of TKIs, the prognosis for patients with metastatic GIST (mGIST) was poor, with a median overall survival (OS) of 1–2 years.[6] Now, long-term survivorship is increasingly appreciated, with up to 50% 5-year OS in patients presenting with synchronous primary and metastatic GISTs, and up to 22% 10-year OS across all patients with mGISTs.[7,8] This improvement is attributed to the high response rates to imatinib, introduced in 2001, which is particularly pronounced for *KIT*-mutated GISTs. In the adjuvant setting, metastatic recurrence within 5 years of primary resection is rare while taking imatinib.[9]

Few detailed investigations of survivorship in mGISTs have been performed to date, as they are logistically difficult and limited by insufficient long-term follow-up. Patients with mGISTs often receive treatment at multiple academic centers over the course of their disease, leading to sparse or incomplete follow-up. Prior studies have cited age, oligometastatic disease, metastatic tumor diameter, and resection for primary tumor and metastatic disease as potential predictors of long-term survival.[10–14] However, it is clear from available data that 10-year survival is increasingly possible with modern multi-line TKI therapy. We therefore sought to improve upon prior studies by focusing on 10-year GIST survivors versus non-survivors treated at our academic medical center during the era of TKI therapy.

METHODS

Study Population/Patient Data

A query of the prospectively maintained Knight Cancer Registry was performed for patients with GIST treated medically or surgically at Oregon Health & Science University (OHSU) for the years 2003–2019 was performed; patients with synchronous and metachronous mGIST were identified. Patients diagnosed before 2003 with ongoing treatment during the study period were included if they received a TKI at initial metastatic diagnosis. Patients with mortality prior to 10-years of follow-up and patients alive at 10 years following diagnosis of metastatic disease were included, while patients alive but with <10 years of follow-up (n = 21) were excluded in order to evaluate the primary binary endpoint of 10-year survivorship. Patients receiving medical or surgical consultation at OHSU but never receiving treatment at OHSU were excluded. Data captured included patient demographics, clinicopathologic characteristics of primary tumors, modified National Institutes of Health (NIH) risk categories, characteristics of metastatic disease, surgical and therapeutic treatment details, and oncologic outcomes, including dates and sites of progression and dates of mortality. Staging for primary tumors was updated to reflect the 8th edition American Joint Committee on Cancer (AJCC) guidelines.

No subjects were excluded from the study based on sex, racial or ethnic origin. There were no age- or treatment-specific exclusion criteria. The study was reviewed and approved by the Institutional Review Board of OHSU and the Knight Cancer Institute Clinical Research Review Committee.

Treatment Protocols

All patients in the present study with *KIT* and non-D842V *PDGFRA* mutations or unknown mutational status were started on imatinib as first-line therapy unless metastasis was diagnosed while taking adjuvant imatinib. Prior to recognition of the imatinib resistance of D842V *PDGFRA* mutations, patients with this mutation also received imatinib as first-line therapy unless metastasis was diagnosed while taking adjuvant imatinib. Second- and third-line agents primarily included sunitinib and regorafenib, with sorafenib and nilotinib occasionally used in patients with non-*KIT* mutated tumors. No patients in the present cohort received avapritinib during ongoing clinical trials at OHSU.

Definitions

Patients were divided into groups based on survivorship, 10-year metastatic survivors, and non-survivors. OS was measured from the date of first radiographic evidence of mGIST; Progression-free survival (PFS) was measured in months from diagnosis of mGIST until radiographic disease progression as defined by the Response Evaluation Criteria in Solid Tumors (RECIST) criteria, with the exception of cases when progression was due to emergent TKI resistance within a single previously stable lesion that was then resected, thereby allowing the patient to remain on the same TKI (n = 3 patients). Notably, results were not meaningfully altered by including resection of a unifocal TKI-resistant lesion in the definition of progression. Therapeutic-intent metastasectomy was defined as either resection of all visible metastatic disease or of a single focus of newly treatment-resistant disease (either peritoneal deposit or liver lesion) in the setting of otherwise stable metastatic disease,[15],thus allowing the patient to continue on TKI therapy. Patients managed with peritoneal or liver cytoreduction of multifocal progressive disease for symptom palliation (n = 3) were not considered to have received a therapeutic-intent metastasectomy due to the known poor oncologic outcomes with this treatment approach.[15] No patients in the present cohort underwent metastasectomy for bleeding, obstruction, perforation, or other urgent indication.

Statistical Analysis

Descriptive statistics of clinicopathologic variables for all patients and treatment groups were tabulated, with Chi-square and independent samples *t*-tests used to compare groups. Binary logistic regression was performed for the primary outcome of 10-year metastatic survivorship to estimate odds ratios (OR). Kaplan–Meier and Cox proportional hazards modeling was used to analyze 10-year PFS and calculate hazard ratios (HR) for predictive variables. Variables with a p-value <0.20 on univariable analysis were included in the initial multivariable models, followed by single backward elimination of variables until further elimination worsened model fit with a p-value <0.05. For Kaplan–Meier and Cox proportional hazards modeling, all patients not experiencing the event of interest were censored at the last date of follow-up. All statistics were performed using SPSS Statistics 26 (IBM Corporation, Armonk, NY, USA).

RESULTS

Clinicopathologic Characteristics

Over the 16-year study period, 109 patients with mGIST who experienced mortality or had ≥10 years of follow-up were identified (Table 1). The median patient age was 57 years at time of mGIST diagnosis, with a slight male predominance ($n = 66$, 60%). The majority of cases were either primary gastric ($n = 49$, 45%) or small bowel ($n = 44$, 40%), with more than half of patients developing metachronous disease ($n = 58$, 53%) at a median of 15 months. Driver mutations were in *KIT* ($n = 68$, 62%), *SDH* ($n = 9$, 8%), *PDGFRA* ($n = 8$, 7%) and other mutations ($n = 6$, 6%). Eighteen patients (17%) were not tested but were presumed to be *KIT* mutant-GIST due to initially stable or responsive disease on imatinib; 14 (78%) of these patients had gastric primaries. The pattern of metastasis at diagnosis was primarily liver-only ($n = 48$, 44%), peritoneum-only ($n = 40$, 37%), or combined liver and peritoneal disease ($n = 18$, 17%), followed by other metastatic site combinations ($n = 3$, 2.7%). Forty-one patients (38%) underwent metastasectomy for liver disease during their disease course, while 29 (27%) underwent peritoneal metastasectomy.

Sixty-three (58%) patients expired in the setting of progressive disease prior to 10 years following diagnosis of metastatic disease, while 46 (42%) were alive at 10 years. No patients died in the absence of disease progression during the study period. Several key clinicopathologic differences were observable in these groups. First, 10-year survivors were significantly younger than non-survivors, with a median age of 49.5 years versus 62.5 years at diagnosis of mGIST ($p < 0.001$). Individual mutational status was not significantly different between the two groups ($p = 0.08$), however of eight patients with *PDGFRA* mutations (D842V: $n = 4$; N659K: $n = 1$; Y849C: $n = 1$; D842-H845 deletion: $n = 1$; unspecified exon 12 point mutation: $n = 1$), only one survived to 10 years (exon 12 mutant). Ten-year survivors were more likely to have undergone curative-intent combined primary and metastatic disease resections, less likely to have tumor rupture noted on pathology of the primary tumor, and more likely to have undergone liver metastasectomy compared with non-survivors. Most strikingly, there was significant separation in survivorship groups by time to first progression: 14% ($n = 8$) of patients progressing within 2 years were 10-year survivors, compared with 35% ($n = 6$) in those progressing within 2–5 years and 88% ($n = 15$) in those progressing within 5–10 years. By definition, 100% of patients with no evidence of progression at 10-years were metastatic survivors.

Ten-Year Survivorship

The median follow-up for the cohort was 79 months (range 2–275 months) from diagnosis of metastatic disease. No patients in our study had incomplete follow-up prior to 10 years. The median OS from diagnosis of mGIST was 79 months (95% CI 55–103 months) for all patients, and 32 months (95% CI 22–42 months), 76 months (95% CI 53–99 months), and 173 months (95% CI 126–220 months) for patients experiencing progression within 2, 2–5, and 5–10 years from mGIST diagnosis, respectively (Fig. 1). No patients without progression at 10 years had died at time of last follow-up.

Given the clear prognostic impact that progression plays on survivorship, we analyzed predictors of 10-year survivorship in patients experiencing progression before 10 years ($n = 17$; patients without progression at 10 years were excluded). On univariable analysis (Table a2), factors associated with odds of 10-year survivorship included age at diagnosis, therapeutic-intent metastasectomy, and years to first progression. Months from diagnosis to metastasis, sex, race, primary location, primary T stage, primary grade, modified NIH frisk category, driver mutation, years of TKI therapy prior to metastasis, and distribution of metastatic sites at diagnosis were not associated with 10-year survivorship ($p > 0.2$ for all). On multivariable analysis following single backward elimination, longer time to first progression was independently associated with higher odds of 10-year survivorship, while increasing age at metastasis was independently associated with lower odds of 10-year survivorship. Therapeutic-intent metastasectomy was not significantly associated with odds of 10-year survival, however was not removed from the final model during single backward elimination. Of note, tumor rupture was

TABLE 1 Clinicopathologic and treatment characteristics of 10-year survivors and non-survivors with metastatic GIST

Variable	Total [*n* = 109]	10-year non-survivors [*n* = 63]	10-year survivors [*n* = 46]	*p*-Value
Age at metastasis, years (median [IQR])	57.0 [47–67.5]	62 [55–76.5]	50 [43.5–59.5]	<0.001
Male	66 (60.6)	40 (63.5)	26 (56.5)	0.46
Race				0.36
White	100 (91.7)	59 (93.6)	41 (89.1)	
African American/Black	6 (5.5)	4 (6.3)	2 (4.3)	
Other	3 (2.7)	0 (0)	3 (6.4)	
Primary disease site				0.38
Colon/rectum	6 (5.5)	5 (7.9)	1 (2.2)	
Esophageal	1 (0.9)	0 (0)	1 (2.2)	
Gastric	49 (44.9)	26 (41.2)	23 (50.0)	
Non-solid organ primary	5 (4.5)	3 (4.7)	2 (4.3)	
Small bowel	44 (40.3)	25 (39.7)	19 (41.3)	
Unknown	3 (3.7)	3 (6.4)	0 (0)	
Neoadjuvant therapy prior to curative-intent metastasectomy	19 (17.4)	11 (17.5)	8 (17.4)	>0.99
T stage				0.24
1	3 (2.8)	2 (3.2)	1 (2.2)	
2	7 (6.4)	4 (6.3)	3 (6.5)	
3	41 (37.6)	18 (28.6)	23 (50.0)	
4	40 (36.7)	27 (42.9)	13 (28.3)	
Tx	18 (16.5)	12 (19.0)	6 (13.0)	
Primary tumor size, cm (median [IQR])	9.5 [6.4–13.5]	10.5 [6.7–15.7]	8.5 [6–11]	0.11
Driver mutation				0.08
KIT	68 (62.4)	38 (60.3)	30 (65.2)	
Not tested	18 (16.5)	11 (17.5)	7 (15.2)	
Other	6 (5.5)	4 (6.3)	2 (4.3)	
PDGFRA	8 (7.3)	7 (11.1)	1 (2.2)	
SDH	9 (8.3)	3 (4.8)	6 (13.0)	
Tumor rupture	12 (11.0)	11 (17.5)	1 (2.2)	0.01
Margins at curative-intent primary resection				0.47
Metastatic at diagnosis	53 (48.6)	33 (52.4)	20 (43.5)	
R0	49 (45.0)	25 (39.7)	24 (52.2)	
R1	7 (6.4)	5 (7.9)	2 (4.3)	
Primary mitotic count (per 50 HPF)				0.21
Unknown	42 (38.5)	20 (31.7)	22 (47.8)	
0–5	14 (12.8)	7 (11.1)	7 (15.2)	
6–10	23 (21.1)	15 (23.8)	8 (17.4)	
>10	30 (27.5)	21 (33.3)	9 (19.6)	
Modified NIH risk				0.58
High	50 (45.9)	28 (44.4)	22 (47.8)	
Intermediate	4 (3.7)	1 (1.6)	3 (6.5)	
Low	2 (1.8)	1 (1.6)	1 (2.2)	
Very low	1 (0.9)	1 (1.6)	0 (0)	
Metastatic at diagnosis	52 (47.7)	32 (50.8)	20 (43.5)	
Curative-intent combined primary resection and metastasectomy	16 (14.7)	5 (8.1)	11 (23.9)	0.02
Site(s) of first metastasis				0.56

Table 1 (continued)

Variable	Total [*n* = 109]	10-year non-survivors [*n* = 63]	10-year survivors [*n* = 46]	*p*-Value
Liver	48 (44.0)	27 (42.9)	21 (45.7)	
Peritoneum	40 (36.7)	24 (38.1)	16 (34.8)	
Liver, bone	1 (0.9)	0 (0)	1 (2.2)	
Liver, bone, peritoneum	2 (1.8)	2 (3.2)	0 (0)	
Liver, peritoneum	18 (16.5)	10 (15.9)	8 (17.4)	
Resected liver metastasis	41 (37.6)	17 (27.0)	24 (52.2)	0.007
Resected peritoneal metastasis	29 (26.6)	13 (20.6)	16 (34.8)	0.10
Months from diagnosis to metastasis (median [IQR])	15 [0–34.5]	13.5 [0–33.5]	16 [0–34.5]	0.99
Months of TKI therapy prior to metastasis (median [IQR])	0 [0–12]	0 [0–12]	0 [0–0]	0.32
Time to first progression				<0.001
<2 years	58 (53.2)	50 (79.4)	8 (17.4)	
2–5 years	17 (15.6)	11 (17.5)	6 (13.0)	
5–10 years	17 (15.6)	2 (3.2)	15 (32.6)	
No progression within 10 years	17 (15.6)	0 (0)	17 (37.0)	

Data are expressed as *n* (%) unless otherwise specified

IQR interquartile range, *HPF* high-powered field, *NIH* National Institutes of Health, *TKI* tyrosine kinase inhibitor, *GIST* gastrointestinal stromal tumor

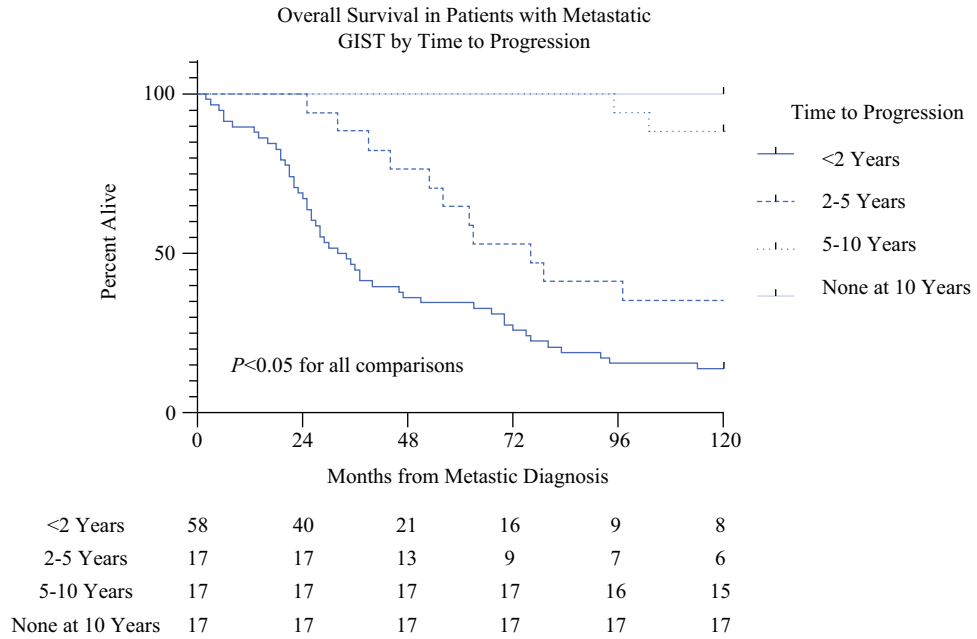

FIG. 1 Kaplan–Meier survival curves for patients with metastatic GIST stratified by time to first progression on first-line therapy. Ten-year overall survival for patients progressing within 2 years, 2–5 years, 5–10 years, and >10 years was 14%, 35%, 88%, and 100%, respectively ($p < 0.05$ for all intergroup comparisons). *GIST* gastrointestinal stromal tumor

not included in modeling, as all but one patient with tumor rupture died prior to 10 years and stable models could not be generated with inclusion of this variable.

Progression-Free Survival

Given the predominant prognostic importance of time to first progression on survivorship for all *KIT*-mutated GISTs, we investigated this variable further in our cohort. On Kaplan–Meier analysis, the estimated median PFS was 23 months overall, 31 months for patients with *KIT* mutations, 13 months for patients with non-*KIT* mutations, and 18 months for patients without sequenced tumors (Fig. 2). Differences between *KIT* and non-*KIT* GISTs were statistically significant ($p = 0.006$) on log-rank testing, while comparisons of *KIT* and non-*KIT* GISTs with non-sequenced tumors were not significant ($p > 0.1$ for both).

On univariable analysis (Table 3), compared with patients with *KIT* mutations, those with *PDGFRA* mutations had worse 10-year PFS, as did older patients. Patients

TABLE 2 Clinicopathologic and treatment factors associated with 10-year survivorship in patients with metastatic GIST demonstrating progression before 10 years

Variable	Univariable OR (95% CI)	*p*-Value	Multivariable OR (95% CI)	*p*-Value
Months from diagnosis to metastasis (per 6-month interval)	1.00 (0.88–1.13)	0.94	–	–
Age at metastasis (per additional year)	0.94 (0.91–0.97)	<0.001	0.96 (0.92–0.99)	0.03
Male	0.71 (0.29–1.73)	0.45	–	–
Therapeutic-intent metastasectomy	6.76 (2.48–18.41)	<0.001	3.06 (0.87–10.70)	0.08
White/Caucasian	0.59 (0.12–2.81)	0.51	–	–
Gastric primary	1.33 (0.55–3.22)	0.53	–	–
Primary size	–	–	–	–
T1/T2 primary	Referent	–	–	–
T3/T4 primary	0.98 (0.22–4.28)	0.98	–	–
Unknown primary size	0.67 (0.11–3.99)	0.66	–	–
Driver mutation	–	–	–	–
Non-*KIT* mutation	Referent	–	–	–
KIT driver mutation	1.00 (0.35–2.89)	>0.99	–	–
Untested mutational status	0.55 (0.11–2.61)	0.45	–	–
Primary mitotic count	–	–	–	–
≤5 per 50 HPF	Referent	–	–	–
>5 per 50 HPF	0.44 (0.11–1.83)	0.26	–	–
Unknown	1.4 (0.35–5.64)	0.64	–	–
Modified NIH risk at diagnosis			–	–
Metastatic at diagnosis	Referent		–	–
Very low to intermediate	2.13 (0.38–11.84)	0.39	–	–
High	0.84 (0.33–2.12)	0.71	–	–
Liver-only disease at metastatic diagnosis	1.24 (0.52–3.01)	0.63	–	–
Months of TKI therapy prior to metastasis (per additional year)	0.99 (0.96–1.02)	0.47	–	–
Years to progression (per additional year)	1.88 (1.43–2.46)	<0.001	1.71 (1.30–2.24)	<0.001

OR odds ratio, *CI* confidence interval, *HPF* high-powered field, *NIH* National Institutes of Health, *TKI* tyrosine kinase inhibitor, *GIST* gastrointestinal stromal tumor

undergoing therapeutic-intent metastasectomy had improved PFS. On multivariable analysis, *PDGFRA* mutations and other non-*KIT* mutations were independently associated with worse PFS compared with *KIT* mutations, as was increasing age at metastasis. Therapeutic-intent metastasectomy was independently associated with improved 10-year PFS.

For patients with known *KIT* mutations ($n = 68$), PFS on imatinib was very heterogeneous, ranging from first progression at 2–160 months following metastatic diagnosis. Fifty-five (81%) patients had exon 11 mutations. To further evaluate factors associated with these heterogeneous outcomes, we performed Cox proportional hazards analysis of 10-year PFS in this subgroup. On univariable analysis, age at metastatic diagnosis and increasing years of TKI therapy prior to metastatic diagnosis was significantly associated with inferior 10-year PFS, while a *KIT* exon 11 driver mutation was associated with improved 10-year PFS (Table 4). Therapeutic intent metastasectomy, duration of TKI therapy prior to metastatic diagnosis, primary tumor grade, and liver-only metastatic disease were not associated with 10-year PFS but met thresholds for inclusion in the initial multivariable model ($p < 0.2$ for all).

On multivariable analysis following single backward elimination, older age at metastasis was associated with inferior 10-year PFS, while therapeutic-intent metastasectomy and *KIT* exon 11 mutations were associated with improved 10-year PFS. Primary tumor grade and liver-only metastatic distribution were not independently associated with 10-year PFS.

Post-Progression Survival

In patients experiencing progression, the estimated median post-progression survival was 28 months (95% CI 10–46 months). Given the lack of prognostic tools for this

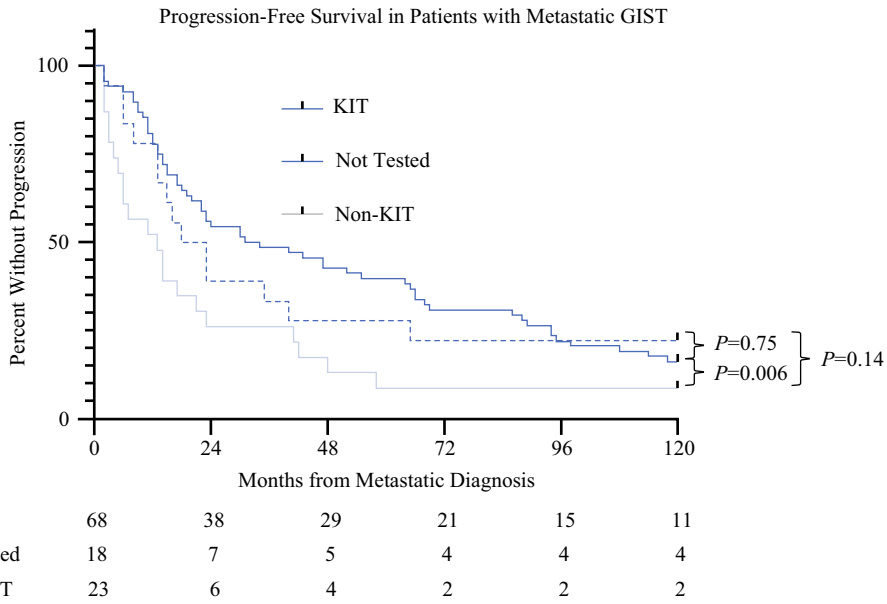

FIG. 2 Kaplan–Meier survival curves for patients with metastatic GIST stratified by driver mutation. Patients with *KIT* mutations have improved survival at 10 years compared with patients with non-*KIT* mutations ($p = 0.006$). No survival difference was noted for patients with untested mutational status compared with *KIT* ($p = 0.75$) or non-*KIT* mutations ($p = 0.14$). *GIST* gastrointestinal stromal tumor

TABLE 3 Multivariable regression For 10-year progression-free survival in Patients with metastatic GIST

Variable	Univariable HR (95% CI)	*p*-Value	Multivariable HR (95% CI)	*p*-Value
Age at metastasis (per additional year)	1.02 (1.01–1.04)	0.005	1.04 (1.02–1.05)	<0.001
Male	1.07 (0.70–1.63)	0.75	–	–
Therapeutic-intent metastasectomy	0.57 (0.38–0.87)	0.008	0.63 (0.40–0.99)	0.04
White/Caucasian	1.49 (0.67–3.13)	0.35	–	–
Gastric primary	0.98 (0.65–1.49)	0.94	–	–
Neoadjuvant therapy prior to primary resection	1.22 (0.72–2.07)	0.46	–	–
Primary T stage	–	–	–	–
T1/T2	Referent	–	–	–
T3/T4	0.96 (0.48–1.93)	0.92	–	–
Tx	1.23 (0.54–2.79)	0.62	–	–
Driver mutation	–	–	–	–
KIT driver mutation	Referent	–	Referent	–
SDH	1.41 (0.67–2.97)	0.36	3.84 (1.54–9.56)	0.004
PDGFRA	3.19 (1.48–6.87)	0.003	2.33 (1.06–5.10)	0.04
Not tested	1.1 (0.61–1.98)	0.75	0.70 (0.38–1.29)	0.25
Other mutation	2.13 (0.85–5.35)	0.11	3.57 (1.38–9.27)	0.009
Primary mitotic count	–	–	–	–
≤5 per 50 HPF	Referent	–	–	–
>5 per 50 HPF	1.48 (0.76–2.87)	0.25	–	–
Unknown	1.25 (0.63–2.47)	0.52	–	–
NIH risk group	–	–	–	–
High	Referent	–	–	–
Very low to intermediate	1.02 (0.43–2.41)	0.96	–	–
Synchronous disease	1.32 (0.87–2.03)	0.20	–	–
Liver-only disease at metastasis diagnosis	1.26 (0.84–1.91)	0.27	–	–
Months of TKI therapy prior to metastatic diagnosis	1.01 (0.99–1.02)	0.23	–	–

HR hazard ratio, *CI* confidence interval, *HPF* high-powered field, *NIH* National Institutes of Health, *TKI* tyrosine kinase inhibitor, *GIST* gastrointestinal stromal tumor

TABLE 4 Multivariable analysis of 10-year progression-free survival in patients with *KIT*-mutated metastatic GIST

Variable	Univariable HR (95% CI)	*p*-Value	Multivariable HR (95% CI)	*p*-Value
Age at metastasis (per additional year)	1.03 (1.01–1.06)	0.009	1.03 (1.01–1.06)	0.01
Male	1.13 (0.66–1.92)	0.66	–	–
Therapeutic-intent metastasectomy	0.61 (0.36–1.04)	0.07	0.54 (0.31–0.96)	0.04
White/Caucasian	1.58 (0.63–3.96)	0.33	–	–
Gastric primary	0.85 (0.48–1.50)	0.58	–	–
Primary T stage	–	–	–	–
T1/T2	Referent	–	–	–
T3/T4	0.69 (0.31–1.54)	0.36	–	–
Tx	0.95 (0.35–2.56)	0.92	–	–
KIT mutation location	–	–	–	–
Exon 9	Referent	–	Referent	–
Exon 11	0.37 (0.19–0.71)	0.003	0.32 (0.15–0.71)	0.005
Primary mitotic count	–	–	*	–
≤5 per 50 HPF	Referent	–	–	–
>5 per 50 HPF	1.76 (0.80–3.90)	0.16	–	–
Unknown	1.24 (0.55–2.82)	0.61	–	–
Modified NIH risk	–	–	–	–
High risk	Referent	–	–	–
Very low to intermediate	1.42 (0.49–4.09)	0.52	–	–
Synchronous disease	1.35 (0.79–2.33)	0.27	–	–
Liver-only disease at metastatic diagnosis	1.69 (0.99–2.89)	0.06	*	–
Months of TKI therapy prior to metastatic diagnosis	1.02 (1.01–1.03)	0.04	*	–

*Removed from the final model following single backward elimination

HR hazard ratio, *CI* confidence interval, *HPF* high-powered field, *NIH* National Institutes of Health, *TKI* tyrosine kinase inhibitor, *GIST* gastrointestinal stromal tumor

population, we sought to characterize survival outcomes following first progression of metastatic disease. On univariable analysis, older age at first progression was associated with worse post-progression survival, while increasing years to first progression was associated with improved post-progression survival (Table 5). Male sex was not significantly associated with post-progression survival but met thresholds for inclusion in the initial multivariable model. Following single backward elimination, older age at first progression and additional years to first progression were independently associated with worse and improved post-progression survival, respectively.

DISCUSSION

Factors influencing long-term prognosis in patients with mGIST remain poorly understood. To our knowledge, the present study is the largest study of mGIST patients in which all subjects have a minimum of 10 years of follow-up or death, making its conclusions uniquely precise for estimating survival and progression-related factors up to this timepoint. Our results show that 10-year survivorship is increasingly possible in patients with mGIST with modern targeted therapies, a benchmark that will only become more achievable as additional therapies are developed. Additionally, we present a novel analysis suggesting that the time to first progression following diagnosis of mGIST is an independent prognostic factor of both overall and post-progression survival. We have recently reported similar findings in patients with recurrent GIST following curative-intent resection, where longer disease-free intervals are associated with improved post-recurrence survival and PFS.[16] Together, these findings suggest that such intervals play an important and previously unrecognized role in prognosticating patients with GIST in many settings.

Our results also support the important role of metastasectomy in mGIST, when possible, which was independently associated with improved PFS in all patients and those with *KIT*-mutated tumors. The fact that improved PFS did not translate to a significantly improved OS is likely reflective of the exclusion of patients who did not progress at 10 years

TABLE 5 Multivariable analysis of post-progression survival in patients with metastatic GIST

Variable	Univariable HR (95% CI)	*p*-Value	Multivariable HR (95% CI)	*p*-Value
Age at first progression (per additional year)	1.04 (1.02–1.05)	<0.001	1.03 (1.02–1.05)	<0.001
Male	1.42 (0.87–2.34)	0.16	*	–
White/Caucasian	1.58 (0.58–4.34)	0.37	–	–
Gastric primary	0.84 (0.52–1.36)	0.48	–	–
Primary T stage	–	–	–	–
T1/T2	Referent	–	–	–
T3/T4	0.77 (0.36–1.62)	0.48	–	–
Tx	1.09 (0.46–2.57)	0.85	–	–
Driver mutation	–	–	–	–
Non-*KIT* mutation	Referent	–	–	–
KIT mutation	1.25 (0.68–2.29)	0.48	–	–
Untested mutational status	1.45 (0.67–3.14)	0.35	–	–
Modified NIH risk at diagnosis	–	–	–	–
Metastatic at diagnosis	Referent	–	–	–
Very low to intermediate	1.04 (0.41–2.67)	0.93	–	–
High	1.22 (0.75–1.98)	0.42	–	–
Years to first progression (per additional year)	0.85 (0.77–0.95)	0.004	0.87 (0.78–0.97)	0.01

*Removed from the final model following single backward elimination

HR hazard ratio, *CI* confidence interval, *NIH* National Institutes of Health, *GIST* gastrointestinal stromal tumor

(many of whom underwent metastasectomy) from the analysis, which was necessary to investigate time to first progression as a prognostic variable. Additionally, given the observed association of metastasectomy itself with PFS, our cohort may have been underpowered to detect an independent effect of metastasectomy on survival after accounting for time to first progression. In the modern era of multiple lines of TKI therapy, studies investigating the impact of metastasectomy on outcomes may require larger numbers or >10 years of follow-up to be suitably powered, given the excellent outcomes experienced by many patients. Regardless, in patients for whom R0 metastasectomy is technically possible, the present results support the continuation of this practice.

This study is limited by its retrospective nature and by its grounding in a prospectively maintained database. Additionally, the method of patient collection for the study makes it ill-suited to draw conclusions as to the relative frequencies of 10-year survivors versus non-survivors in mGIST. It was not uncommon for 10-year survivors to have been treated medically and surgically at multiple GIST centers in addition to OHSU, and patients referred to our center may not have been representative of the population at large. Additionally, patients undergoing curative-intent (R0/R1) metastasectomy may have inherently better prognosis than patients not undergoing metastasectomy (due to lower disease burden or other unmeasured factors), and the present study is not well-suited to evaluate whether an independent benefit of metastasectomy in this population exists for either OS or PFS after accounting for disease characteristics. Additionally, the present study is limited by sample size due to the rarity of patients with mGIST, which hampers efforts to collect large cohorts of this population with long-term follow-up data.

CONCLUSION

Patients with metastatic GIST have experienced dramatically improved outcomes in the modern era of the multiple TKI therapies available, with 10-year survivorship likely achievable in at least 40% of patients compared with 25% 5-year survival in the pre-imatinib era.[6] The principal driver of prognosis in this population is time to first progression on first-line therapy; however, disease progression is an apparently stochastic event, with progression at times separated by 5 years or more in patients with identical driver mutations. Given the importance that time to first progression plays in survival, additional study of contributory factors to this phenomenon may lead to improved prognostic capability and therapies in treating patients with metastatic GIST.

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