

ORIGINAL ARTICLE



Prediction of long-term survival in patients with metastatic gastrointestinal stromal tumor: analysis of a large, single-institution cohort

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ABSTRACT

Background: A subset of patients with metastatic GIST become long-term survivors, and a more precise prediction of outcome could improve clinical decision-making.

Material and methods: One-hundred and thirty-three patients diagnosed with metastatic GIST from 1995 to 2013 were identified from the sarcoma database at Oslo University Hospital. Clinical data prospectively registered in the database were supplemented with retrospective review of medical records. Factors associated with survival were analyzed using Kaplan–Meier curves, log-rank test, univariate and multivariate Cox regression analyses.

Results: One-hundred and fifteen patients with metastatic GIST were included in the final study cohort. Median overall survival (OS) was 6.9 years (95% CI 5.6–8.3). Factors associated with long-term survival in univariate analysis were good baseline performance status (ECOG ≤ 1 ; $p < .001$), young age ($p = .022$), oligometastatic disease (OMD) (≤ 3 metastases; $p < .001$), maximum tumor diameter < 5 cm ($p < .001$), surgery for metastatic disease ($p = .005$), surgery of the primary tumor ($p < .001$), normal baseline hemoglobin level ($p = .05$), normal baseline albumin level ($p = .001$) and normal baseline neutrophil count ($p = .03$). On multivariate analysis, good performance status, small tumor diameter and, OMD were the factors associated with long-term survival. Five and 10-year OS for patients with OMD were 89% and 71%, respectively, compared to 38% and 20% for patients with polymetastatic disease ($p < .001$).

Conclusions: In this single-institution cohort of patients, OMD was as a strong prognostic factor in patients with metastatic GIST. Patients with OMD had an outcome similar to patients with high-risk localized disease, and should be regarded as a separate category among patients with metastatic GIST.

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Introduction

Gastrointestinal stromal tumor (GIST) is a mesenchymal neoplasm thought to originate from the interstitial cells of Cajal in the myenteric plexus [1]. Mutations in genes coding for either the stem cell factor receptor *KIT* or the platelet-derived growth factor receptor alpha (*PDGFRFA*) are found in the majority of GISTs, and these mutations are considered the main drivers of tumor development and progression [2]. Historically, patients with metastatic GIST had a poor prognosis with a median overall survival (OS) of 1–2 years [3,4]. Treatment was mostly limited to surgery as the response to conventional chemotherapy and radiotherapy was poor [5]. Imatinib mesylate (IM) is an inhibitor of tyrosine kinase receptors. It was introduced in the treatment of GIST in 2001, leading to a substantial improvement in clinical outcome [6]. Median OS of six years may now be expected in metastatic GIST [7,8], and IM is the standard of care [9]. Sunitinib and regorafenib are considered the best second and third line drugs, respectively [9]. Efficacy of IM has also been proven in

the adjuvant setting after complete resection of primary high-risk GIST [10]. At present, three years of adjuvant treatment is recommended [9].

There is considerable variation in outcome among patients with metastatic GIST. Some have rapid tumor progression whereas others may live for more than 10 years with metastatic disease [11]. In clinical trials, resistance to IM has occurred at a median time of 18–26 months [7,12]. Studies in real-life practice show a median progression free survival (PFS) of 30–40 months [8,13,14]. Treatment resistance is usually caused by secondary *KIT* mutations [15], and time to development of TKI-resistant disease is probably a key determinant of survival. Factors associated with long-term survival in clinical trials include *KIT* exon 11 mutation, female sex, normal albumin levels, neutrophil and lymphocyte count, good performance status and small tumor diameter [7,8]. Nomograms for PFS and OS have been developed, and risk factors included are size of the largest metastasis, tumor genotype, primary tumor mitotic count, hemoglobin and neutrophil count at commencement of IM [16]. There are

limited data regarding treatment and long-term outcome in routine practice. In a single-institution study from Taiwan, good performance status, absence of primary IM resistance and small tumor volume was associated with longer OS [14]. A nationwide study from Poland reported that long-term survivors were characterized by small maximum tumor diameter at IM start, better hematological and clinical chemistry parameters, good performance status, and surgical removal of residual disease [13].

In this study, the treatment of patients with metastatic GIST at Oslo University Hospital (OUH) over a 18-year period is reported. Our primary goal was to identify factors associated with long-term survival after the introduction of IM, aiming to improve prediction of survival and, subsequently, clinical decision-making.

Material and methods

The Sarcoma Group at the Norwegian Radium Hospital, OUH, is a referral center for bone and soft tissue sarcoma in the south-eastern region of Norway, with a population of 2.8 million. Demographical, clinical and pathology data are recorded prospectively in a database.

Patients

One hundred and thirty-three patients diagnosed with metastatic GIST from 1 January 1995 to 1 January 2013 were identified from the sarcoma database. The diagnosis was confirmed by a sarcoma pathologist according to the World Health Organization recommendations [17]. All tumors were either positive for CD 117 (*KIT*) by immunostaining AND/OR had a mutation in the *KIT* gene. Metastatic GIST was defined as metastases to the liver, intraperitoneal cavity or other organs. Eighteen patients were excluded from the final study cohort for the following reasons: diagnosis and death before the introduction of IM (four patients); death before admission (four patients); surgery at OUH, but medical treatment and followed-up at other sarcoma centers (seven patients); and metastatic GIST later disproved (three patients). The final cohort consisted of 115 patients with metastatic GIST. Data were retrieved from the sarcoma database and supplemented by retrospective review of medical records. The study was approved by the local data protection officer and informed consent was obtained from all patients.

Definitions

The number of metastases and the size of the largest tumor were retrospectively classified. Maximal diameter of the largest tumor (primary tumor or metastasis) was defined as the largest diameter of the largest tumor at the start of systemic treatment. Oligometastatic disease (OMD) was defined as ≤ 3 tumors detectable on computed tomography (CT) at commencement of systemic treatment of metastatic disease, including patients who had undergone complete resection of the primary tumor and metastatic lesions before start of systemic treatment. Polymetastatic disease (PMD) was defined

as ≥ 4 detectable tumors on CT scan at the beginning of systemic treatment.

Statistical analysis

All analyses were performed using SPSS 21.0 (SPSS, Chicago, IL). For the survival analysis, the Kaplan–Meier estimator was used with the log-rank test for categorical comparisons and Cox regression model for continuous variables. OS was calculated from the date of diagnosis of metastatic disease to the date of death from any cause or 1 January 2016 for patients still alive. Survival data were retrieved from the National Registry of Norway. Associations between OS and the following variables were assessed: age at diagnosis of metastatic disease, gender, primary tumor genotype, maximum diameter of the largest tumor at the start of systemic treatment, OMD versus PMD, site of metastasis (liver, intraperitoneal, both and others), primary tumor site (stomach, small bowel and other), baseline (1–7 days before start of IM) albumin level (low < 35 g/L versus normal ≥ 35 g/L), baseline hemoglobin level (low < 11 g/100 mL or normal ≥ 11 g/100 mL), baseline neutrophil count (high $> 5.0 \times 10^9$ /L versus normal $\leq 5.0 \times 10^9$ /L), baseline lactate dehydrogenase (LD) (normal ≤ 205 U/L or high > 205 U/L), baseline performance status according to Eastern Cooperative Oncology group (ECOG) system (good: 0 and 1 and poor ≥ 2), surgery of primary tumor (yes or no), and any surgery of metastatic disease (yes or no). For multivariate analysis, we used a Cox regression model that included gender, age and all covariates significant at the 5% level in univariate analysis. Differences were considered statistically significant if the *p* values were $< .05$. Chi-squared test, Fisher's exact test or Student's *t*-test were used to compare groups (OMD versus PMD) as appropriate.

Results

Patient characteristics

The clinical and histopathological data are summarized in Table 1. There were 69 males and 46 females, and the median age at diagnosis of metastatic disease was 64 years (range 31–88). The majority of the primary tumors were located in the small intestine and the stomach. Fifty-six percent had metastasis at the time of primary diagnosis. Of the 50 patients with localized disease, 43 had high-risk tumors according to modified National Institute of Health criteria, three had intermediate, one had low and three could not be determined. The median time to development of metachronous metastasis was 20 months (range 3–156). Nine of 50 patients with localized disease received adjuvant IM (median duration 12 months; range 6–36). Forty percent had liver metastases only, 29% had peritoneal metastases only, 27% had both liver and peritoneal disease, and 4% had metastasis to other organs (lung and/or bone). Thirty-six percent of the patients had ≤ 3 detectable metastases at the start of systemic treatment (defined as OMD), whereas 64% had ≥ 4 metastases (defined as PMD). Mutation status was available for 94 patients and the most frequent was *KIT* exon 11 mutation followed by *KIT* exon 9 (Table 1). Comparing patients

Table 1. Baseline clinical and histopathological data of the study cohort.

Gender	
Female	46 (40)
Male	69 (60)
Localization	
Stomach	49 (43)
Small bowel	52 (45)
Colon/rectum	7 (6)
Peritoneal	3 (3)
Unknown ^a	4 (3)
Histological subtype	
Spindle cell	85 (81)
Epithelioid	5 (5)
Mixed	15 (14)
ND	10
<i>KIT/PDGFR</i> A mutations	
<i>KIT</i> exon 11	68 (72)
<i>KIT</i> exon 9	11 (12)
<i>KIT</i> exon 13	2 (2)
<i>PDGFR</i> A exon 18	2 (2)
<i>PDGFR</i> A exon 12	1 (1)
Analyzed, not detected	10 (11)
ND	21
Metastatic site	
Liver	46 (40)
Peritoneal	33 (29)
Liver and peritoneal	31 (27)
Others	5 (4)
Metastasis at diagnosis	
Yes	65 (56)
No	50 (44)
Number of metastases	
Oligometastatic (≤ 3)	41 (36)
Polymetastatic (≥ 4)	74 (64)
Max. size of the largest tumor	
<5 cm	65 (57)
≥ 5 cm	50 (43)
Mitotic count	
<10	29 (41)
≥ 10	41 (59)
ND	45
Baseline hemoglobin level	
Normal (≥ 11 g/100 ml)	91 (87)
Low (<11 g/100 ml)	14 (13)
ND	10
Baseline albumin level	
Normal (≥ 35 g/ml)	86 (84)
Low (<35 g/ml)	16 (16)
ND	13
Baseline neutrophil count	
Normal ($\leq 5 \times 10^9/L$)	67 (64)
High ($> 5 \times 10^9/L$)	37 (36)
ND	11
Baseline lactate dehydrogenase level	
Normal (≤ 205 U/L)	69 (66)
High (> 205 U/L)	35 (34)
ND	11
Performance status	
ECOG ≤ 1	88 (85)
ECOG ≥ 2	15 (15)
ND	12

ND: not determined; ECOG: Eastern Cooperative Oncology group; *PDGFR*A: platelet-derived growth factor α .

Values in parenthesis are percentages.

^aPrimary tumor localization not established.

Table 2. Systemic treatment.

Medication	1. Line (n = 112)	2. Line (n = 35)	3. Line (n = 19)	4. Line (n = 11)	5. Line (n = 3)
Imatinib	110	2	4	3	1
Nilotinib	2	–	1	–	1
Sunitinib	–	33	2	–	–
Pazopanib	–	–	6	1	–
Regorafenib	–	–	4	4	–
Sorafenib	–	–	2	3	1

with OMD more often underwent surgery of the primary tumor, surgery of metastatic disease and surgery during systemic treatment (Table 2, supplementary).

Treatment

Before the decision to start systemic treatment, our multidisciplinary team considered the appropriateness of radical surgical resection. Thirty-eight of 64 patients with synchronous metastasis underwent surgery before start of systemic treatment. Twelve of these patients had complete resection of the primary tumor and metastases, whereas 26 patients underwent limited surgery of the primary tumor or selected metastatic lesions with metastases left behind. One hundred and twelve of 115 patients started systemic treatment for metastatic disease. Two patients underwent complete resection of a gastric primary tumor and synchronous intraperitoneal metastases but never started systemic treatment. Neither of these have developed disease recurrence. One patient with a *PDGFR*A D842V substitution never started systemic treatment and has undergone surgery for metastatic disease twice. IM was first-line treatment for 110 patients and nilotinib for two patients. Thirty-five patients received second line treatment, and 19 received third line treatment. Subsequently, patients were treated with experimental therapy (nilotinib/pazopanib), off-label use of sorafenib, reintroduction of IM or best supportive care without systemic therapy. The systemic treatment given is summarized in Table 2. Median time on first, second and third lines of treatment were 49 months (range 1–161), 7 months (range 0.2–74) and 5 months (range 1–32), respectively. Thirty patients underwent a surgical procedure during the course of systemic treatment (Table 3). Patients were submitted to surgery for various reasons; nine patients for residual disease after response to IM, 12 patients for one or two progressive metastases and continued IM, and nine patients had symptomatic, non-progressive metastases that were resected due to pain, pressure on vital organs, tumor perforation or tumor bleeding. Four patients received palliative radiotherapy due to symptomatic metastases.

Outcome

The median OS was 6.9 years (CI: 5.6–8.3) (Figure 1(a)). After a median follow-up of 9.0 years, 52 patients (43%) were still alive. Of the 63 patients registered as dead, 57 died of metastatic GIST, whereas six died of other or unknown causes. The following factors were significantly associated with longer OS in univariate analysis: good baseline performance

with OMD and PMD we observed no difference in terms of age, sex, site of the primary disease, mutations, site of metastatic disease, metastasis at diagnosis, mitotic count, baseline neutrophil count or baseline LD. However, patients with OMD had significantly better performance status, smaller diameter of the largest tumor, and higher hemoglobin and albumin level (Table 1, supplementary). Furthermore, patients

Table 3. Treatment in metastatic setting.

Number of surgical procedures (including primary surgery)	
0	22 (19)
1	59 (51)
2	27 (24)
3	4 (4)
4	1 (1)
5	2 (2)
Surgery of primary tumor	
Yes	89 (77)
No	26 (23)
Surgery for metastatic disease	
Yes	49 (43)
No	66 (66)
Surgery after start of systemic treatment	
No	85 (74)
Surgery of residual disease	9 (8)
Surgery of progressive metastasis	12 (10)
Surgery of symptomatic metastasis ^a	9 (8)
Radiotherapy	
Yes	4 (3)
No	111 (97)
Systemic treatment	
Yes	112 (97)
No	3 (3)

Values in parenthesis are percentages.

^aNon-progressive metastasis.

status (ECOG status ≤ 1), age below median (64 years), OMD (≤ 3 metastases), small diameter of the largest tumor (< 5 cm), surgery for metastatic disease, surgery of the primary tumor, normal baseline hemoglobin level (≥ 11.0 g/100 mL), normal baseline albumin level (≥ 35 g/L), and normal baseline neutrophil count ($\leq 5.0 \times 10^9/l$) (Figure 1(b–d); Table 4).

Patients with OMD had a five-year and 10-year OS of 89% and 71%, respectively, compared to 38% and 20% for patients with PMD ($p < .001$; Figure 1(b)). The OMD group comprised 12 patients who had undergone complete resection before the start of systemic treatment. There was no difference in OS between patients with a complete resection and patients with 1–3 metastases ($p = .38$; Supplementary Figure 1a). OS was similar in patients with 4–5 metastases compared to patients with ≥ 6 metastases ($p = .38$; Supplementary Figure 1b). There was no difference in outcome for patients with synchronous and metachronous metastatic disease (Figure 2, supplementary).

Multivariate analysis was performed with gender, age, baseline performance status, baseline hemoglobin level, baseline albumin level, baseline neutrophil count, maximum

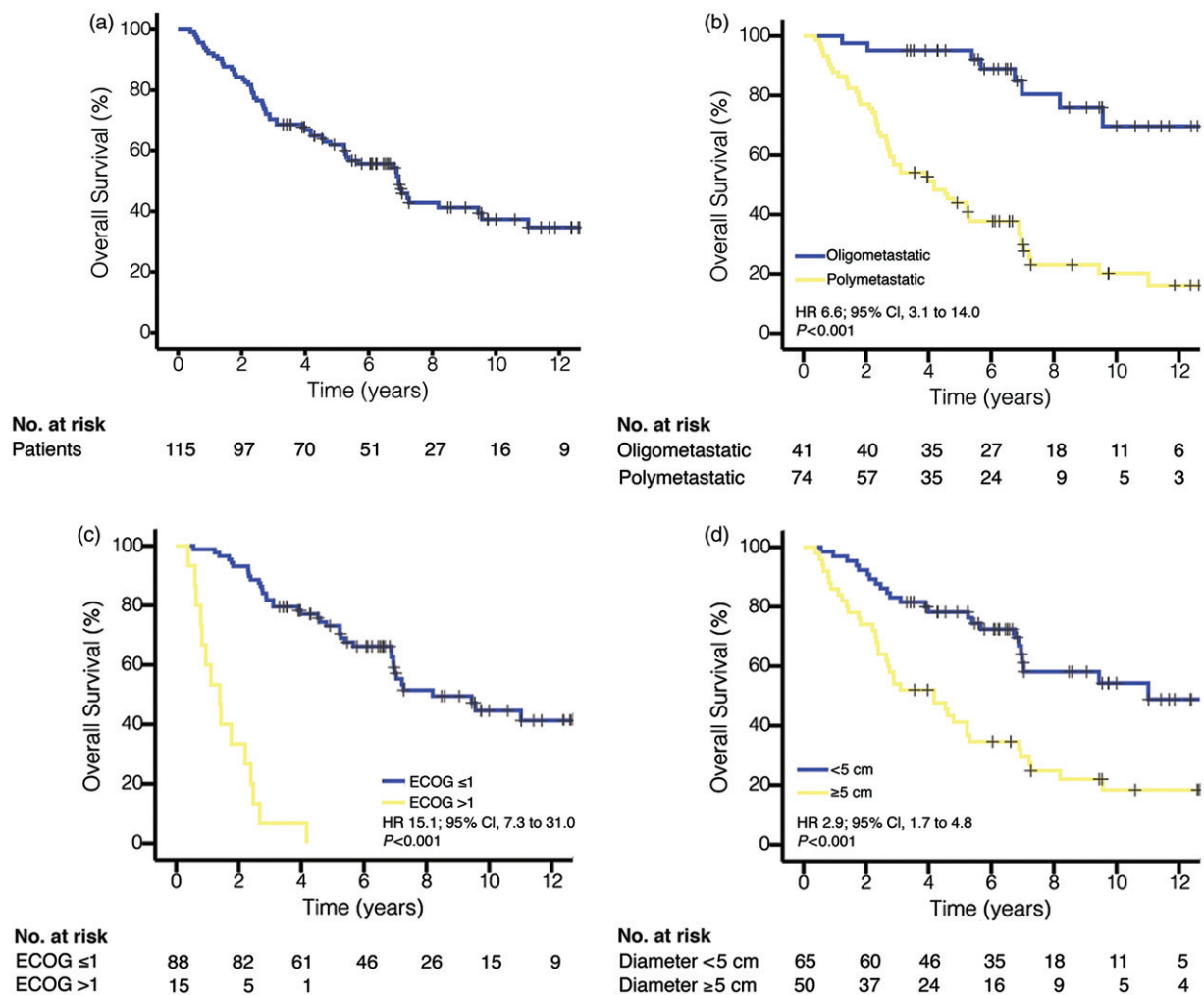


Figure 1. (a–d) Kaplan–Meier survival curves of overall survival. (a) For the complete cohort; (b) stratified according to number of metastases; (c) stratified according to performance status; (d) stratified according to maximum size of the largest tumor. HR: hazard ratio; CI: confidence interval.

Table 4. Univariate and multivariate survival analyses.

Parameter	Univariate		Multivariate	
	HR (95% CI)	p Value	HR (95% CI)	p Value
Gender		.22		.70
Female	1.0		1.0	
Male	1.4 (0.8–2.3)		1.1 (0.6–2.1)	
Age		.02		.20
<64 years	1.0		1.0	
≥64 years	1.8 (1.1–3.0)		1.5 (0.8–2.8)	
Primary tumor site		.73		
Stomach	1.0			
Small bowel	0.8 (0.5–1.4)			
Others	0.9 (0.5–1.9)			
Surgery of primary tumor ^a		<.001		
Yes	1.0			
No	2.9 (1.7–4.9)			
Metastasis at diagnosis		.31		
No	1.0			
Yes	1.3 (0.8–2.2)			
Metastatic site		.48		
Liver	1.0			
Intraperitoneal	0.9 (0.5–1.8)			
Liver and intraperitoneal	1.5 (0.8–2.6)			
Others	1.5 (0.5–5.1)			
Number of metastases		<.001		<.001
Oligometastatic (≤3)	1.0		1.0	
Polymetastatic (≥4)	6.6 (3.1–14.0)		6.8 (2.6–17.8)	
Max. size of the largest tumor		<.001		.04
<5 cm	1.0		1.0	
≥5 cm	2.9 (1.7–4.8)		1.8 (1.0–3.2)	
KIT/PDGFRα mutations		.54		
KIT exon 11	1.0			
KIT exon 9	1.3 (0.6–2.9)			
Analyzed, not detected	1.6 (0.7–3.6)			
Others	0.5 (0.1–3.6)			
Mitotic count		.14		
<10	1.0			
≥10	1.8 (0.8–4.0)			
Surgery of metastatic disease ^a		<.001		
Yes	1.0			
No	2.1 (1.2–3.5)			
Baseline hemoglobin level		.05		.08
Normal (≥11 g/100 ml)	1.0		1.0	
Low (<11 g/100 ml)	1.9 (1.0–3.6)		2.7 (0.9–8.2)	
Baseline albumin level		<.001		.17
Normal (≥35 g/ml)	1.0		1.0	
Low (<35 g/ml)	2.9 (1.6–5.2)		1.8 (0.8–2.7)	
Baseline neutrophil count		.03		.24
Normal (≤5 × 10 ⁹ /L)	1.0		1.0	
High (>5 × 10 ⁹ /L)	1.8 (1.1–3.0)		1.5 (0.8–2.7)	
Baseline lactate dehydrogenase level		.13		
Normal (≤205 U/L)	1.0			
High (>205 U/L)	1.5 (0.9–2.5)			
Performance status		<.001		<.001
ECOG ≤1	1.0		1.0	
ECOG >1	15.6 (7.3–31.0)		11.4 (4.9–26.6)	

ECOG: Eastern Cooperative Oncology group; PDGFRα: platelet-derived growth factor α.

^aNot included in multivariate analysis.

tumor diameter and OMD/PMD as covariates. The variables significantly associated with longer OS were OMD ($p < .001$; HR 6.8; CI 95% 2.6–17.8), small diameter of the largest tumor ($p = .04$; HR 1.8; CI 95% 1.0–3.2), and good baseline performance status ($p < .001$; HR 11.4; CI 95% 4.9–26.6) (Table 4).

Discussion

In the present study, we have identified OMD, defined as the presence of ≤3 metastases at commencement of systemic treatment, as a strong predictor of long-term survival in patients with metastatic GIST. Patients with OMD had an

excellent prognosis, with estimated 5- and 10-year OS of 89% and 71%, respectively. To our knowledge, this is the first study demonstrating OMD as a powerful prognostic factor in metastatic GIST.

It is well known that some sarcoma and colorectal cancer patients with OMD may be cured by metastasectomy combined with systemic treatment, and five-year survival rates above 30% have been reported [18,19]. In metastatic GIST, a few retrospective studies [20–22] and two small prospective studies [23,24] have reported favorable outcomes after surgery of residual disease in patients responding to IM. It has, on a general basis, been suggested that OMD could be

regarded as an intermediate disease state between locoregional and widespread metastatic disease, with the implication that patients with OMD should be considered for curative treatment [25]. The five-year OS in our cohort was 89% and the five-year OS in the Scandinavian Sarcoma Group (SSG) XVIII/Arbeitsgemeinschaft Internistische Onkologie (AIO) trial, where patients with high-risk, localized tumors received adjuvant IM for three years, was 91% [10,26]. Based on our findings, we suggest that oligometastatic GIST should be regarded as a separate disease category more similar to high-risk primary tumors than disseminated metastatic disease.

The excellent OS in patients with OMD raises the question whether a curative treatment strategy is realistic. In the BRF 14 trial, metastatic GIST patients responding to first-line IM were randomly assigned to continue or stop IM, and nearly all patients who stopped had disease progression within two years, regardless of whether they had used IM for 1, 3 or 5 years prior to discontinuation [27–29]. However, stopping IM did not significantly influence OS, probably because most patients in the interruption group responded well to IM reinstitution. Surgical resection of metastatic lesions was not required for inclusion, and the majority of patients had residual disease at IM discontinuation [27–29]. We have recently hypothesized that surgical removal of residual metastatic disease is a prerequisite for discontinuation of IM [30], and that such a strategy for highly selected patients with OMD may be curative. This is now being explored in a prospective phase II trial ('SSG XXV: The STOP-GIST trial'; Clin. Gov. NTC02924714).

Patients with large tumors had inferior survival in our study, and previous studies have also shown that a high maximum tumor diameter is associated with shorter PFS [7,13,14]. The most important IM resistance mechanism is the occurrence of secondary *KIT* mutations [15], and time to IM resistance is closely related to OS. The probability of developing such mutations is largely dependent on the degree of genomic instability (i.e., the frequency by which new mutations occur) and the tumor burden (i.e., the number of dividing tumor cells). Our findings support this notion, as both patients with small tumor diameter and patients with OMD have a low tumor volume. The degree of genomic instability is unknown in routine clinical practice. Algorithms to classify primary GISTs according to genomic alterations have been proposed [31], but whether they predict IM resistance has not been investigated. Assessing genomic instability may further improve outcome prediction in metastatic GIST, and should be explored in future studies.

Contrary to other studies [7,8,13], we were not able to detect any statistically significant association between *KIT* exon 11 mutations and favorable prognosis. However, mutation analysis was not performed in all patients, and the number of mutations other than *KIT* exon 11 (*KIT* exon 9, $n = 11$; mutations not detected, $n = 10$; and other mutations, $n = 5$) was too small to perform robust statistical analysis.

All patients were discussed in a multidisciplinary team when progressive disease was detected. Surgical resection or local ablation of focally progressive disease [22,32] was regularly recommended, in order to postpone a change of systemic therapy if medically justifiable. In selected cases, IM

was continued beyond progression based on formal response criteria such as RECIST, when the team considered this as the best option for the patient. The median treatment duration of IM was 49 months. Even though time on IM and PFS cannot be directly compared, 49 months is considerably longer than the PFS of 18–37 months reported in other studies [6,12–14]. Whether continuation of IM beyond progression in selected cases could be beneficial is not adequately studied in our cohort, but the long median OS suggests that prolonging the time on IM and delaying a change of systemic therapy should be further investigated.

There are limitations to this study. The majority of the clinical data were retrospectively collected. PFS and response rates were not investigated since radiology review would have been mandatory and a consistent response evaluation was unavailable. However, of the 63 patients registered as dead, 57 died of metastatic GIST; hence, we believe that the reported OS data reflect disease mortality and that OS is a valid endpoint in this cohort. Finally, it is a strength, that all patients had follow-up in one institution and were treated by a limited number of sarcoma specialists who all belong to the same multidisciplinary team.

In conclusion, we have identified OMD as a strong prognostic factor in this single-institution cohort of patients with metastatic GIST. Patients with OMD had an outcome similar to patients with high-risk localized disease, and should be regarded as a separate category among patients with metastatic GIST.

Disclosure statement

The authors report no conflict of interest.

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