

ORIGINAL RESEARCH

Sex differences in patients with gastrointestinal stromal tumours: do they exist and does it affect survival?

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Background: Sex differences in cancer have gained attention in recent years. The role of sex as a prognostic factor in gastrointestinal stromal tumours (GIST) has not been well established. The aim of this research was to elucidate potential sex differences in GIST patients and the influence of sex on disease-specific survival (DSS).

Methods: A review of the literature was carried out to obtain an overview of all literature with sex as a covariate on GIST survival analyses. Furthermore, in the Dutch GIST Registry, GIST characteristics between males and females were compared and the influence of sex on DSS was analysed.

Results: A total of 118 articles from the review of the literature met our selection criteria; 58% of the articles found no sex difference in survival and 42% did find a sex difference. All differences favoured female patients, although there was substantial overlap of individual patients in the various reported groups. The Dutch GIST Registry cohort consisted of 1425 patients (46% female). Compared with female patients, male patients had larger tumours (mean 9.0 cm versus 7.9 cm) and higher mitotic rates (34.4% versus 28.0% >5 mitoses/5 mm²). GIST in males was more often metastasized at diagnosis (21.3% versus 13.7%) and incurable (38.5% versus 31.0%). Male patients less often received surgery of the primary tumour (71.7% versus 78.9%), but did experience more tumour ruptures (18.2% versus 13.3%). Male patients had a worse DSS than females. This was not statistically significant when corrected for differences in GIST characteristics.

Conclusions: In case of sex differences in GIST in the literature, male patients have a worse outcome. In our Dutch GIST cohort a similar finding was made, but sex was shown not to be an independent factor. Male patients more often had aggressive GISTs, with larger tumours, higher mitotic rates, more tumour ruptures, and metastases, which could explain the sex differences in DSS.

Key words: GIST, sex differences, sex factors, gender, disease-specific survival

INTRODUCTION

Sex and gender are important determinants in medicine. Although sex and gender are often used interchangeably in practice, both terms have a different meaning. Gender considers socially constructed roles and behaviours that influence self-identity and self-expression and is influenced by social, environmental, cultural, and behavioural factors.¹ Sex refers specifically to biological differences, such as sex chromosomes, sexual hormone levels, and reproductive

anatomy.¹ Sex differences in cancer patients have gained attention in recent years.^{2,3} In cancer in non-reproductive organs, the presentation, incidence, and prognosis can differ considerably between males and females. Female patients are more often diagnosed with breast cancer and tumours of the endocrine system, but the cancer incidence rate in the United States was higher for male patients in the majority of other cancer sites.⁴ Furthermore, survival of Kaposi sarcoma patients was worse for female patients, but for all other major cancer site groupings (e.g. digestive system, soft tissue, endocrine system, lymphoma) age-adjusted survival was worse for male patients.⁴ These sex differences seem to be caused by behavioural and environmental factors or by physiological differences. A report from a European Society of Medical Oncology (ESMO) workshop on sex medicine and oncology in 2019

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summarizes that clinically relevant physiological sex differences in oncology include differences in tumour biology, immune system activity, body composition, and drug pharmacokinetics and pharmacodynamics.³

Gastrointestinal stromal tumours (GISTs) arise throughout the gastrointestinal tract, originate from the interstitial cells of Cajal in the gastrointestinal tract,⁵ and are therefore classified as soft tissue sarcoma. Although it is the most common gastrointestinal sarcoma subtype, the estimated incidence of GIST is only 10-15 patients per million per year.⁶ Median age at diagnosis is 60-65 years and there is a slightly higher incidence in males.⁷ Oncogenic driver mutations in GIST are mostly *KIT* (75%) or *PDGFRA* mutations (10%-15%).⁸⁻¹⁰ Systemic therapy targeting these mutations with tyrosine kinase inhibitors (TKIs), such as imatinib, sunitinib, and regorafenib, have considerably improved overall survival (OS).¹¹ Important prognostic factors for GIST include the mitotic rate, tumour size, and tumour site.¹² Perioperative tumour rupture is also recognized as an adverse prognostic factor.^{7,13} The role of sex as a prognostic factor, however, has not yet been well established.

A recent paper by Rong et al.¹⁴ compared the presentation of gastric GIST between males and females and their OS. Male sex was an adverse prognostic factor for OS according to their multivariable Cox regression analysis. Although sex quite often has been included as a covariate on multivariable survival analyses, no articles compared male and female GIST characteristics in all GIST patients. Besides, the studies that did include sex as a covariate on multivariable analyses did not provide an unequivocal conclusion.

Therefore, the present paper aims to clarify the issue of possible sex differences in GIST patients, focussing on potential differences in tumour and treatment characteristics, and disease-specific survival (DSS). First, a review of the literature on sex as a prognostic factor in GIST patients will be carried out and discussed. Second, tumour and patient characteristics and DSS of male and female GIST patients will be compared in a large Dutch GIST cohort.

METHODS

Review of the literature on sex differences in GIST survival

Two searches were carried out in PubMed on 28 October 2021. We used both MeSH terms and searched in the title, abstract, and keywords. In the first search, we searched for GIST in combination with 'sex factors'. To expand the search strategy, we added the results from a second search for GIST in combination with 'gender' or 'male and female' and 'overall survival or disease specific survival'. We applied no limits for publication date. All available articles written in English with >100 GIST patients and sex as a factor in the survival analysis were eligible.

Cohort study

All patients registered in the Dutch GIST Registry (DGR), who were diagnosed with GIST between January 2009 and

June 2021, were included in the cohort study. The DGR is a database containing data of adult GIST patients treated in one of the five Dutch GIST centres (LUMC Leiden, Erasmus MC Rotterdam, UMC Groningen, Radboudumc Nijmegen, and the Netherlands Cancer Institute Amsterdam). Data on patient characteristics, tumour characteristics, treatment and side-effects, laboratory results, and outcome are prospectively maintained in the DGR. The DGR was approved by the local independent ethics committee (IRBd20-212). For the cohort study, patient and tumour characteristics, including molecular pathology reports, and treatment and follow-up data were collected from the DGR. Tumour status at diagnosis was considered as localized disease for patients with a local or locally advanced GIST, and as metastasized for patients with distant metastases. The required total count of mitoses in GIST is per 5 mm². With the use of older microscope models, 50 high power fields (HPF) was used, which we considered semi-equivalent to 5 mm². Low mitotic rate was defined as ≤5 mitoses/5 mm² and high as >5 mitoses/5 mm². Patients were subdivided into risk groups based upon the risk classification as specified by Miettinen's criteria.¹² Response evaluation and follow-up of GIST patients treated in Dutch GIST centres is done according to national guidelines that are based on the most recent ESMO guidelines.⁷ Considered as patients in the palliative setting are patients with incurable, advanced GIST (mostly patients with distant metastases or sometimes locally advanced inoperable GIST).

Statistical analyses

Differences between males and females were investigated using Fisher's exact test for categorical variables and Mann-Whitney *U* tests for numeric variables. DSS was calculated from the date of diagnosis to the date of death from GIST or last follow-up. Follow-up time was estimated using the reverse Kaplan-Meier method. The Kaplan-Meier method was used to estimate DSS, censoring deaths from other causes. For a separate analysis, DSS after the start of palliative treatment was calculated in the subgroup of patients with systemic palliative treatment. DSS was compared between males and females using the log-rank test, and multivariable Cox regression analysis for DSS was done to adjust for potential differences between males and females at baseline. At first, separate variables were included in a univariable analysis. Thereafter, sex and variables with a *P* value <0.10 in the univariable analysis were included in the multivariable model. Variables with a *P* value <0.05 in the multivariable model were considered significant. Additionally, a propensity score was estimated using factors that differed between males at baseline, were identified in the DSS analysis, or found in the literature review. The propensities given these factors were then used as regression weights (one divided by the propensity of the actual sex) in a proportional hazards model to analyse DSS by sex. Multiple imputation was carried out (with 20 imputations) to account for missing values in factors used for the propensity score. Statistical analyses were carried out in

SPSS Statistics Version 25 and R version 4.4.4 (R Project, Vienna, Austria) with the multiple-imputation algorithm from package *mice* version 3.13.

RESULTS

Review of the literature on sex differences in GIST patients' survival

The search strategy resulted in a total of 819 articles. Based on the abstract, 598 articles were excluded (Supplementary Figure S1, available at <https://doi.org/10.1016/j.esmoop.2022.100649>). The three most common reasons for exclusion were <100 included patients ($n = 367$), no GIST ($n = 76$), or were not available in English ($n = 76$). Thereafter, another 103 articles were excluded after full read, mostly because sex was not incorporated as a variable in the survival model ($n = 75$).

Finally, 118 articles met the selection criteria. Supplementary Table S1, available at <https://doi.org/10.1016/j.esmoop.2022.100649>, contains an overview of these 118 articles. Within this selection, several publications included patients who had an overlapping presence in different groups. For example, 24 articles described patient groups from the Surveillance, Epidemiology, and End Results (SEER) program, 5 articles patient groups from the National Cancer Database (NCDB), and 4 articles patient groups from the Memorial Sloan Kettering Cancer Center (MSKCC). The SEER program publishes population-based cancer incidence and survival data from different states in the United States (US), covering ~48% of the US population.¹⁵ The SEER program includes the New York State Cancer Registry¹⁶ and since the MSKCC is located in New York, patients registered in the MSKCC database are most likely also present in the SEER program. The NCDB is a non-population-based cancer registry sourced from hospital registry data covering ~70% of all newly diagnosed cancer cases in the US.¹⁷ Substantial overlap of patients within the SEER program with the NCDB is therefore expected.

From all 118 articles, 68 articles (58%) found no sex difference for survival on univariable analysis ($n = 46$) or multivariable analysis ($n = 22$). In contrast, 50 articles (42%) did find a sex difference on their survival analyses: 8 on univariable analyses [outcome measures: OS, $n = 3$; disease-free survival (DFS), $n = 1$; recurrence-free survival (RFS), $n = 1$; risk of mortality, $n = 1$; relative survival, $n = 1$; DSS, $n = 1$] and 42 on multivariable analyses (outcome measures: OS, $n = 25$; DSS, $n = 13$; RFS, $n = 2$; DFS, $n = 1$; progression-free survival, $n = 1$).

In all the articles that found a significant sex difference for survival, female patients had a better outcome. On the multivariable analysis, female hazard ratio (HR) varied from 0.56 to 0.79 for DSS and from 0.18 to 0.83 for OS.

Of note, at least 26 articles (53%) that found a sex difference for survival conceivably used overlapping datasets, partially reporting on the same patients (SEER database $n = 19$, NCD $n = 5$, MSKCC $n = 2$). From a total of 13 articles with a better DSS for female patients on multivariable analyses, 11 articles were SEER cohorts and 2 articles were

MSKCC cohorts, which obviously would introduce bias if included in a classical meta-analysis. Besides, from the 13 articles that found a better DSS for female GIST patients, only 2 articles did correct for three other established prognostic factors (i.e. tumour size at diagnosis, stage at diagnosis, and mitotic rate at baseline) in the multivariate model (both SEER cohorts, one gastric only and one all patients).

Just one paper compared GIST characteristics between male and female patients as a primary objective. In the study by Rong et al.,¹⁴ 1050 gastric GIST patients (51% females) at all stages were selected from the SEER program. Male patients underwent surgery less often (95.9% versus 98.1% for females, $P = 0.032$), had relatively larger tumours (>5 cm in 49.6% versus 39.4% for females, $P = 0.001$), and were significantly more often married. Mitotic index appeared to be lower in female patients (<5/50 HPF in 82.9% versus 77.0% for males, $P = 0.044$). After propensity score matching, the OS was worse for male patients with an HR of 1.7 [95% confidence interval (CI) 1.2-2.4, $P = 0.007$] on multivariate analysis.

Cohort study

Patient and tumour characteristics of males and females with GIST from the DGR. From the 1425 GIST patients who were included, 766 patients were male (53.8%) and 659 female (46.2%). Mean age at diagnosis was 63.4 years and did not differ between males and females (Table 1). The most common primary tumour location for both female and male GIST patients was gastric and no sex difference was observed in the incidence of second malignancies. Male GIST patients, however, did have significantly larger tumours at baseline compared with female patients (9.0 cm versus 7.9 cm, respectively, $P = 0.02$). In addition, male patients had considerably more often metastatic disease at time of diagnosis (21.3% versus 13.7% for females, $P < 0.001$).

Regarding tumour characteristics, male GIST patients more often had a high mitotic rate compared with females (34.4% versus 28.0%, $P = 0.02$). No difference in the histology of GIST was found for males and females, with mostly spindle cell type GIST (77.6% in all patients). GIST driver mutations did not differ significantly between males and females, with *KIT* (62.6%) and *PDGFR* (10.8%) mutations accounting for the majority of all mutations in both sexes. Male patients had a baseline high-risk GIST in 35.6% of cases, while female patients had a high-risk GIST in 26.9% of cases ($P = 0.06$).

Treatment of males and females with GIST. Overall, 875 patients were treated with imatinib at any time point during their course of treatment (Table 2). Neoadjuvant imatinib was given in 24.5% of all patients, whereas adjuvant imatinib was prescribed to 27.2% of the patients after surgery. Overall, males more often received imatinib (65.3% versus 56.9%, $P = 0.001$), but this difference did not remain significant for the neoadjuvant, adjuvant, and palliative imatinib treatments separately. Female patients more

Table 1. Baseline characteristics of males and females with GIST in the DGR

	Total (%) N = 1425	Males (%) N = 766 (53.8)	Females (%) N = 659 (46.2)	P value ^a
Mean age at diagnosis (SD)	63.4 (12.9)	63.3 (12.7)	63.5 (13.2)	0.59
Mean tumour size at diagnosis in cm (SD)	8.5 (6.2)	9.0 (6.7)	7.9 (5.6)	0.02*
Primary tumour site				0.28
Stomach	868 (61.8)	457 (60.5)	411 (63.2)	
Small intestine	389 (27.7)	217 (28.7)	172 (26.5)	
Rectum	73 (5.2)	45 (6.0)	28 (4.3)	
Other ^b	75 (5.3)	36 (4.8)	39 (6.0)	
Unknown	20	11	9	
Tumour status at diagnosis				<0.001*
Localized disease	1172 (82.2)	603 (78.7)	569 (86.3)	
Metastasized disease	253 (17.8)	163 (21.3)	90 (13.7)	
Second malignancy				0.85
No	1088 (76.4)	583 (76.1)	505 (76.6)	
Yes	337 (23.6)	183 (23.9)	154 (23.4)	
Histology				0.11
Spindle cell	1023 (77.6)	529 (75.4)	494 (80.2)	
Epithelioid	140 (10.6)	81 (11.5)	59 (9.6)	
Mixed type	155 (11.8)	92 (13.1)	63 (10.2)	
Unknown	107	64	43	
Baseline mitotic rate				0.02*
Low (<=5/5 mm ²)	772 (68.7)	386 (65.6)	386 (72.0)	
High (>5/5 mm ²)	352 (31.3)	202 (34.4)	150 (28.0)	
Unknown	301	178	123	
Baseline risk according to Miettinen				0.06
None	91 (9.6)	44 (9.2)	47 (10.1)	
Very low	150 (15.9)	73 (15.3)	77 (16.6)	
Low	228 (24.1)	111 (23.1)	117 (25.2)	
Moderate	180 (19.0)	81 (16.9)	99 (21.3)	
High	296 (31.3)	171 (35.6)	125 (26.9)	
Unknown	227	123	104	
Not applicable (M1 at diagnosis)	253	163	90	
GIST driver mutation				0.59
KIT	892 (62.6)	481 (62.8)	411 (62.4)	
PDGFR	154 (10.8)	86 (11.2)	68 (10.3)	
NF1 associated	28 (2.0)	11 (1.4)	17 (2.6)	
SDH deficiency	17 (1.2)	7 (0.9)	10 (1.5)	
Other (e.g. BRAF, NTRK, unclassified)	91 (6.4)	50 (6.5)	41 (6.2)	
No mutation analysis carried out	243 (17.1)	131 (17.1)	112 (17.0)	

DGR, Dutch GIST Registry; GIST, gastrointestinal stromal tumour; SD, standard deviation.

^aFisher's exact test for categorical variables and Mann–Whitney *U* tests for numeric variables.

^bOther tumour locations such as colon, oesophagus, liver, multifocal, peritoneum, or small pelvis not further specified.

*P value <0.05 was considered significant.

frequently underwent surgery of the primary tumour (78.9% versus 71.7%, *P* = 0.002), which might be explained by the finding that more males had metastatic disease at diagnosis and therefore were no longer eligible for primary surgery. From the patients that had surgery of the primary GIST (*n* = 1069), 159 patients had perioperative tumour rupture, being more common in male than in female patients (18.2% versus 13.3%, respectively, *P* = 0.04).

Not only did more males have metastatic disease at diagnosis, male GIST patients also developed metastases more often during follow-up in this cohort (male 38.5% versus female 31.0%, median follow-up 3.43 years for males

Table 2. Treatment characteristics and metastatic patterns of males and females with GIST in the DGR

	Total (%) N = 1425	Males (%) N = 766 (53.8)	Females (%) N = 659 (46.2)	P value ^a
Imatinib in any setting				0.001*
No	550 (38.6)	266 (34.7)	284 (43.1)	
Yes	875 (61.4)	500 (65.3)	375 (56.9)	
Neoadjuvant imatinib				0.62
No	1076 (75.5)	574 (74.9)	502 (76.2)	
Yes	349 (24.5)	192 (25.1)	157 (23.8)	
Surgery of primary tumour				0.002*
No	356 (25.0)	217 (28.3)	139 (21.1)	
Yes	1069 (75.0)	549 (71.7)	520 (78.9)	
Perioperative tumour rupture				0.04*
No	812 (84.2)	400 (81.8)	412 (86.7)	
Yes	152 (15.8)	89 (18.2)	63 (13.3)	
Unknown	105	60	45	
Adjuvant imatinib				0.09
No	778 (72.8)	387 (70.5)	391 (75.2)	
Yes	291 (27.2)	162 (29.5)	129 (24.8)	
Palliative setting anytime during follow-up ^b				0.003*
No	926 (65.0)	471 (61.5)	455 (69.0)	
Yes	499 (35.0)	295 (38.5)	204 (31.0)	
Palliative imatinib				0.36
No	49 (9.8)	26 (8.8)	23 (11.3)	
Yes	450 (90.2)	269 (91.2)	181 (88.7)	
Palliative sunitinib				0.23
No	304 (60.9)	173 (58.6)	131 (64.2)	
Yes	195 (39.1)	122 (41.4)	73 (35.8)	
Palliative regorafenib				0.19
No	411 (82.4)	237 (80.3)	174 (85.3)	
Yes	88 (17.6)	58 (19.7)	30 (14.7)	
Other palliative systemic treatment ^c				0.008*
No	430 (86.2)	244 (82.7)	186 (91.2)	
Yes	69 (13.8)	51 (17.3)	18 (8.8)	
Local treatment of metastases				0.90
No	428 (85.8)	252 (85.4)	176 (86.3)	
Yes	71 (14.2)	43 (14.6)	28 (13.7)	
Patients with metastases ^d	482 (100)	286 (59.3)	196 (40.7)	
Liver metastases				0.15
No	182 (37.8)	100 (35.0)	82 (41.8)	
Yes	300 (62.2)	186 (65.0)	114 (58.2)	
Peritoneal metastases				0.04*
No	185 (38.4)	121 (42.3)	64 (32.7)	
Yes	297 (61.6)	165 (57.7)	132 (67.3)	
Non-liver/non-peritoneal metastases				0.28
No	417 (86.5)	243 (85.0)	174 (88.8)	
Yes	65 (13.5)	43 (15.0)	22 (11.2)	
Lymph node metastases				0.03*
No	460 (95.4)	268 (93.7)	192 (98.0)	
Yes	22 (4.6)	18 (6.3)	4 (2.0)	

DGR, Dutch GIST Registry; GIST, gastrointestinal stromal tumour.

^aFisher's exact test for categorical variables and Mann–Whitney *U* tests for numeric variables.

^bConsidered as patients in the palliative setting are patients with incurable, advanced GIST (mostly patients with distant metastases or sometimes locally advanced inoperable GIST).

^cOther than imatinib, sunitinib, or regorafenib.

^dPatients can have multiple distant metastases locations (e.g. liver and peritoneum or liver and lymph node).

*P value <0.05 was considered significant.

versus 3.39 years for females). Once in the palliative treatment setting, no differences were found between males and females regarding percentage of patients

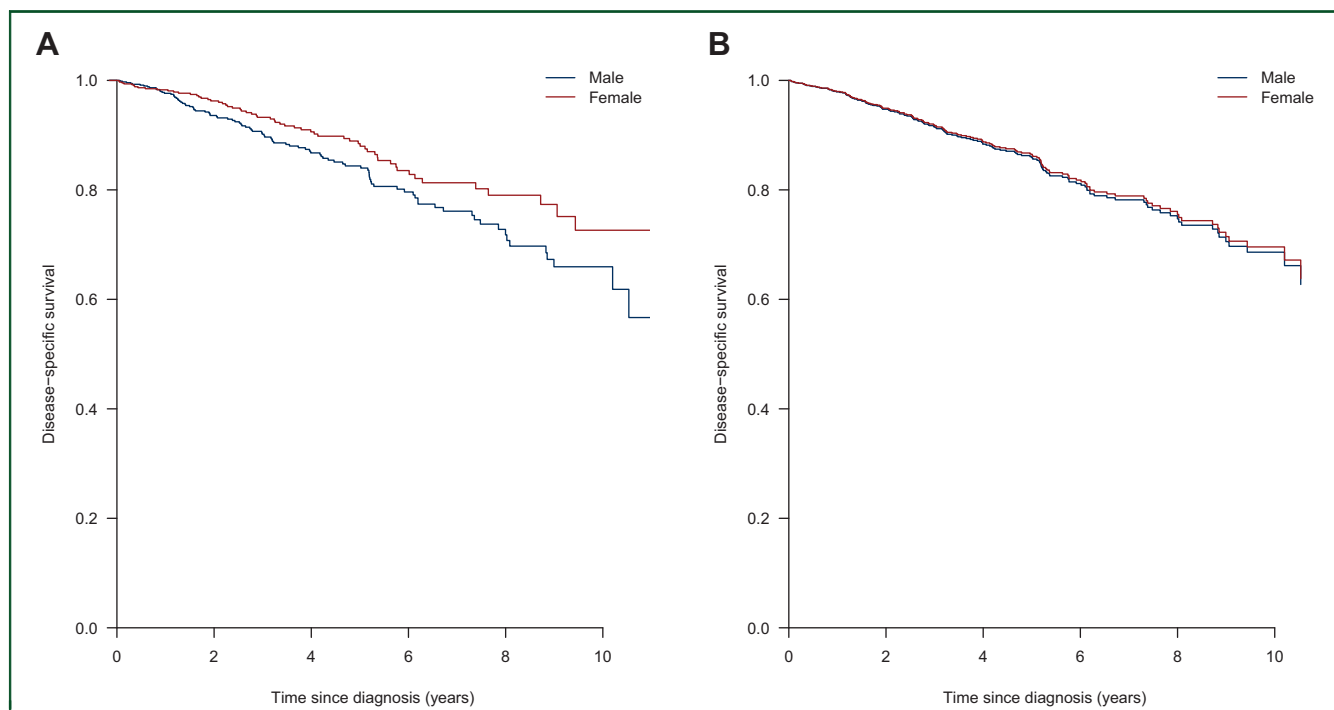


Figure 1. (A) Kaplan–Meier estimated disease-specific survival. (B) Predicted disease-specific survival curves after weighting and multiple imputation.

receiving palliative imatinib, sunitinib, or regorafenib treatment. Furthermore, local treatment of metastases occurred both in males and females with GIST.

Metastatic patterns among males and females with GIST.

From the patients with GIST metastases, several sex differences were found regarding the location of GIST metastases (Table 2). Firstly, females more often had peritoneal metastases (67.3% versus 57.7% for males, $P = 0.04$). By contrast, males significantly more often had lymph node metastases, although the number of patients with lymph node metastases was low (6.3% males versus 2.0% females, $P = 0.03$). No significant sex differences were found in the frequency of liver metastases or metastases outside of the liver and peritoneum.

Survival of males and females with GIST. The median follow-up time in the cohort was 3.4 years (interquartile range 1.1–6.1 years). Within the follow-up time, 158 patients died due to disease progression. Using the Kaplan–Meier method, the DSS was significantly longer for female GIST patients compared with male GIST patients ($P = 0.04$, median not reached) (Figure 1A).

Multiple imputation was carried out for missing values of likely confounders (percentage missing values: number of mitoses 21.1%, *KIT* exon 11 mutation status 17.1%, histology 7.5%, tumour rupture 7.4%, baseline primary tumour size 4.1%, location primary tumour 1.4%). After multiple imputation, a Cox regression analysis was carried out. Using the P value threshold of 0.05, higher age, larger baseline tumour size, metastatic disease at diagnosis, and no surgery of the primary tumour were associated with worse DSS on multivariable Cox regression analysis (Table 3). Sex was not

a significant prognostic factor for DSS on multivariable Cox regression analysis after multiple imputation (female HR 0.86, 95% CI 0.61–1.22, $P = 0.41$, Figure 1B), nor in a propensity-score weighted Cox model after multiple imputation (female HR 0.96, 95% CI 0.69–1.33, $P = 0.82$).

DSS was also analysed for the 470 patients treated with systemic treatment in the palliative setting (281 males and 189 females). No multiple imputation or weighting was carried out in this subgroup. In this analysis, 109 patients were excluded for analysis due to missing data and therefore 361 patients were included in the model, 97 of who died from the disease (Table 4). Females did not have a significantly better DSS than males on univariable analysis (HR 1.18, 95% CI 0.85–1.65 compared with males) or in a multivariable model (HR 1.13, 95% CI 0.73–1.77) after start of palliative systemic therapy. Patients without surgery of the primary tumour (HR 1.78) and patients without *KIT* exon 11 mutation (HR 2.10) had a significantly higher risk for death from disease.

DISCUSSION

Although some previous studies suggest that female GIST patients have a better outcome, and female patients also had a better outcome in a large Dutch GIST cohort on univariable analysis, sex was not an ‘independent’ prognostic variable for DSS in a multivariable analysis, nor when using the propensity score. The reason why sex seems prognostic in our univariable analyses is possibly because males have more aggressive GIST characteristics at baseline (i.e. larger tumours, with high mitotic rate, and more often ruptured) and are more likely to have metastatic GIST. Once

Table 3. Multivariable model of disease-specific survival in entire DGR cohort after multiple imputation (n = 1425, 158 events)

	Univariable analysis			Multivariable analysis		
	HR	95% CI	P value	HR	95% CI	P value
Sex						
Male	Reference			Reference		
Female	0.71	0.52-0.98	0.04*	0.86	0.61-1.22	0.41
Age at diagnosis (years)	1.03	1.01-1.04	<0.001*	1.02	1.01-1.03	0.01**
Tumour size at diagnosis (cm)	1.08	1.05-1.10	<0.001*	1.05	1.02-1.07	<0.001**
Primary site			<0.001* (3 df)			0.43 (3 df)
Stomach	Reference			Reference		
Small intestine	0.96	0.66-1.38	0.82	1.05	0.71-1.54	0.82
Rectum	0.60	0.26-1.38	0.23	0.71	0.31-1.64	0.42
Other	3.31	1.97-5.57	<0.001	1.48	0.84-2.61	0.18
Tumour status at diagnosis						
Local disease	Reference			Reference		
Metastatic disease	7.37	5.36-10.14	<0.001*	2.99	1.96-4.54	<0.001**
Baseline mitotic rate						
Low ($\leq 5/5 \text{ mm}^2$)	Reference			Reference		
High ($> 5/5 \text{ mm}^2$)	1.93	1.33-2.79	0.001*	1.50	1.05-2.13	0.03
KIT status						
KIT exon 11	Reference					
Non-KIT exon 11	1.26	0.90-1.77	0.18			
Surgery of primary tumour						
Yes	Reference			Reference		
No	6.96	5.07-9.55	<0.001*	2.96	1.97-4.44	<0.001**
Perioperative tumour rupture						
Yes	0.82	0.49-1.37	0.45			
No	Reference					

CI, confidence interval; df, degrees of freedom; DGR, Dutch GIST Registry; HR, hazard ratio.

*Variables with $P < 0.10$ in univariable analysis were included in multivariable analysis.

** $P < 0.05$ is considered significant in multivariable analysis.

started with palliative systemic treatment, no association of sex with DSS was found, not even in univariable analysis.

This is the first study specifically looking at sex differences in GIST at all locations and comparing GIST-specific survival in male and female GIST patients. As mentioned before, Rong et al.¹⁴ recently published a paper on sex differences in gastric GIST patients. As outcome measure, they used OS. Because females have a longer life expectancy in the general population worldwide,¹⁸ however, DSS seems a more appropriate outcome measure to assess the prognostic value of sex. Another statistical limitation in the analysis of Rong et al.¹⁴ is that they did not correct for stage of disease in their multivariable model. This could have affected the results since we know survival is worse for patients with metastatic disease compared with those with local disease only.¹⁹ In a sensitivity analysis on our dataset, the difference in DSS between males and females disappeared even in a model with sex and disease stage without any further covariates (results not shown), although removal of disease stage from the multivariable presented in Table 3 did not change much in the estimated HR of sex.

Several limitations are inherent to the retrospective design of this study. For example, we had to use multiple imputation to handle missing baseline characteristics. Nevertheless, this is a large GIST cohort with real-world data from GIST expertise centres with uniform practices, enabling the comparison of GIST characteristics and GIST-specific survival between males and females.

As reported in the ESMO report on gender medicine, differences in drug pharmacokinetics and pharmacodynamics could play a role in why cancer outcome differs for males and females.³ These factors were not taken into account in the current cohort study, nor in the survival analyses described in the current review of the literature. For GIST patients, however, previous studies have shown that the exposure to the TKIs imatinib and sunitinib differed between male and female GIST patients. Male GIST patients more often have a low imatinib exposure,²⁰ probably because of a higher imatinib clearance.²¹ Also for sunitinib, female sex was identified as a covariate that significantly increases sunitinib exposure in a population pharmacokinetic analysis.²² These differences in exposure might have contributed to the survival difference found in the US cohorts, since adequate exposure to imatinib or sunitinib is correlated with a better outcome.²³ In the current Dutch cohort, the majority of patients received therapeutic drug monitoring, where the TKI dose was adjusted based on measured drug levels. It could be that more males in the Dutch cohort did have an adequate TKI exposure after dose increases based on therapeutic drug monitoring. For future research, it would be interesting to include adequate TKI exposure, TKI dose and toxicity in the survival model to establish their role in potential sex differences for GIST survival.

It remains unclear why some historical cohorts did find a sex difference in relation to outcome and in the current Dutch cohort sex was shown not to be an independent

Table 4. Disease specific survival in GIST patients of the DGR treated with palliative systemic treatment (n = 361 patients / 97 events in multivariable analysis)

	Univariable analysis			Multivariable analysis		
	HR	95% CI	P value	HR	95% CI	P value
Sex						
Male	Reference			Reference		
Female	1.18	0.85-1.65	0.32	1.13	0.73-1.77	0.58
Age at diagnosis (years)	1.01	1.00-1.03	0.04*	1.01	0.99-1.03	0.29
Tumour size at diagnosis (cm)	1.03	1.00-1.05	0.06*	1.02	0.99-1.05	0.30
Primary site			0.004* (3 df)			0.15 (3 df)
Stomach	Reference			Reference		
Small intestine	0.56	0.38-0.83	0.004*	0.68	0.42-1.09	0.11
Rectum	0.47	0.19-1.15	0.10*	0.59	0.22-1.59	0.30
Other	1.24	0.72-2.12	0.44	1.41	0.72-2.74	0.31
Tumour status at diagnosis						
Local disease	Reference			Reference		
Metastatic disease	1.40	1.00-1.96	0.05*	0.83	0.51-1.35	0.45
Baseline mitotic rate						
Low ($\leq 5/5$ mm ²)	Reference					
High ($> 5/5$ mm ²)	1.31	0.86-1.98	0.21			
KIT status						
KIT exon 11	Reference			Reference		
Non-KIT exon 11	1.89	1.33-2.69	<0.001*	2.10	1.38-3.19	<0.001**
Surgery of primary tumour						
Yes	Reference			Reference		
No	1.83	1.32-2.53	<0.001*	1.78	1.07-2.94	0.03**
Perioperative tumour rupture						
No	Reference			Reference		
Yes	0.48	0.27-0.83	0.009*	0.63	0.32-1.22	0.17
Peritoneal metastases						
No	Reference					
Yes	1.18	0.84-1.65	0.35			
Lymph node metastases						
No	Reference					
Yes	1.13	0.56-2.31	0.73			

CI, confidence interval; df, degrees of freedom; DGR, Dutch GIST Registry; GIST, gastrointestinal stromal tumour; HR, hazard ratio.

* $P < 0.10$ in univariable analysis was included in multivariable analysis.

** $P < 0.05$ is considered significant in multivariable analysis.

prognostic factor. There may be several explanations. First, the sex difference in historical cohorts could be present due to inadequate correction for confounders. Only two cohorts corrected for all three prognostic factors that were found to be different between males and females in the current cohort study: tumour size, mitotic rate at diagnosis, and stage at diagnosis. None of these cohorts did compare male and female GIST characteristics. These two cohorts both concern patients from the SEER program.^{24,25} Liu et al.²⁴ included only gastric patients in their analysis (diagnosed between 1998 and 2015) and found an HR of 1.3 for male DSS. Song et al.²⁵ included 2841 GIST patients diagnosed between 2004 and 2015 in a training set and found a significant sex difference in DSS as well. Median follow-up time in their SEER cohort was 34 months. Song et al.²⁵ excluded patients with a second malignancy ($n = 1390$), although these patients were included in the current cohort. Nevertheless, the proportion of patients with a second malignancy was comparable for males and females, so this unlikely causes the conflicting results. Second, another possible source of error could be the smaller sample size of the Dutch cohort. Furthermore, there could be unclarified differences between GIST patients in the US and in the Netherlands, regarding for example prescriptions and compliance explaining the contradictory results. Future

studies should focus on comparing characteristics between female and male GIST patients to further establish the role of sex in GIST patients.

A possible interpretation of the results of the current analysis is as follows: on average, male GIST patients have a worse prognosis than female patients. It could be more important, however, to consider other factors than sex, such as tumour size, resectability, and presence of metastases for a good prediction of prognosis. Nevertheless, worse prognosis of males on average may be an indication that there exist problems that are particularly pronounced within the male subgroup. Questions that arise from this hypothesis are among others: does untreated GIST grow or metastasize faster in males than in females? Are males waiting longer to see a doctor than females? Is it more difficult to establish the diagnosis of GIST in males? There could be much to gain if these problems could be identified and then addressed.

In conclusion, unlike what several historical cohorts from the United States suggest, sex was not an 'independent' prognostic factor for DSS in the current Dutch GIST cohort.

The reason why sex seems prognostic in our univariable analysis seems to be that male patients more often have aggressive GISTs, characterised by larger tumours, more often ruptured with a high mitotic rate, and are more frequently metastasized. These factors are all associated

with a worse outcome. Future research is necessary to understand these sex differences in GIST presentation and biology.

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