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SPECIAL ISSUE ARTICLE

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Quality of life of GIST patients with and without current tyrosine kinase inhibitor treatment: Cross-sectional results of a German multicentre observational study (PROSa)

Martin Eichler[1,2] | Daniel Pink[3,4] | Franka Menge[5] | Jens Jakob[6] | Leopold Hentschel[2] | Stephan Richter[1] | Peter Hohenberger[5] | Bernd Kasper[7] | Dimosthenis Andreou[4,8] | Susanne Singer[9] | Robert Grützmann[10] | Diana I. Dmytrow[11] | Karin Arndt[12] | Armin Tuchscherer[13] | Peter Reichardt[14] | Marit Ahrens[15] | Annegret Kunitz[16] | Johannes Mohm[17] | Martin Bornhäuser[1,2] | Jochen Schmitt[2,18] | Markus K. Schuler[1]

[1]Clinic and Polyclinic for Internal Medicine I, University Hospital Carl Gustav Carus, Technical University Dresden, Dresden, Germany

[2]National Center for Tumor Diseases (NCT/UCC), Dresden, Germany

[3]Department of Internal Medicine C, University Hospital Greifswald, Greifswald, Germany

[4]Sarcoma Center Berlin-Brandenburg, Helios Hospital Bad Saarow, Bad Saarow, Germany

[5]Division of Surgical Oncology & Thoracic Surgery, Mannheim University Medical Centre, University of Heidelberg, Mannheim, Germany

[6]Clinic for General, Visceral, and Pediatric Surgery, University Hospital Goettingen, Goettingen, Germany

[7]Interdisciplinary Tumour Centre, Sarcoma Unit, University Medical Center Mannheim, Mannheim, Germany

[8]Department of General Orthopedics and Tumor Orthopedics, University Hospital Munster, Muenster, Germany

[9]Institute of Medical Biostatistics, Epidemiology and Informatics, University Hospital Mainz, Mainz, Germany

[10]Department of Surgery, University Hospital Erlangen, Erlangen, Germany

[11]Hospital Frankfurt Hoechst, Hoechst, Germany

[12]German Sarcoma Foundation, Woelfersheim, Germany

[13]Department I of Internal Medicine, Center for Integrated Oncology Aachen Bonn Cologne Duesseldorf, University of Cologne, Cologne, Germany

[14]Sarcoma Center Berlin-Brandenburg, Helios Hospital Berlin Buch, Berlin, Germany

[15]Medical Clinic II, University Hospital Frankfurt, Frankfurt, Germany

[16]Vivantes Hospital, Berlin, Germany

[17]Onkopraxis, Joint Practice for Hematology and Oncology, Dresden, Germany

[18]Center for Evidence-Based Healthcare, University Hospital Carl Gustav Carus, Technical University Dresden, Dresden, Germany

Correspondence
Martin Eichler, National Center for Tumor Diseases (NCT/UCC), Technical University Dresden, Medical Faculty, Fetscherstr. 74, 01307 Dresden, Germany.
Email: martin.eichler@uniklinikum-dresden.de

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Abstract

Objective: We investigated the health-related quality of life (HRQoL) of patients with gastrointestinal stromal tumours (GIST).

Methods: In the multicentre PROSa study, the HRQoL of adult GIST patients was assessed between 2017 and 2019 using the European Organisation for Research and Treatment of Cancer HRQoL questionnaire (EORTC QLQ-C30). We performed group comparisons and multivariate linear regressions.

Results: Among 130 patients from 13 centres, the mean global HRQoL was 63.3 out of 100 points. Higher sores indicate better HRQoL. The highest restrictions were in emotional, social, role functioning, insomnia, fatigue, and pain. In multivariate linear regression, we found no significant differences between patients receiving tyrosine kinase inhibitor (TKI) treatment and those without TKI treatment as well as between patients treated with curative or with palliative intent. Patients who received multiple lines of TKI treatment had the most restrictions, notably in physical (unstandardized regression coefficient [B] = −15.7), role ($B = -25.7$), social ($B = -18.4$), and cognitive functioning ($B = -19.7$); fatigue ($B = 15.93$); general health ($B = -14.23$); and EORTC-sum score ($B = -13.82$) compared to all other patients.

Conclusion: The highest HRQoL restrictions were in GIST patients receiving multiple lines of TKI therapy. Underlying causes need further investigation.

KEYWORDS

clinically important restrictions and symptoms, gastrointestinal stromal tumours, health-related quality of life, observational study, rare disease, tyrosine kinase inhibitors

1 | INTRODUCTION

Gastrointestinal stromal tumours (GISTs) are rare cancers with an incidence of around 1 to 1.5 per 100,000 people per year (Ressing et al., 2018; Stiller et al., 2013). They are of mesenchymal origin, situated in the gastrointestinal tract, and most commonly found in the stomach (60%) and small intestine (35%) (Miettinen & Lasota, 2006). GISTs usually occur in middle-aged adults (median age: 55–60 years), with a slightly higher incidence in men (Casali et al., 2018). Tumour size, mitotic activity, and intraoperative tumour rupture are the most predictive prognostic features, but small-intestinal tumours behave more aggressively than gastric tumours with similar parameters (Miettinen & Lasota, 2006). In a Swedish population-based study, 44% of all GIST-patients were high risk or overtly malignant cases, 14% had residual tumour after surgery (Nilsson et al., 2005). While surgical treatment of many localised GISTs is associated with a very good prognosis, treatment options for advanced GISTs were limited until the end of the 20th century. The discovery that most GISTs express a mutation in a tyrosine kinase, KIT (CD117) or PDGFR (Hirota, 1998; Miettinen & Lasota, 2006), or another mutation susceptible to targeted agents led to the development of and treatment with different tyrosine kinase inhibitors (TKIs) since the early 2000s. TKIs are associated with relatively high response rates in susceptible tumours. However, because tumours may develop TKI resistance over time, a variety of TKIs are now available for advanced disease. Imatinib serves as the first-line treatment for most advanced tumours, sunitinib as the second-line treatment, and regorafenib as the third-line treatment. In localised GISTs, surgery is still the treatment of choice, followed by adjuvant imatinib for 3 years in patients with high-risk tumours (Casali et al., 2018).

So far, data on the health-related quality of life (HRQoL) of GIST patients have mainly focused on the treatment symptoms of individual TKIs. Imatinib has been described as well tolerated, yet almost all patients experience side effects of some grade (Dematteo et al., 2009). A comprehensive symptom list for patients with GISTs treated with targeted therapies includes 54 entries that derived from interviews with patients and health care professionals as well as a literature review (Sodergren et al., 2020). A systematic review of 82 papers with 5,977 total patients compared the side effects of the two most commonly used TKIs: imatinib and sunitinib (Sodergren et al., 2014). Common symptoms occurring with both drugs were diarrhoea (imatinib: 39% and sunitinib: 36%) and fatigue (both: 40%). Those more common with imatinib treatment were: nausea (imatinib: 39% vs. sunitinib: 23%), oedema (imatinib: 37% vs. sunitinib: <1%), muscle pain (imatinib: 15% vs. sunitinib: 0%) and chest pain (imatinib: 13% vs. sunitinib: 0%). Patients treated with sunitinib were more likely to suffer from hand-foot syndrome (sunitinib: 37% vs. imatinib: <1%), anorexia/loss of appetite (sunitinib: 31% vs. imatinib: 12%), and a sore/sensitive mouth (sunitinib: 34% vs. imatinib: 1%). For regorafenib, a third-line treatment option, the most-commonly described symptoms were hand-foot skin reaction (44%), gastrointestinal symptoms (36%), fatigue (35%), anorexia (13%), and oral mucositis (11%) (Nannini et al., 2017).

Few studies analysed HRQoL issues in GIST-patients beside treatment side effects or with regard to the heterogeneity of the disease given the different tumour sites. A qualitative study of 20 patients living with metastatic GIST in long-term clinical remission (median time in systemic treatment: 6 years) identified four major themes for long-term survivors: the adaptation and normalisation of family life, adjustment made to vocational life, limitations to one's social life, and managing negative mental-health issues. Lack of energy was one of the most frequent symptoms (Fauske et al., 2020). An ethnographic investigation on patient experiences and perspectives during the disease course identified five stages of disease management: crisis, hope, adaptation, new normal, and uncertainty (Macdonald et al., 2012).

Because HRQoL analyses in GIST patients are rare, often focused on the symptoms of TKI treatment, and not undertaken in a standard clinical care setting, this explorative analysis aimed to tackle the following research questions:

1. How does the HRQoL of GIST patients in Germany compare to the general German population?
2. Are GIST patients receiving current TKI-therapy, later lines of TKI therapy or palliative care more affected by HRQoL limitations than other GIST patients; and if so, to what extent?

2 | METHODS

We analysed cross-sectional data from the prospective PROSa cohort study (www.uniklinikum-dresden.de/prosastudie), which was conducted nationwide between September 2017 and February 2019 in 39 German study centres (ClinicalTrials.gov ID: NCT03521531). The PROSa study (Burden and Medical Care of Sarcoma in Germany: Nationwide Cohort Study Focusing on Modifiable Determinants of Patient-Reported Outcome Measures in Sarcoma Patients) aimed to gather information on a variety of patient-reported outcomes (for example, HRQoL and distress), clinical data (diagnosis and treatment), as well as structural data of the participating study centres (certifications and numbers of treated patients). More detailed descriptions of the PROSa study have previously been published (Eichler et al., 2020; Eichler, Richter, et al., 2019; Schoffer et al., 2021).

Eligible adult patients and survivors were primarily asked to take part during visits to the recruiting study centres (for diagnosis, treatment, or follow-up), and some were invited to participate by phone or letter. Participation required written informed consent. The study was approved by the ethics committees of the Technical University of Dresden (EK1790422017) and the participating centres (Eichler, Schmitt, et al., 2019). Data were collected by the study coordination centre at the University Hospital Dresden. HRQoL data and sociodemographic data were sent by the participants to the study coordination centre by mail or online. Clinical information was submitted to the study coordination centre online by the participating study centres using documentation forms. Data collection was performed using REDCap electronic data capture tools (Vanderbilt University, Nashville, United States) hosted at the Technical University Dresden (Harris et al., 2009). For this analysis, we included adult patients and survivors with histologically confirmed GIST from all 13 study centres. We excluded patients who were mentally or linguistically unable to complete the questionnaires. Only participants with HRQoL data were analysed.

For HRQoL measurement, we used the European Organisation for Research and Treatment of Cancer Quality of Life Core Questionnaire (EORTC QLQ-C30) (Aaronson et al., 1993). This instrument measures global quality of life with a range of values from 0 to 100 in five functioning and nine symptom scales (3 multi-item scales, 6 single-item scales). Higher scores indicate a better quality of life for the functioning scales and a higher symptom burden for the symptom scales. Additionally, we used 11 single items concerning symptoms from the EORTC item library—a list of them is to be found in Table 3 (Kulis et al., 2017). The items from the EORTC item library were chosen with regard to sarcoma patients in general in a two-stage process. First, we tried to identify the most common issues not included in the EORTC QLQ-C30 in an unsystematic literature search. In a second step the issues found were circulated in and discussed and approved by our scientific advisory board. The decision to use all 11 items for the purpose of this analysis was made in consultation with the physicians involved in this publication. These items were transformed into single-item scales similar to the symptom scales of the EORTC QLC-C30. The same applies to the EORTC QLQ-C30 sum score (Giesinger et al., 2016). Here higher scores indicate a better HRQoL.

2.1 | Statistical analysis

For the description of the study population, we evaluated the variables from the multivariable model (see below) as well as metastases until baseline, tumour recurrence and treatment status. For age, time since diagnosis and socio-economic status, the median and the interquartile range (IQR) were calculated. For HRQoL measures, mean and standard deviation (SD) were calculated. Categorical variables were presented as absolute numbers and relative frequencies. Descriptive variables were stratified according to the grouping of the univariate analysis (see below). A nonresponder analysis was performed to assess potential selection bias.

An age- and sex-standardised comparison was performed using reference values from the healthy German population (Nolte et al., 2019). The relevance of the differences was tested using reference values from Cocks et al. and Osoba et al. (Cocks et al., 2011; Osoba et al., 1998). Differences were classified by these publications as "small," "moderate," or "large" (Osoba) or "trivial," "small," "medium," or "large" (Cocks). The latter ones were defined as: "Large: one representing unequivocal clinical relevance. Medium: likely to be clinically relevant but to a lesser extent. Small: subtle but nevertheless clinically relevant. Trivial: circumstances unlikely to have any clinical relevance or there was no difference" (Cocks et al., 2011).

Differences between distinct groups of GIST patients were examined for all domains of the EORTC QLQ-C30, 11 additionally selected single-item scales, and the EORTC QLQ-C30 sum score. Three patient-group comparisons were performed: (a) patients who never received or only formerly received TKI treatment vs. patients currently receiving TKI treatment, (b) patients receiving TKI treatment with curative intent vs. patients receiving TKI treatment with palliative intent, and (c) patients being treated with palliative intent with a first-line TKI vs. a multiple-line TKI. Independent samples were tested for significance with *t* tests. A p value less than 0.05 was considered to be statistically significant.

All HRQoL domains were analysed by multivariate linear regression to control for potentially confounding variables in the analysis of the number of TKI treatment lines (0–1 line vs. more than 1 line), TKI

treatment (none or former vs. current treatment), and treatment intention (curative vs. palliative). Unstandardized regression coefficient (*B*), 95% confidence intervals (95% CI), *p* values, and coefficient of determination (R^2) were evaluated in a model that was adjusted for age at baseline, sex, socio-economic status, surgery, disease status (complete remission, partial remission/stable disease, progress, unknown), time since diagnosis (up to 1 year, 1–2 years, 2–5 years, more than 5 years), tumour site (stomach, small bowel, rectum, other/unknown) and tumour size (T1/T2, T3/T4, unknown). Socio-economic status (SES) was assessed using the Winkler Index (Lampert et al., 2013).

Full results of multivariable linear regression were shown and discussed in the online supplement.

3 | RESULTS

3.1 | Sample description

The PROSa study recruited 1,309 sarcoma patients. The analysis included 130 GIST patients with questionnaire data, of whom, 54% were female, the median age at diagnosis was 58.6 years (IQR: 49.4–66.8), and the median age at study inclusion was 63.0 years (IQR: 53.3–73.4). Primary tumours were located in the stomach in 44% of the patients and in the small intestine in 28% of the patients. Metastases developed in 43% of the patients during the course of their disease, and 23% had a local recurrence. With respect to treatment intent, 39% were receiving palliative care, 55% were being treated with curative intent, 39% were undergoing follow-up evaluation, and 5% had a treatment planned. With respect to treatment approach, 85% had at least one surgery, 56.9% received one TKI treatment, 21.5% had two TKI treatments, and 10% had three or more lines of TKI treatment (Table 1). Patients were stratified by number of TKI treatments and treatment intent for analyses. One group consisted of the 28 patients (21.5%) who never received TKI treatment combined with the 33 patients (25.4%) no longer receiving treatment, for a total of 61 patients (46.9%) not currently receiving TKI treatment. Of those patients, 51 (83.6%) were in follow up. The remaining 69 patients in the study cohort (53.1%) were currently being treated with a TKI: 41 (31.5%) with palliative and 27 (20.8%) with curative intent. Within the palliative group, 20 patients (15.4%) were being treated with first-line TKI and 21 (16.2%) received multiple lines of TKIs.

3.2 | Nonresponder analysis

Of the 159 recruited GIST patients 29 (18.2%) failed to return their questionnaires and were therefore classified as nonresponders. They were more commonly men (52% of the nonresponders compared to 46% of the responders). Nonresponders also had a longer mean time since their diagnosis than responders (4.5 years vs. 3.2 years) and were more often in complete remission (41% vs. 26%) (Table 1).

3.3 | Quality of life

Mean global HRQoL was 63.3 out of 100 points (SD: 22.0). Among the functioning scales, emotional (61.8, SD: 28.1), social (64.6, SD: 33.2), and role functioning (64.6, SD: 32.1) had the lowest values. Insomnia (41.3, SD: 35.0), fatigue (41.2, SD: 28.8), pain (32.6, SD: 33.6), and diarrhoea (26.4, SD: 34.2) showed the highest symptom loads. The EORTC QLQ-C30 sum score was 71.5 points (SD: 20.0). In scales derived from the EORTC item library, lack of energy (45.0, SD: 32.2), loss of interest in sexuality (39.2, SD: 38.2), and bloated stomach (30.8, SD: 32.8) had the highest values, indicating greater HRQoL deficits (Table 2).

In age- and sex-matched comparisons with a healthy German population, most scales showed significant differences; exceptions were general health, physical functioning, pain, and dyspnoea. Large differences were observed in social functioning (20.3 points) and diarrhoea (17.3 points), and moderate differences occurred in financial difficulties (13.0 points), insomnia (15.8), and emotional functioning (14.7 points) (Figure 1).

3.4 | Stratified univariate analyses

Patients with no or former TKI treatment had a better overall HRQoL (EORTC sum score: 7.4-point difference, small difference) compared to those in treatment. Moderately significant differences were observed in cognitive functioning (11.2 points), fatigue (16.2 points), diarrhoea (13.7 points), financial difficulties (7.4 points), lack of energy (15.5 points), and burning eyes (16.2 points) (Table 2).

The curative treatment group had a slightly higher overall HRQoL sum score than palliative patients, but the difference was trivial (3.8 points) and not significant. Moderately significant differences were observed in diarrhoea (18.4 points) and hair loss (17.4 points), with the curative group performing better. On the other hand, the curative group reported less interest in sexuality (18.6 points) than the palliative group (Table 2).

Palliative patients receiving fist-line TKI treatment had a higher overall HRQoL sum score than those receiving multiple lines. The difference was moderate (12.7 points) but not significant. In general, patients in first-line TKI treatment had lower symptom loads. Large, significant differences were found in physical function (14.5 points), cognitive function (21.3 points), mouth pain (22.2 points), and headache (28.1 points) (Table 2).

3.5 | Multivariate linear regression

The linear regression tended to reduce the differences detected by the stratified analysis between patients with no/former TKI treatment and patients in current TKI treatment. The EORTC sum score differed by 4.0 points (95% CI: −13.1–5.6, trivial difference, not significant). Significant differences were not observed, in three domains *p* value was below 0.06. Patients in TKI treatment showed higher fatigue

TABLE 1 Description study population stratified by TKI treatment

Variable	Value	All responder $N = 130$ N (%)/median (IQR)	No TKI/former TKI $N = 61$ (46.9%) N (%)/median (IQR)	Current TKI treatment $N = 69$ (53.1%) N (%)/median (IQR)	TKI current—Curative ($N = 27$)[a] N (%)/median (IQR)	TKI current—Palliative ($N = 41$)[a] N (%)/median (IQR)	TKI current—Palliative—TKI first ($N = 20$) (%)/median (IQR)	TKI current—Palliative—Multiple lines ($N = 21$) N (%)/median (IQR)	Non-responder $N = 29$ N (%)/median (IQR)
Sex	Female	70 (53.8)	28 (45.9)	42 (60.9)	16 (59.3)	25 (61.9)	13 (65.0)	12 (57.1)	14 (48.3)
	Male	60 (46.2)	33 (54.1)	27 (39.1)	11 (40.7)	16 (39.0)	7 (35.0)	9 (42.9)	15 (51.7)
Age at diagnosis		58.6 (49.4; 66.8)	58.3 (49.3; 70.8)	58.9 (49.2; 64.6)	60.2 (54.5; 65.5)	58.2 (44.3; 63.8)	57.2 (48.6; 63.3)	58.1 (39.5; 65.4)	57.4 (52.2; 65.4)
Age at study inclusion		63.0 (53.3; 73.4)	63.6 (53.2; 73.6)	62.2 (53.1; 73.2)	62.2 (55.1; 69.4)	61.5 (51.7; 73.5)	62.4 (52.3; 73.3)	61.5 (51.6; 74.6)	64.2 (55.6; 72.8)
Socio-economic status (3–21 points)		13.05 (10.05; 15.85)	12.8 (10.0; 15.9)	13.3 (10.3; 15.9)	13.9 (9.9; 16.8)	12.7 (10.3; 15.4)	12.2 (10.0; 14.5)	12.7 (10.4; 16.3)	-
Time since diagnosis		3.4 (0.9; 9.5)	2.7 (0.9; 5.9)	4.5 (0.8; 10.1)	0.8 (0.3; 2.9)	8.1 (3.3; 12.4)	8.8 (2.0; 13.2)	6.4 (3.6; 11.6)	4.5 (0.9; 9.3)
	0–<0.5 years	23 (17.7)	10 (16.4)	13 (18.8)	19 (37.0)	3 (7.3)	3 (15.0)	0	4 (13.8)
	0.5–<1 year	13 (10.0)	7 (11.5)	6 (8.7)	6 (22.0)	0	0	0	4 (13.8)
	1–<2 years	11 (8.5)	6 (9.8)	5 (7.2)	1 (3.7)	4 (9.8)	2 (10.0)	2 (9.5)	1 (3.4)
	2–<5 years	30 (23.1)	19 (31.1)	11 (15.9)	5 (18.5)	6 (14.6)	1 (5.0)	5 (23.8)	7 (24.1)
	More than 5 years	53 (40.8)	19 (31.1)	34 (49.3)	5 (18.5)	28 (68.3)	14 (70.0)	14 (66.7)	13 (44.8)
Site	Stomach	57 (43.8)	39 (63.9)	18 (26.1)	6 (22.2)	12 (29.3)	5 (25.0)	7 (33.3)	12 (41.4)
	Small bowel	36 (27.7)	11 (18.0)	25 (36.2)	11 (40.7)	13 (31.7)	6 (30.0)	7 (33.3)	11 (37.9)
	Rectum	10 (7.7)	4 (6.6)	6 (8.7)	4 (14.8)	2 (4.9)	0	2 (9.5)	3 (10.3)
	Duodenum	3 (2.3)	0	3 (4.3)	0	3 (7.3)	2 (10.0)	1 (4.8)	1 (3.4)
	Oesophagus	4 (3.1)	1 (1.6)	3 (4.3)	1 (3.7)	2 (4.9)	1 (5.0)	1 (4.8)	0
	Other/unknown	20 (15.4)	6 (9.8)	14 (20.3)	5 (18.5)	9 (22.0)	6 (30.0)	3 (14.3)	2 (6.9)
T-stage at diagnosis	T1	3 (2.3)	1 (1.6)	2 (2.9)	1 (3.7)	1 (2.4)	0	1 (4.8)	2 (6.9)
	T2	22 (16.9)	14 (23.0)	8 (11.6)	3 (11.1)	5 (12.2)	1 (5.0)	4 (19.0)	6 (20.7)
	T3	45 (34.6)	29 (47.5)	16 (23.3)	5 (18.5)	11 (26.8)	7 (35.0)	4 (19.0)	8 (27.6)
	T4	13 (10.0)	4 (6.6)	9 (13.0)	7 (25.9)	2 (4.9)	0	2 (9.5)	1 (3.4)
	Tx	2 (1.5)	0	2 (2.9)	0	2 (4.9)	1 (5.0)	1 (4.8)	1 (3.4)
	Unknown	45 (34.6)	13 (21.3)	32 (46.4)	11 (40.7)	20 (48.8)	11 (55.0)	9 (42.9)	11 (37.9)

(Continues)

TABLE 1 (Continued)

Variable	Value	All responder $N = 130$ N (%)/median (IQR)	No TKI/former TKI $N = 61$ (46.9%) N (%)/median (IQR)	Current TKI treatment $N = 69$ (53.1%) N (%)/median (IQR)	TKI current—Curative ($N = 27$)[a] N (%)/median (IQR)	TKI current—Palliative ($N = 41$)[a] N (%)/median (IQR)	TKI current—Palliative—TKI first ($N = 20$) (%)/median (IQR)	TKI current—Palliative—Multiple lines ($N = 21$) N (%)/median (IQR)	Non-responder $N = 29$ N (%)/median (IQR)
Metastasis until baseline	No	63 (48.8)	43 (70.5)	20 (29.0)	18 (66.7)	2 (4.9)	1 (5.0)	1 (4.8)	12 (41.4)
	Yes	56 (43.3)	10 (16.4)	45 (65.2)	7 (25.9)	37 (90.2)	17 (85.0)	20 (95.2)	13 (44.8)
	Unknown	10 (7.8)	8 (13.1)	4 (5.8)	2 (7.4)	2 (4.9)	2 (10.0)	0	4 (13.8)
Tumour recurrence	No recurrence	97 (74.6)	52 (85.2)	45 (65.2)	24 (88.9)	20 (48.8)	14 (70.0)	6 (28.6)	24 (82.8)
	Recurrence	30 (23.1)	8 (13.1)	22 (31.9)	3 (11.1)	19 (46.3)	6 (30.0)	13 (61.9)	5 (17.2)
	Suspicion	2 (1.5)	1 (1.6)	1 (1.4)	0	1 (2.4)	0	1 (4.8)	0
	Unknown	1 (0.8)	0	1 (1.4)	0	1 (2.4)	0	1 (4.8)	0
Disease status	Complete remission	34 (26.2)	24 (39.6)	10 (14.5)	9 (33.3)	1 (2.4)	1 (5.0)	0	12 (41.4)
	Partial remission/stable disease	70 (53.8)	31 (50.8)	39 (56.5)	12 (44.4)	26 (63.4)	14 (70.0)	12 (57.1)	7 (24.1)
	Progress	15 (11.5)	3 (4.9)	12 (17.4)	2 (7.4)	10 (24.4)	2 (10.0)	8 (38.1)	4 (13.8)
	Unknown	11 (8.5)	3 (4.9)	8 (12.7)	4 (14.8)	4 (9.8)	3 (15.0)	1 (4.8)	6 (20.7)
Surgery	No	18 (13.8)	2 (3.3)	16 (23.2)	8 (29.6)	8 (19.5)	4 (20.0)	4 (19.0)	4 (13.8)
	Yes (all)	110 (84.6)	69 (96.7)	51 (73.9)	19 (70.4)	31 (75.6)	15 (75.0)	16 (76.2)	24 (82.8)
	Yes—1 surgery	94 (72.3)	54 (88.5)	40 (58.0)	17 (63.0)	22 (53.7)	13 (65.0)	9 (42.9)	21 (72.4)
	Yes—2 surgeries	11 (8.5)	5 (8.2)	6 (8.7)	1 (3.7)	5 (12.2)	1 (5.0)	4 (19.0)	2 (6.9)
	Yes—>2 surgeries	5 (3.8)	0	5 (7.2)	1 (3.7)	4 (9.8)	1 (5.0)	4 (19.0)	1 (3.4)
	Unknown	2 (1.5)	0	2 (2.9)	0	2 (4.9)	1 (5.0)	1 (4.8)	1 (3.4)
TKI	No	28 (21.5)	28 (45.9)	0	-	-	-	-	6 (20.7)
	Yes	102 (78.5)	33 (54.1)	69 (100)	27 (100)	41 (100)	20 (100)	21 (100)	23 (79.3)
	Yes—first line	74 (56.9)	28 (45.9)	46 (66.7)	25 (92.6)	20 (48.8)	20 (100)	-	19 (65.5)
	Yes—second line	15 (11.5)	3 (4.9)	12 (17.4)	1 (3.7)	11 (16.8)	-	11 (52.4)	3 (10.3)

TABLE 1 (Continued)

Variable	Value	All responder $N = 130$ N (%)/median (IQR)	No TKI/former TKI $N = 61$ (46.9%) N (%)/median (IQR)	Current TKI treatment $N = 69$ (53.1%) N (%)/median (IQR)	TKI current—Curative ($N = 27$)[a] N (%)/median (IQR)	TKI current—Palliative ($N = 41$)[a] N (%)/median (IQR)	TKI current—Palliative—TKI first ($N = 20$) (%)/median (IQR)	TKI current—Palliative—Multiple lines ($N = 21$) N (%)/median (IQR)	Non-responder $N = 29$ N (%)/median (IQR)
	Yes—>2nd line	13 (10.0)	2 (3.3)	11 (15.9)	1 (3.7)	10 (24.4)	-	10 (47.6)	1 (3.4)
Treatment status	In treatment	71 (54.6)	2 (3.3)	69 (100)	27 (100)	41 (100)	20 (100)	21 (100)	15 (51.7)
	Not in treatment—Aftercare	51 (39.2)	51 (83.6)	-	-	-			11 (37.9)
	Not in treatment—Treatment in planning	7 (5.4)	7 (11.5)	-	-	-			3 (21.4)
	Unknown	1 (0.8)	1 (1.6)	-	-	-			0
Treatment intention	Curative	77 (59.2)	50 (82.0)	27 (39.1)	27 (100)	-	-	-	19 (65.5)
	Palliative	51 (39.2)	10 (16.4)	41 (59.4)	-	41 (100)	20 (100)	21 (100)	10 (34.5)
	Unknown	2 (1.5)	1 (1.6)	1 (1.4)	-	-	-	-	0

Abbreviation: TKI, tyrosine kinase inhibitors; IQR, interquartile range.

[a]Patients in current TKI treatment stratified by treatment intention do not add up to 69 because for one person treatment intention was unknown.

TABLE 2 Health-related quality of life scores of GIST patients

Variable	All participants $N = 130$mean (SD)	No TKI/former TKI $N = 61$ (46.9%)mean (SD)	TKI current $N = 69$ (53.1%) mean (SD)	*T* test *p* value	Difference (95% CI)	TKI current—Curative ($N = 27$)[e]mean (SD)
EORTC QLQ-C30						
General health	63.3 (22.0)	64.9 (23.2)	62.0 (21.0)	0.45	2.9[a] (−4.7; 10.6)	59.6 (22.4)
Physical functioning	78.4 (20.9)	82.6 (20.8)	74.8 (20.4)	0.03	7.8[b](0.7; 15.1)	73.0 (21.7)
Role functioning	64.6 (32.1)	69.7 (34.4)	60.1 (29.5)	0.09	9.6[b] (−1.5; 20.7)	64.8 (28.6)
Emotional functioning	61.8 (28.1)	63.6 (29.8)	60.2 (26.7)	0.49	3.5[a] (−6.3; 13.3)	63.6 (27.6)
Cognitive functioning	78.2 (25.0)	84.1 (19.3)	72.9 (28.1)	<0.01	11.2[c] (2.8; 19;5)	79.0 (22.9)
Social functioning	64.6 (33.2)	68.9 (33.4)	60.9 (32.8)	0.17	5.8[b] (3.5; 19.5)	65.4 (31.0)
Fatigue	41.2 (28.8)	32.7 (26.5)	48.9 (28.7)	<0.01	−16.2[c] (−25.8; −6.5)	48.3 (28.5)
Nausea/vomiting	12.4 (20.4)	8.5 (17.6)	15.9 (22.0)	0.03	−7.5[b](−14.4; −0.6)	17.3 (22.4)
Pain	32.6 (33.6)	30.6 (31.9)	34.3 (35.1)	0.53	−3.7[a](−15.4; 8.0)	34.0 (34.1)
Dyspnea	24.1 (28.8)	19.1 (28.2)	28.5 (28.7)	0.06	−9.4[c] (−19.3; 0.5)	24.7 (30.1)
Insomnia	41.3 (35.0)	38.3 (32.4)	44.0 (37.7)	0.36	−5.6[b](−17.0; 6.7)	43.2 (37.9)
Appetite loss	20.5 (30.3)	13.7 (26.8)	26.6 (32.1)	0.01	−12.9[b](−23.1; −2.7)	25.9 (28.2)
Constipation	16.2 (28.5)	20.2 (30.0)	12.6 (26.9)	0.13	7.7[b](−2.2; 17.5)	13.6 (28.1)
Diarrhoea	26.4 (34.2)	19.1 (28.8)	32.9 (37.3)	0.02	−13.7[c](−25.4; −2.1)	22.2 (30.7)
Financial difficulties	21.5 (31.8)	15.3 (28.3)	27.0 (34.0)	0.03	−11.8[c](−22.6; −1.0)	21.0 (29.5)
EORTC-C30—Sum score	71.5 (20.0)	75.5 (18.8)	68.1 (20.4)	0.04	7.4[b] (0.5; 14.4)	70.5 (19.7)
EORTC—item bank						
Cough	17.9 (25.0)	21.3 (25.1)	15.0 (24.6)	0.15	6.3[b] (−2.3; 15.0)	12.3 (24.7)
Lack of energy	45.0 (32.2)	37.2 (33.1)	51.7 (30.0)	0.01	−15.5[c] (−25.5; −3.4)	58.0 (27.1)
Bloated stomach	30.8 (32.8)	30.3 (3.9)	32.9 (35.0)	0.44	−4.4[a](−15.9; 7.0)	33.3 (37.0)
Affected by hair loss	18.0 (33.4)	15.8 (30.5)	19.8 (35.8)	0.50	−4.0[a](−15.7; 7.8)	8.6 (23.7)
Mouth pain	7.8 (21.5)	3.3 (14.7)	11.8 (25.6)	0.02	−8.4[b](−15.6; 1.2)	8.6 (21.9)
Heartburn	24.6 (28.6)	21.9 (25.0)	27.1 (31.5)	0.3	−5.2[b](−15.1; 4.8)	27.2 (38.2)
Burning eyes	24.7 (32.5)	16.1 (27.1)	32.4 (35.0)	<0.01	−16.2[c] (−27.1; −5.4)	35.8 (35.7)
Less interest in sexuality	39.2 (38.2)	32.7 (35.4)	44.8 (40.8)	*0.09*	−12.1[c](−25.9; 1.8)	55.6 (39.2)
TinglingHands/feed	24.0 (31.8)	22.4 (32.6)	25.4 (31.3)	0.60	−3.0[a](−14.2; 8.2)	17.9 (25.4)
Rash	14.7 (27.1)	10.7 (20.9)	18.1 (31.2)	0.12	−7.4[b](−16.6; 1.8)	14.8 (28.2)
Headache	19.0 (27.3)	15.0 (22.5)	22.5 (30.7)	0.11	−7.5[b](−16.9; 1.8)	23.5 (29.0)

Note: Selected group-comparisons using *T* tests.
[a]Trivial/no differences.
[b]Small differences.
[c]Medium/moderate differences.
[d]Large differences (Cocks et al., 2011, Osoba et al., 1998).
[e]Patients in current TKI treatment stratified by treatment intention do not add up to 69 because for one person treatment intention was unknown.

TABLE 2 (Continued)

Variable	TKI current—Palliative ($N = 41$)[e]mean (SD)	*T* test *p* value	Difference (95% CI) mean (SD)	TKI current—Palliative—TKI first line ($N = 20$)	TKI current—Palliative—Multiple lines ($N = 21$) mean (SD)	*T* test *p* value	Difference (95% CI)
EORTC QLQ-C30							
General health	63.6 (20.5)	0.44	−4.1[b](−14.6; 6.5)	69.6 (19.6)	57.9 (20.2)	0.07	11.6[c](−0.9; 24.2)
Physical functioning	76.3 (19.8)	0.53	−3.2[a](−13.4; 6.9)	83.7 (16.4)	69.2 (20.5)	0.02	14.5[c](2.8; 26.2)
Role functioning	57.3 (30.3)	0.31	7.5[b](−7.2; 22.2)	65.0 (30.0)	50.0 (29.3)	0.11	15.0[b](−3.8; 33;8)
Emotional functioning	58.3 (26.4)	0.43	5.2[b](−8.1; 18.5)	65.0 (28.4)	52.0 (23.1)	0.12	13.0[c](−3.3; 29.3)
Cognitive functioning	69.1 (31.1)	0.14	9.9[c] (−3.2; 23.0)	80.0 (23.3)	58.7 (34.4)	0.03	21.3[d](2.7; 39.8)
Social functioning	58.1 (34.4)	0.38	7.3[b](−9.1; 23.7)	67.5 (32.7)	49.2 (34.3)	0.09	18.3[d] (−2.9; 39.5)
Fatigue	48.8 (29.4)	0.95	−0.49[a](−15.0; 14.1)	40.0 (30.9)	57.1 (25.9)	0.06	−17.1[c](−35.1; 0.8)
Nausea/vomiting	13.8 (20.7)	0.52	3.4[b](−7.1; 14.0)	15.8 (23.9)	11.9 (17.6)	0.55	3.93[b](−9.3; 17.1)
Pain	33.7 (36.2)	0.98	0.2[a](−17.3; 17.7)	30.0 (40.0)	37.3 (32.9)	0.53	−7.3[b](−30.4; 15.8)
Dyspnea	31.7 (27.8)	0.33	−7.0[b](−21.2; 7.2)	23.3 (28.8)	39.7 (25.0)	*0.06*	−16.3[d](−33.4; 0.7)
Insomnia	44.7 (38.5)	0.88	−1.5[a](−20.4; 17.4)	35.0 (36.6)	54.0 (37.7)	0.12	−19.0[c](−42.8; 4.9)
Appetite loss	26.0 (34.6)	0.99	−0.1[a](−16.0; 15.9)	21.7 (34.7)	30.2 (34.8)	0.44	−8.5[b](−30.4; 13.5)
Constipation	12.2 (26.6)	0.84	1.4a(−12.1; 14.9)	8.3 (21.3)	15.9 (31.0)	0.37	−7.5[b](−24.4; 9.3)
Diarrhoea	40.7 (39.8)	0.04	−18.4[c](−35.6; −1.3)	35.0 (35.0)	46.0 (44.1)	0.38	−11.0[c](−36.2; 14.2)
Financial difficulties	30.1 (36.4)	0.28	−9.1[b](−25.8; 7.6)	35.0 (36.6)	25.4 (36.4)	0.41	9.6[b](−13.5; 32.7)
EORTC-C30—Sum score	66.7 (21.2)	0.46	3.8[a](−6.5; 14.1)	73.2 (20.0)	60.5 (20.8)	*0.054*	12.7[c](−0.2; 25.6)
EORTC—item bank							
Cough	16.3 (24.9)	0.53	−3.9[a](−16.2; 8.4)	11.7 (22.4)	20.6 (26.8)	0.25	−9.0[b](−24.6; 6.7)
Lack of energy	47.2 (31.6)	0.15	10.9[c](−3.9; 25.7)	38.3 (31.1)	55.6 (30.4)	*0.08*	−17.2[c](−36.7; 2.2)
Bloated stomach	33.3 (34.2)	1.00	0	23.3 (30.8)	42.9 (35.2)	*0.07*	−19.5[c](−40.5; 1.4)
Affected by hair loss	26.0 (40.5)	0.03	−17.4[c](−33.0; −1.8)	20.0 (38.1)	31.7 (42.8)	0.36	−11.7[c](−37.4; 13.9)
Mouth pain	11.7 (24.5)	0.61	−3.0[a](−14.7; 8.7)	0	22.2 (30.4)	<0.01	−22.2[d](−36.6; −8.4)
Heartburn	27.6 (26.8)	0.95	−0.5[a](−16.2; 15,2)	20.0 (19.9)	34.9 (30.7)	*0.07*	−14.9[c](−31.4; 1.5)
Burning eyes	28.3 (33.4)	0.39	7.5[b](−9.6; 24.5)	19.3 (32.0)	36.5 (33.2)	*0.10*	−17.2[c](−38.1; 3.7)
Less interest in sexuality	36.9 (40.7)	*0.07*	18.6[c](−1.7; 38.9)	37.3 (42.3)	36.7 (40.3)	0.59	0.6[a](−27.0; 28.2)
TinglingHands/feed	29.2 (33.9)	0.15	−11.2[c](−26.7; 4.3)	21.1 (35.5)	36.5 (31.5)	0.15	−15.5[c](10.6; −36.9)
Rash	19.2 (32.8)	0.58	−4.4[a](−19.8; 11.1)	10.5 (27.3)	27.0 (35.9)	0.11	−16.5[c](10.0; −36.8)
Headache	20.0 (30.0)	0.64	3.4[a](−11.3; 18.2)	5.3 (12.5)	33.3 (35.0)	<0.01	−28.1[c](8.1; −44.8)

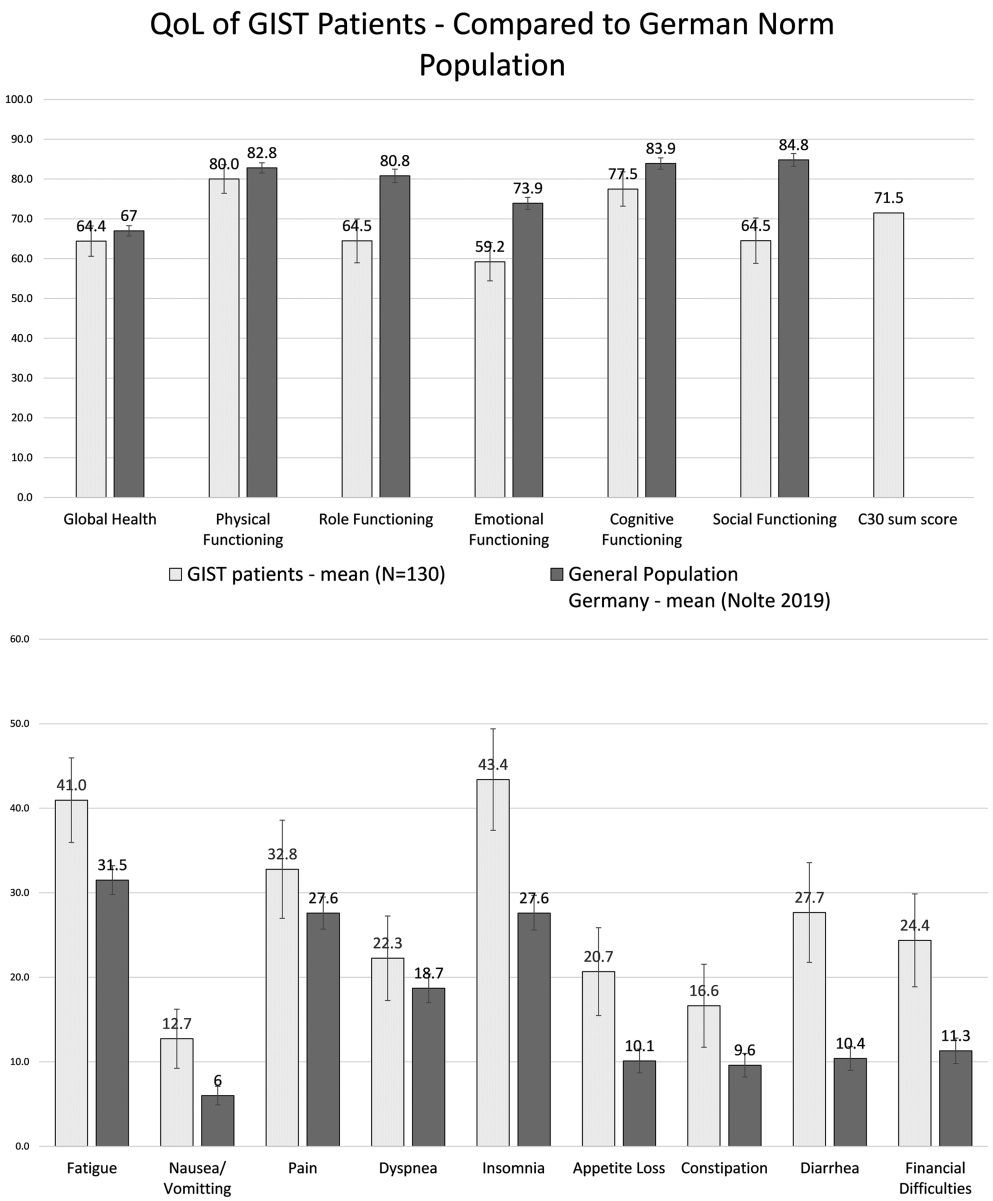

FIGURE 1 Age and sex standardised comparison to a German norm population (Nolte et al., 2019). C30 sum score not standardised and without comparable data. ↕ 95% confidence interval. Large differences: Social functioning, Diarrhoea; medium/moderate differences: Financial difficulties, emotional functioning, insomnia; small differences: Role functioning, cognitive functioning, fatigue, nausea/vomiting, appetite loss, constipation; trivial differences: Global Health, physical functioning, pain, dyspnea

($B = 13.1$, 95% CI: −0.2–26.3, medium effect), less interest in sexuality ($B = 18.2$, 95% CI: −0.1–36.5, moderate effect) and more appetite loss ($B = 13.8$, 95% CI: −0.2–27.8, small effect) than patients not in TKI treatment. We found insignificant moderate effect sizes in lack of energy ($B = 13.2$, 95% CI: −1.5–27.8), burning eyes ($B = 11.2$, 95% CI: −3.4–25.7) and being affected by hair loss ($B = -13.5$, 95% CI: −28.2–1.3) (Table 3).

No outcome was significantly associated with treatment intention. The moderate effects observed in the stratified analysis were similar in strength but not statistically significant. The EORTC sum score differed by 0.3 points (trivial difference, not significant) (Table 3).

Patients who received multiple TKI lines had the strongest impairments and highest symptom loads in the linear regression. The EORTC sum score differed by −13.8 points (95% CI: −24.7 to −3.0, medium difference) comparing patients in multiple lines vs. all others. In all functioning scales, patients receiving multiple lines of TKI treatment showed lower scores than all other patients, with moderate to large (cognitive functioning, social functioning) effect sizes. Except for emotional functioning, those differences were significant. In symptom scales, moderately sized, statistically significant effects were observed in fatigue ($B = 15.9$, 95% CI: 0.9–30.9), mouth pain ($B = 17.4$, 95% CI: 6.1–28.6) and rash ($B = 17.9$, 95% CI: 3.3–32.5), large effect sizes in headache ($B = 23.8$, 95% CI: 9.7–37.9) and burning eyes ($B = 21.3$, 95% CI: 4.6–38.0) (Table 3).

4 | DISCUSSION

4.1 | Results in context

As expected, GIST patients had worse HRQoL scores than the general German population. Social functioning and diarrhoea are the most

TABLE 3 Health-related quality of life scores of GIST patients

	Treatment intention curative vs. palliative			TKI treatmentnone/former vs. current			TKI treatment lines0/1 line vs. multiple lines		
Outcomes	**B**	***p***	**95% CI**	**B**	***p***	**95% CI**	**B**	***p***	**95% CI**
EORTC QLQ-C30									
General health ($R^2 = 0.21$)	8.50[b]	0.13	−2.54; 19.53	−1.74[a]	0.73	−11.59; 8.11	−14.23[c]	**0.01**	−25.56; −2.89
Physical functioning($R^2 = 0.27$)	7.56[b]	0.14	−2.39; 17.59	−6.97[b]	0.12	−15.88;1.95	−17.33[c]	**<0.01**	−27.59; −7.01
Role functioning($R^2 = 0.20$)	−2.14[a]	0.79	−18.32; 14.04	−2.69[a]	0.72	−17.31; 11.94	−25.70[c]	**<0.01**	−42.61; −8.80
Emotional functioning($R^2 = 0.14$)	−4.56[a]	0.54	−19.24; 11.12	3.49[a]	0.60	−9.61; 16.59	−14.13[c]	0.07	−29.21; 0.95
Cognitive functioning($R^2 = 0.20$)	−2.05[a]	0.75	−14.63; 10.51	−5. 91[b]	0.30	−17.11; 5.30	−19.74[d]	**<0.01**	−32.64; −6.84
Social functioning($R^2 = 0.16$)	−3.85[a]	0.66	−20.97; 13.26	−0.52[a]	0.95	−15.80; 14.78	−18.36[d]	**0.04**	−35.94; −0.77
Fatigue($R^2 = 0.18$)	−1.44[a]	0.85	−16.26; 13.37	13.07[c]	0.054	−0.20; 26.33	15.93[c]	**0.04**	0.92; 30.93
Nausea/vomiting($R^2 = 0.13$)	−3.26[b]	0.55	−13.93; 7.40	7.92[b]	0.10	−1.60; 17.44	−3.01[b]	0.59	−4.85; 11.13
Pain($R^2 = 0.13$)	−11.49[b]	0.20	−29.11; 6.14	0.87[a]	0.91	−14.86; 16.61	16.43[c]	0.08	−1.68; 34.54
Dyspnea($R^2 = 0.18$)	0.60[a]	0.94	−14.08; 15.27	8.50[b]	0.20	−4.60; 21.60	10.85[c]	0.16	−4.22; 25.93
Insomnia($R^2 = 0.17$)	1.99[a]	0.83	−16.09; 20.01	8.59[b]	0.30	−7.60; 24.79	12.14[b]	0.20	−6.42; 30.71
Appetite loss($R^2 = 0.16$)	−7.54[b]	0.34	−23.20; 8.11	13.83[b]	0.052	−0.15; 27.80	7.08[b]	0.39	−9.01; 23.16
Constipation($R^2 = 0.22$)	−2.86[a]	0.69	−17.02; 11.31	−8.37[b]	0.19	−21.01; 4.28	13.51[c]	0.07	−1.04; 28.06
Diarrhoea($R^2 = 0.14$)	9.34[c]	0.30	−8.46; 27.15	6.27[b]	0.44	−9.62; 22.16	5.13[b]	0.58	−13.16; 23.42
Financial difficulties($R^2 = 0.26$)	14.39[b]	0.07	−1.04; 29.82	2.23[a]	0.75	−11.54; 16.01	−8.01[b]	0.32	−23.86; 7.85
EORTC-C30—Sum score ($R^2 = 0.15$)	0.31[a]	0.95	−10.24; 10.87	−4.04[a]	0.41	−13.65; 5.57	−13.82[c]	**0.01**	−24.69; −2.95
EORTC—item library									
Cough($R^2 = 0.14$)	−6.81[b]	0.30	−19.82; 6.21	−9.88[b]	0.10	−21.50; 1.74	5.38[b]	0.43	−7.99; 18.75
Lack of energy($R^2 = 0.19$)	−7.02[b]	0.40	−23.31; 9.28	13.15[c]	0.08	−1.48; 27.78	12.68[c]	0.14	−4.07; 29.43
Bloated stomach($R^2 = 0.10$)	−4.71[a]	0.60	−22.22; 12.81	−1.58[a]	0.84	−17.21; 14.05	16.02[c]	0.08	−1.94; 34.05
Affected by hair loss($R^2 = 0.23$)	7.95[b]	0.34	−8.56; 24.45	−13.47[c]	0.07	−28.23; 1.30	14.16[c]	0.10	−2.80; 31.13
Mouth pain($R^2 = 0.19$)	−4.91[b]	0.38	−15.83; 6.01	6.82[b]	0.17	−2.92; 16.56	17.36[c]	**<0.01**	6.14; 28.58
Heartburn($R^2 = 0.09$)	−1.95[a]	0.80	−17.27; 13.37	3.09[a]	0.66	−10.59; 16.76	12.38[c]	0.12	−3.36; 28.12
Burning eyes($R^2 = 0.21$)	−10.29[c]	0.21	−26.58; 6.00	11.16[c]	0.13	−3.37; 25.69	21.30[d]	**0.01**	4.56; 38.04
Less interest in sexuality($R^2 = 0.16$)	−11.52[c]	0.29	−32.81; 9.76	18.17[c]	0.051	−0.12; 36.46	16.39[c]	0.14	−5.28; 38.07
Tingling hands/feed($R^2 = 0.14$)	2.48[a]	0.77	−14.64; 19.61	1.84[a]	0.81	−13.05; 16.74	9.65[b]	0.27	−7.57; 26.85
Rash($R^2 = 0.14$)	−2.37[a]	0.74	−16.56; 11.82	1.32[a]	0.84	−11.43; 14.07	17.90[c]	**0.02**	3.31; 32.50
Headache($R^2 = 0.21$)	−12.93[c]	0.07	−26.65; 0.80	8.45[b]	0.17	−3.80; 20.69	23.83[d]	**<0.01**	9.73; 37.93

Note: Results of a multivariate linear regression. Variables in the model (results not shown): Age, sex, socio-economic status, tumour size, surgery, disease status, time since diagnosis, tumour site.
[a]Trivial/no differences.
[b]Small differences.
[c]Medium/moderate differences.
[d]Large differences (Cocks et al., 2011; Osoba et al., 1998). Significant differences bold. R^2 = coefficient of determination, B = nonstandardised regression coefficient (indicating a B point increase or decrease in the respective QoL scale); 95% CI: 95% confidence interval; $p = p$ value.

affected domains measured by the EORTC-C30, while general health, physical functioning, pain, and dyspnoea were in ranges similar to the general population. The small or non-existent observed differences in general health could be due to patient adjustment over time.

While a variety of significant differences was observed in the stratified univariate analysis, the differences between patients currently receiving TKI treatment and patients with no/former TKI treatment did not remained significant after the multivariate logistic regression. This does not mean that differences do not exist, but on the basis of our relatively small sample size we were not be able to verify them statistically. Especially in those domains in which moderate/medium differences were found (notably fatigue, lack of energy, burning eyes and less interest in sexuality) further research is needed.

The observed differences due to the number of TKI treatment lines received during the disease course were remarkable. Patients who received multiple lines of treatment had stronger impairments in all functioning scales (except emotional functioning) than all other patients. We also observed higher symptom loads in a variety of domains, notably, fatigue, mouth pain, rash, burning eyes and headache. There are a variety of potential causes for this observation, which this study could not further disentangle. One possibility is that the specific medications given at later treatment lines have more negative effects. However, it is also possible that the duration of the disease course played a role or that an increase in disease severity precipitated the change to a subsequent line of treatment. We adjusted for disease severity through a variety of variables (treatment intention, tumour size at diagnosis, disease status) but it might be the case that we could not fully measure the impact of disease severity. We were not able to calculate interaction terms between disease severity and number of treatment lines.

Our observational HRQoL study of GIST patients used different instruments to evaluate HRQoL than previous studies that almost exclusively focused on evaluating treatment side effects of different TKIs. Side effects are often not measured as patient-reported outcomes but as expert-reported adverse events (Sodergren et al., 2014). With the caveat, that we were not able to collect information on the specific medication patients received, symptom loads in univariate group comparisons were in line with previous studies regarding diarrhoea, fatigue, and nausea/vomiting. In the multivariate regression, those results could not be statistically verified. A similar result is to be found in Poort et al., who analysed the prevalence of fatigue in distinct groups of GIST patients ($n = 89$) and matched healthy controls ($n = 234$; (Poort et al., 2016). In that study, 30% of all GIST patients experienced severe fatigue compared to 15% of matched healthy controls. Within the three groups of GIST patients (treatment completed, curative treatment, and palliative treatment) no significant differences were found.

The non-significant but medium-sized differences we found with regard to interest in sexuality between patients currently receiving TKI treatment and patients with no/former TKI treatment should be further investigated. One study in 51 men (49 in TKI treatment) with a variety of cancers reported low to none sexual desire in 29% (no control group) (Tsai et al., 2017). A 2017 review came to the conclusion, that the vast majority clinical trials in TKI reported no effects on sexual function. Exemptions were reported for pazopanib and sorafenib (Atallah et al., 2018). It should also be noted that lesser interest in sexuality was less pronounced in the palliative group as in the curative group. This difference was not statistically significant, but of medium relevance.

Functioning scales are not usually evaluated as treatment side effects; and therefore, comparable data is scarce. An exception is impaired cognitive functioning. An observational study of 30 patients with GIST or metastatic renal cell cancer who were treated with sunitinib or sorafenib found that the group receiving TKIs (20 patients) showed worse performance in a variety of cognitive domains than healthy controls (30 individuals; (Mulder et al., 2014). In an online survey of 485 GIST patients, 63.9% reported cancer-related cognitive impairment, regardless of receiving TKI or not. In this study, patients at least 5 years since their diagnosis had significantly worse perceived cognitive impairment scores than survivors less than 5 years since their diagnosis (Ferguson et al., 2019). Our observations showed the highest symptom loads in patients with multiple lines of TKI treatment. Observational study results therefore seem to indicate that cognitive impairment is a problem within the population of GIST patients, but it remains unclear when this impairment sets in and which factors influence its development.

4.2 | Strengths and limitations

This is, to our knowledge, the first evaluation of the HRQoL of GIST patients in a standard clinical-care setting. We identified HRQoL domains with a high symptom or restriction load and groups of GIST patients that are particularly affected, especially those with multiple TKI treatment lines. Because the EORTC QLQ-C30 is a generic cancer questionnaire and the additional questions from the EORTC item library were chosen with respect to sarcoma patients in general, it is possible that relevant GIST and TKI -specific symptoms were not recorded. This applies, for example, to oedema, hand-foot syndrome, and specific kinds of pain.

Participating patients were recruited in several study centres across Germany. One limitation of the study is that we could not perform a nonparticipant analysis of those who GIST patients who did not wish to take part in our study. Furthermore, the observed differences between responders and nonresponders indicate that the responding patients more commonly had severe disease compared to nonresponding patients. This implies that the absolute figures of HRQoL restrictions and symptoms may be overestimated. The present analysis is an exploratory cross-sectional analysis. Causal conclusions are therefore not possible. It is potentially subject to selection bias. We see this possibility mainly at the level of the study centres. The majority of our patients were recruited in university hospitals and/or specialised centres and those might not to representative for GIST-patients in general.

The comparison between different groups of GIST patients, as well as the multivariate linear regression, sometimes included only a

very small number of individuals within some of the groups, and the corresponding statistical uncertainty was high. Because of this, an insignificant *p* value does not rule out the possibility of there being differences between the groups. The large number of tests ran also increases the possibility of false-positive results. The relatively small sample size increases the probability that only large effect estimates can be ascertained against chance.

Due to limited resources, we were not able to collect all potentially relevant variables for the analyses. Important variables unavailable in our data set were mitosis rate, time since treatment, type of TKI and treatment dose. We were not able to collect information's on duration of treatment, which might be a potentially confounding variable for TKI treatment lines.

4.3 | Conclusion

GIST patients are severely restricted in their HRQoL. Patients receiving at least their second line of TKI therapy had the highest symptom loads and restrictions in their HRQoL. Underlying causes need further investigation.

CONFLICT OF INTEREST

SS received lecture fees from Lilly, BMS, Boehringer-Ingelheim, and Pfizer; none of which directly related to this work. JS received consulting fees from Novartis, Sanofi, ALK, and Lilly; none of which directly related to this work. JJ received fees from Lilly and Boehringer-Ingelheim; neither of which directly related to this work. LH received fees from SERVIER, which did not directly relate to this work. DA received lecture fees from Lilly and Implantcast; neither of which directly related to this work. MA received fees from Blueprint Medicines for conducting contract clinical trials and reimbursement for conference attendance fees from Blueprint Medicines, PharmaMar, and Lilly; none of which directly related to this work. DP received fees for consulting services from Lilly, PharmaMar, Roche, and fees for lectures from Lilly and PharmaMar; none of which directly related to this work. MS received research funding from PharmaMar and Novartis; neither of which directly related to this work. PR received fees from Bayer, Clinigen, BMS, Roche, MSD, Deciphera, Novartis, Pfizer, PharmaMar, Lilly, and Amgen; none of which directly related to this work. ME, BK, KA, MB, RG, PH, FM, DID, JM, AT, and SR declare that no conflicts of interest exist.

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AUTHOR CONTRIBUTIONS

ME wrote the article and analysed the data. ME, MS, and LH developed questionnaires and designed the study. JS and MS conceived the study and supervised the work of the entire study with MB. SS supervised the patient reported outcome analysis. KA supervised the study from a patient's perspective. ME, JJ, FM, and DP conceptualised and developed the statistical analysis plan for this paper. SR, PH, BK, DA, DP, JJ, RG, DIA, AT, PR, MA, AK, JM, and MS were responsible for patient recruitment or recruited patients directly. All authors have revised the manuscript critically and approved the published version.

DATA AVAILABILITY STATEMENT

The data that support the findings of this study are available on request from the corresponding author. The data are not publicly available due to privacy or ethical restrictions.

ORCID

Martin Eichler https://orcid.org/0000-0001-9654-2207

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