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Original Article

The health-related quality of life of sarcoma patients treated with neoadjuvant versus adjuvant radiotherapy – Results of a multi-center observational study

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ABSTRACT

Aim: The sequence of radiotherapy and resection in patients with soft tissue sarcomas is usually discussed on an individual basis. Better understanding of potential differences of health-related quality of life (QoL) between patients undergoing adjuvant (ART) versus neoadjuvant radiotherapy (NART) is therefore helpful for clinical decision making.

Methods: Adult sarcoma patients from 39 hospitals completed the European Organisation for Research and Treatment of Cancer Quality of Life Core Questionnaire (EORTC QLQ-C30). Differences in global QoL, physical functioning, role functioning, fatigue, pain, and insomnia between ART versus NART were investigated with multivariate regression, adjusting for age, gender, chemotherapy, grading, stage, tumor location, recurrence/distant metastasis, sarcoma type, time since last treatment, and treatment status using validated thresholds.

Results: A total of 1110 patients participated. Of them, 340 had received radiotherapy (NART: n = 95, 28%; ART: n = 245, 72%). Global QoL was 59.3 on average after NART and 60.5 after ART (B_{adj} = 1.0, p = 0.74). Physical functioning was 65.9 compared to 70.5 (B_{adj} = 4.2; p = 0.16), role function 48.8 vs. 56.7 (B_{adj} = 7.0, p = 0.08), fatigue 47.5 vs. 45.4 (B_{adj} = -1.2; p = 0.71), pain 40.2 vs. 34.1 (B_{adj} = -6.8; p = 0.08), and insomnia 33.7 vs. 41.6 (B_{adj} = 5.5, p = 0.16). Among patients with NART, clinically relevant QoL impairments were less frequent 2 years after treatment compared to < 2 years thereafter (n = 6 vs. n = 4 on average).

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Conclusion: There is little evidence for QoL differences in most domains and overall QoL between the two irradiation groups. However, patients after NART might experience worse role functioning and pain but fewer problems with insomnia compared to patients after ART.

Radiotherapy is an essential part of the treatment of soft tissue sarcomas, effective in preventing up to half of potential local recurrences [1]. The question of when radiotherapy should take place in relation to the timing of surgery is a subject of debate. Regarding oncologic endpoints, equivalent tumor control, occurrence of distant metastases, and overall survival can be achieved with a lower preoperative radiation dose compared with postoperative radiation [2,3]. On the one hand, a disadvantage of neoadjuvant irradiation is an increased likelihood of wound complications. On the other hand, the lower frequency of long-term tissue changes from which functional limitations can result, such as edema, fibrosis, and joint stiffness, is advantageous [2]. How patients cope with the long-term effects of therapy is crucial for decision-making, which is why studies investigating health-related quality of life (QoL) are particularly important in this respect. However, knowledge about QoL after these treatments is scarce. There are only few trials with well-defined inclusion criteria or large population-based treatment series [4]. To date, decisions are based on the unconfirmed results of the prospective NCIC-SR02 study from Canada showing that there are no differences in quality of life between patients undergoing neoadjuvant and adjuvant radiotherapy, except for pain, which was more severe in patients receiving neoadjuvant therapy [4]. Another study examining the quality of life of patients treated with neoadjuvant radiotherapy versus those without radiotherapy was only able to include 70 patients [5]. In that study, patients who received neoadjuvant radiotherapy were found to score worse in almost all facets of quality of life than patients who did not require any radiotherapy. Unfortunately, the authors did not control for potential confounders that may affect outcomes given the highly heterogeneous baseline values and diverse treatment patterns of sarcoma patients.

The study "Burden and Medical Care of Sarcoma in Germany: Nationwide Cohort Study Focusing on Modifiable Determinants of Patient-Reported Outcome Measures in Sarcoma Patients (PROSa)" offers a unique opportunity to investigate the impact of the timing of radiotherapy on the QoL of soft tissue sarcoma patients in a large population. The size of this study allows potential confounders to be considered in relation to the last status of the disease. In particular, QoL of patients who have not experienced disease recurrence so far can be investigated. For these patients, maintaining their QoL is of particular importance [6].

This study addresses the following research questions:

1) Are there differences in QoL among soft tissue sarcoma patients who underwent neoadjuvant versus adjuvant radiotherapy?
2) If there are differences, do we find them:
a) regardless of disease stage and
b) in patients during follow-up without secondary metastasis or local tumor recurrence?
3) What proportion of patients in follow-up who had received neoadjuvant therapy experiences clinically important symptoms and limitations, stratified by time since treatment (<2 years vs. ≥ 2 years after treatment)?
4) Does the QoL of both patient groups differ from the QoL of the German general population?

Methods

Study design

We conducted an observational study in 39 study centers in Germany between September 2017 and February 2020 (NCT03521531, clinicaltrials.gov). Of the study centers, eight were office-based practices, 22 hospitals of tertiary care and nine other hospitals. Patients could be enrolled at any time during their disease trajectory.

Inclusion criteria were: confirmed sarcoma diagnosis, age ≥ 18 years, and written informed consent. We excluded persons who were mentally or linguistically unable to complete questionnaires. The study was approved by the ethics committees of the Technical University of Dresden (EK1790422017) and the participating centers prior to the beginning of data collection [7].

Eligible patients and survivors were invited to participate at the study centers during visits and sometimes by phone or mail. Data collection was performed using REDCap (Vanderbilt University, Nashville, United States) electronic data capture tools hosted at the Technical University Dresden [8]. QoL data and socio-demographic data were sent by the study centers to the study coordination center at the University Hospital Dresden. Clinical information was submitted to the study coordination center online by the study centers using electronic case report forms. Further information on the PROSa study has been published elsewhere [6,9–14].

Outcomes and variables

QoL was measured using the European Organization for Research and Treatment of Cancer Quality of Life Questionnaire (EORTC QLQ-C30) [15]. This instrument assesses global quality of life, five functioning and nine symptom domains in values from 0 to 100. Higher values indicate better quality of life in the functioning scales and a higher symptom burden in the symptom scales.

Six pre-specified domains of EORTC QLQ-C30 were examined in this study as endpoints: global quality of life, physical functioning, role functioning, pain, fatigue, insomnia, as well as the summary score [16].

Depending on the research question, we considered the following variables as potentially confounding factors: gender (male/female), age, received chemotherapy (yes/no), grading (low/high/unknown/not applicable), T stage (T1/T2-T4/unknown), tumor location (limbs/all other), sarcoma type (unclassified sarcoma/fibroblastic, myofibroblastic, fibrohistiocytic sarcoma/liposarcoma/leiomyosarcoma/all other), time since last treatment (0-<1 year/1-<3 years/3-<5 years/≥5 years/not determined), metastasis at diagnosis (yes/no/unknown), tumor progression after diagnosis (yes/no/unknown), and currently in follow-up (yes/no). Note that time since last treatment was only captured until patients experienced a progression, since the treatment schemes after such events usually become fuzzy. Hence, all patients with progression were considered to have unknown time since last treatment (category "not determined"). For descriptive purposes, the time since diagnosis is reported in addition to the time since last treatment.

Statistical analysis

For this paper, we used cross-sectional data of the patients. The PROSa study was prospective and included multiple time points of QoL data collection. However, patients could be included at any time during their disease course, as explained earlier. To capture the effects of radiotherapy, we adopted a "staggered entry" approach in this study. That is, whenever a patient received radiotherapy, the time point before radiotherapy was disregarded, and QoL data collected after radiotherapy were used as the outcome variable. In other words, for the purposes of this paper, the study was analyzed cross-sectionally to be able to use as much information about radiotherapy as possible.

Only participants with QoL data were included in the analysis. To answer research questions 1 and 2, we restricted the study population to patients who were treated either with neoadjuvant or adjuvant radiotherapy.

The sample characteristics were evaluated using absolute and relative frequencies or means and standard deviations (SD) for continuous variables, stratified by the radiotherapy treatment received (neoadjuvant vs. adjuvant).

We calculated generalized linear models to investigate differences in QoL between the two treatment groups. For each endpoint, we computed two models: In model 1, we analyzed all sarcoma patients with adjuvant or neoadjuvant radiotherapy. whereas in model 2, only those in follow-up and without metastatic or progressive disease were included. This approach was chosen to see whether the findings from model 1 were also applicable to a more homogeneous patient population.

The coefficients were adjusted for age, gender, clinical characteristics before and during treatment (including chemotherapy received, grading, T-stage, tumor location, distant metastasis at diagnosis, and sarcoma type) as well as clinical characteristics at the time of the survey (time since last treatment, treatment status, and tumor recurrence/metastasis after diagnosis).

The relevance of the differences in QoL was evaluated using reference values from Cocks et al. [17]. With these reference values, each score difference can be classified as “trivial”, “small”, “medium”, or “large”.

To answer research question 3, we analyzed the QoL data of patients in follow-up who were treated with neoadjuvant radiotherapy. We calculated the proportion of patients with clinically important symptoms and limitations in the QoL domains using the thresholds of Giesinger et al. [18]. These thresholds were empirically defined based on several external criteria, reflecting the clinical importance of a health problem. Clinical importance is any aspect of a health problem that makes it relevant for the clinical encounter [18]. The proportion of problems in each group was compared using Fisher’s exact test.

To answer research question 4, we used the data of all patients with soft tissue sarcoma in the PROSa study and compared it with reference values of the German general population [19].

Statistical analyses were performed with SPSS v27 (IBM Corporation, Armonk, New York, USA). Graphs were produced using STATA v15 (StataCorp LLC, College Station, Texas, USA).

Results

Of all soft tissue sarcoma patients enrolled in the PROSa study, 340 had received either neoadjuvant (n = 95, 28%) or adjuvant (n = 245, 72%) radiotherapy and had completed the EORTC QLQ-C30 (Fig. 1). Of them, 146 were in follow-up and had no evidence of recurrence or disease progression at the time of the interview.

Among the 340 included patients, the time since diagnosis was on average 5 years (range: 5 months to 24 years); 4 years in those after neoadjuvant treatment (5 months to 18 years) and 5 years in those after adjuvant treatment (5 months to 24 years). The time since last treatment in those without progression was on average 2.8 years (range: several days to 11 years); on average 2 years in the group after neoadjuvant (range: several days to 6 years) and 3 years after adjuvant (range: 3 months to 11 years). The majority had liposarcoma (31%), and the sarcoma was most often located at the lower limbs (50%), though there was a good representation of various sarcoma types (see Table 1 for details).

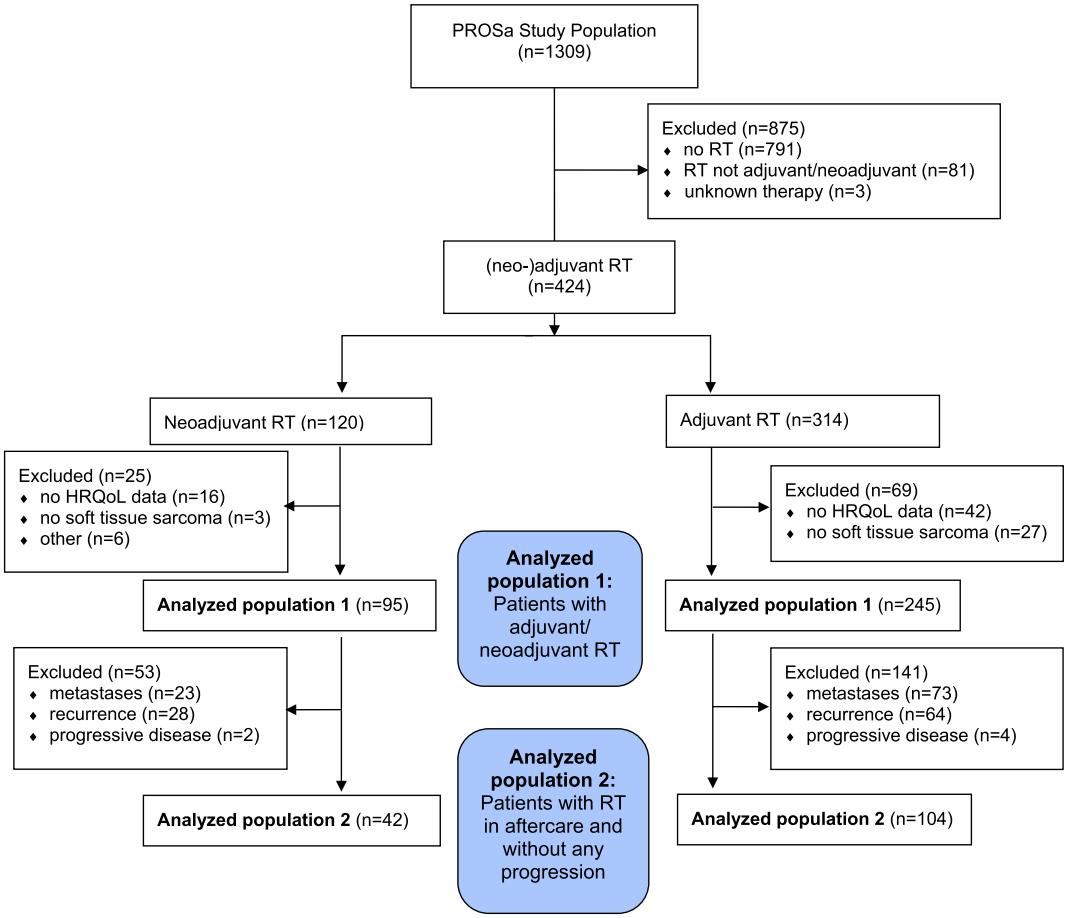

Fig. 1. Flow of patients through the study. RT = radiotherapy.

Table 1
Sample characteristics, stratified by type of radiotherapy (adjuvant/neoadjuvant).

	Sarcoma patients			Sarcoma patients in follow-up, without recurrence or metastatic disease		
	neo-adjuvant RT	Adjuvant RT	all	neo-adjuvant RT	Adjuvant RT	all
Number of patients (%)	**95 (28%)**	**245 (72%)**	**340 (100%)**	**42 (29%)**	**104 (71%)**	**146 (100%)**
	n (%) /mean (SD)	n (%) /mean (SD)	n (%) /mean (SD)	n (%) /mean (SD)	n (%) /mean (SD)	n (%) /mean (SD)
Gender						
female	36 (37.9)	113 (46.1)	149 (43.8)	13 (31.0)	48 (46.2)	61 (41.8)
male	59 (62.1)	132 (53.1)	191 (56.2)	29 (69.0)	56 (53.8)	85 (58.2)
Age at study inclusion, in years (SD)	59.1 (13.1)	58.4 (13.7)	58.6 (13.5)	59.9 (11.9)	58.3 (13.4)	58.7 (13.0)
Time since diagnosis, in years (SD)	3.8 (3.5)	5.4 (4.3)	4.9 (4.1)	2.3 (1.5)	3.5 (2.3)	3.1 (2.2)
Time since last treatment						
0-<1 year	11 (11.6)	18 (7.3)	29 (8.4)	11 (26.2)	18 (17.3)	29 (19.9)
1-<3 years	22 (23.2)	47 (19.2)	69 (20.3)	22 (52.4)	47 (45.2)	69 (47.3)
3-<5 years	6 (6.3)	20 (8.2)	26 (7.6)	6 (14.3)	20 (19.2)	26 (17.8)
>5 years	3 (3.2)	19 (7.8)	22 (6.5)	3 (7.1)	19 (18.3)	22 (15.1)
not determined	53 (55.8)	141 (57.6)	194 (57.1)	–	–	–
Sarcoma Type						
fibroblastic, myofibroblastic, fibrohistiocytic sarcoma	9 (9.5)	47 (19.2)	56 (16.5)	3 (7.1)	20 (19.2)	23 (15.8)
liposarcoma	40 (42.1)	64 (26.1)	194 (30.6)	20 (47.6)	24 (23.1)	44 (30.1)
leiomyosarcoma	11 (11.6)	30 (12.2)	41 (12.1)	6 (14.3)	9 (8.7)	15 (10.3)
unclassified sarcoma	26 (27.4)	58 (23.7)	84 (24.7)	11 (26.2)	28 (26.9)	39 (26.7)
all other*	9 (9.5)	46 (18.8)	55 (16.1)	2 (4.8)	23 (22.1)	25 (17.1)
Site						
trunk	48 (50.5)	79 (32.2)	127 (37.4)	24 (57.1)	17 (16.3)	41 (28.1)
- abdomen	6 (6.3)	15 (6.1)	21 (6.2)	2 (4.8)	3 (2.9)	5 (3.4)
- retroperitoneum	25 (26.3)	19 (7.8)	44 (12.9)	12 (28.6)	3 (2.9)	15 (10.3)
- thorax	8 (8.4)	22 (9.0)	30 (8.8)	4 (9.5)	6 (5.8)	10 (6.8)
- pelvis	9 (9.5)	23 (9.4)	32 (9.4)	6 (14.3)	5 (4.8)	11 (7.5)
extremities	45 (47.4)	148 (60.4)	193 (56.8)	17 (40.5)	83 (79.8)	100 (68.5)
- lower limbs	42 (44.2)	129 (52.7)	171 (50.3)	17 (40.5)	73 (70.2)	90 (61.6)
- upper limbs	3 (3.2)	19 (7.8)	22 (6.5)	0	10 (9.6)	10 (6.8)
head & neck	1 (1.1)	11 (4.5)	12 (3.5)	0	2 (1.9)	2 (1.4)
back	1 (1.1)	6 (2.4)	7 (2.1)	1 (2.4)	2 (1.9)	3 (2.1)
unknown	0	1 (0.4)	1 (0.3)	0	0	0
T stage						
T1	8 (8.4)	45 (18.4)	53 (15.6)	5 (11.9)	23 (22.1)	28 (19.2)
T2-T4	68 (71.6)	134 (54.7)	202 (59.4)	32 (76.2)	60 (57.7)	92 (63.0)
unknown	19 (20.0)	66 (26.9)	85 (25.0)	5 (11.9)	21 (20.2)	26 (17.8)
Grading at diagnosis						
low grade	12 (12.6)	30 (12.2)	42 (12.4)	3 (7.1)	11 (10.6)	14 (9.6)
high grade	66 (69.5)	176 (71.8)	242 (71.2)	32 (76.2)	74 (72.6)	106 (72.6)
not applicable/ unknown	17 (17.9)	39 (15.9)	56 (16.5)	7 (16.7)	19 (18.3)	26 (17.8)
Chemotherapy until time of interview						
no	40 (42.1)	124 (50.6)	164 (48.2)	24 (57.1)	74 (71.2)	98 (67.1)
yes	55 (57.9)	121 (49.4)	176 (51.8)	18 (42.9)	30 (28.1)	48 (32.9)
Disease status at time of interview						
complete remission	31 (32.6)	129 (52.7)	160 (47.1)	20 (47.6)	88 (84.6)	108 (74.0)
partial remission/ stable disease	32 (33.7)	41 (16.7)	73 (21.5)	17 (40.5)	11 (10.6)	28 (19.2)
progress	20 (21.1)	44 (18.0)	64 (18.8)	0	0	0
unknown/ not accessible	12 (12.6)	31 (12.7)	43 (12.6)	5 (11.9)	5 (4.8)	10 (6.8)
Metastasis at diagnosis						
no	85 (89.5)	186 (76.2)	271 (79.9)	39 (92.9)	90 (86.5)	129 (88.4)
yes	2 (2.1)	7 (2.9)	9 (2.7)	0	0	0
unknown	8 (8.4)	51 (20.9)	59 (17.4)	3 (7.1)	14 (13.5)	17 (11.6)
Recurrence/ metastasis after diagnosis						
no	47 (49.5)	120 (49.0)	167 (49.1)			
yes	48 (50.5)	122 (49.8)	170 (50.0)			
unknown	0	3 (1.2)	3 (0.9)			
Currently in follow-up						
no	22 (23.2)	54 (22.0)	76 (22.4)			
yes	73 (76.8)	191 (78.0)	264 (77.4)			
Treatment intent at time of interview						
curative	74 (77.9)	185 (75.5)	259 (76.2)			
palliative	19 (20.0)	58 (23.7)	77 (22.6)			
unknown	2 (2.1)	2 (0.8)	4 (1.2)			

Notes: STS = soft tissue sarcoma, n = number of patients, SD = standard deviation, RT = Radiotherapy.
*Other: vascular tumor, osteosarcoma (STS), skeletal muscle tumor, nerve sheath tumor, Ewing sarcoma (STS), chondrosarcoma (STS), stromasarcoma, synovial sarcoma.

Table 2
Health-Related Quality of Life in patients treated with neoadjuvant versus adjuvant radiotherapy.

Quality of Life Domain	All patients (n = 340)					Patients in follow-up without progressive disease (n = 146)				
	Mean		**B**	**95% CI**	***p***	**Mean**		**B**	**95% CI**	***p***
	Neoadj	**Adj**				**Neoadj**	**Adj**			
Summary Score	68.9	70.3	1.0	−3.5; 5.6	*0.66*	71.3	74.2	3.3	−4.3; 10.8	*0.39*
Global Quality of Life	59.3	60.5	1.0	−4.7; 6.6	*0.74*	62.3	66.1	3.2	−5.9; 12.3	*0.49*
Physical Functioning	65.9	70.5	4.2	−1.6; 10.0	*0.16*	71.6	74.9	7.0*	−2.0; 16.0	*0.13*
Role Functioning	48.8	56.7	7.0*	−0.8; 14.8	*0.08*	51.2	64.9	15.4*	2.7; 28.0	*0.02*
Fatigue	47.5	45.4	−1.2	−7.6; 5.2	*0.71*	46.8	39.6	−7.3*	−18.2; 3.7	*0.19*
Pain	40.2	34.1	−6.8*	−14.4; 0.8	*0.08*	41.7	32.1	−14.1**	−25.5; −2.6	*0.02*
Insomnia	33.7	41.6	5.5*	−2.2; 13.3	*0.16*	27.0	42.2	14.6**	1.5; 27.8	*0.03*

Note: Mean = unadjusted mean score in the respective domain, B = non-standardized regression coefficient (indicating a point increase or decrease in the respective domain), CI = confidence interval, p = p-value. Neoadj = neoadjuvant radiotherapy, adj = adjuvant radiotherapy.
Coefficients are adjusted for age, sex, chemotherapy, grading, T-stage, tumor location, recurrence/ distant metastasis at diagnosis or thereafter, sarcoma type, time since last treatment, treatment status.
Relevance of differences: * small, **medium (Cocks et al., 2011).

Patients after neoadjuvant radiotherapy reported overall QoL (e.g., in the global QoL scale and the summary score) similar to patients after adjuvant radiotherapy (Table 2). They suffered from worse role functioning and more pain but less from insomnia. This was the case both for the entire patient sample and for those in follow-up. In this latter group, the differences between patients with and without neoadjuvant radiotherapy were more pronounced (Fig. 2).

When controlling for potential confounders, there was no convincing evidence for differences in QoL after neoadjuvant vs. adjuvant therapy (Table 2). The full regression models can be found in the supplemental material.

In patients during follow-up and without metastasis or tumor recurrence, we found evidence for a few differences after adjustment for age, sex, chemotherapy, grading, stage, tumor location, recurrence or distant metastases at the time of diagnosis or thereafter, sarcoma type, time since last treatment, and treatment status. Role functioning and pain were worse in patients after neoadjuvant radiotherapy, and at the same time these patients reported fewer problems with insomnia. Global QoL and the summary score did not differ between patients with and without neoadjuvant radiotherapy among patients in follow-up.

Of the patients who had received neoadjuvant radiotherapy and who were currently in follow-up (n = 42), those ≥ 2 years after treatment experienced on average fewer clinically relevant restrictions (N = 4) compared to the patients whose treatment ended < 2 years prior to the study enrollment (N = 6). We found statistically insignificant differences larger than 20% in role functioning, fatigue, and dyspnea (Table 3).

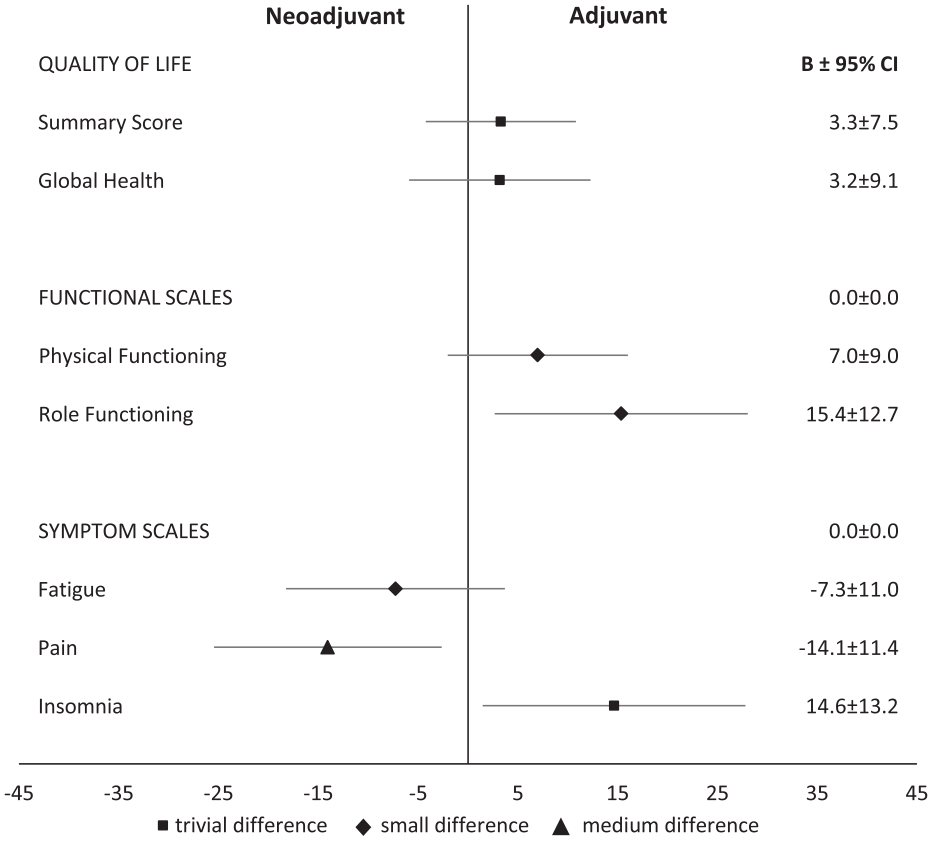

Fig. 2. Differences in quality of life between sarcoma patients who received neoadjuvant versus adjuvant radiotherapy, in follow-up and without progressive disease. Displayed are the regression coefficients (B), adjusted for age, sex, chemotherapy, grading, T-stage, tumor location, recurrence/ distant metastasis at diagnosis, sarcoma type, time since last treatment, treatment status. The relevance of differences was defined according to Cocks et al., 2011.

Table 3
Proportion of patients with clinically important restrictions in quality of life among sarcoma patients currently in follow-up (without recurrence or metastases) and treated with neoadjuvant radiotherapy (n = 42), stratified by time since treatment.

Quality of Life Domain	< 2 years post treatment (n = 33)	≥ 2 years post treatment (n = 9)	p-value
	n (%)	n (%)	
Physical Functioning	20 (61%)	3 (33%)	*0.14*
Role Functioning	19 (58%)	3 (33%)	*0.18*
Emotional Functioning	19 (58%)	4 (44%)	*0.37*
Cognitive Functioning	16 (49%)	3 (33%)	*0.34*
Social Functioning	15 (46%)	3 (33%)	*0.40*
Fatigue	21 (64%)	3 (33%)	*0.11*
Nausea/ Vomiting	8 (24%)	1 (11%)	*0.37*
Pain	25 (76%)	6 (67%)	*0.44*
Dyspnea	19 (58%)	2 (22%)	*0.07*
Insomnia	5 (15%)	1 (0%)	*0.62*
Appetite Loss	2 (6%)	1 (11%)	*0.53*
Constipation	2 (6%)	1 (11%)	*0.53*
Diarrhea	11 (33%)	2 (22%)	*0.42*
Financial Difficulties	16 (49%)	3 (33%)	*0.34*
Average number of restrictions and symptoms	6.0	4.0	

Note: The decision whether a clinically important restriction was present was taken based on the thresholds provided by Giesinger et al. 2020.
n = number of patients; p-value derived from Fishers exact tests.

In both groups, problems with pain occurred most frequently (in 76% of the patients earlier and in 67% more than 2 years after the end of treatment). In the group < 2 years after treatment, this was combined with fatigue and poor physical functioning (both in 64% and 61% of the cases). In the group ≥ 2 years after treatment, emotional functioning was the second most relevant problem (in 44% of the cases).

Compared to the general population, all groups of soft tissue sarcoma patients reported worse functioning and higher symptom burden (Fig. 3). The largest differences were observed in role functioning, i.e., problems with work or education / school.

Discussion

With this study, we investigated QoL differences after treatment of soft tissue sarcomas depending on the time of radiotherapy. The varying proportions of functional preservation and wound complications are currently the main factors driving decision making regarding the timing of radiotherapy for soft tissue sarcomas [20,21]. In contrast, little is known about the QoL of patients treated either with adjuvant or neoadjuvant irradiation.

In a cross-sectional monocentric study, QoL was lower in patients who underwent preoperative radiotherapy [5]. However, the heterogeneity of the patient sample was not sufficiently considered in the statistical analysis, making confounding likely. In a randomized trial of pre- versus postoperative radiotherapy for soft tissue sarcomas of the extremities at Princess Margret Hospital in Toronto, the timing of radiotherapy was shown to have little effect on patient functionality and QoL. Within the first six weeks after resection, patients receiving postoperative radiation still had better functioning and less pain than patients receiving preoperative radiation, which leveled off over time and continued to improve over the course of two years, although average scores for the Canadian population were not used as a reference. No QoL domain particularly stood out. The strongest recovery occurred between months 6 and 12 [4]. However, the results of this study are now more than 20 years old and were collected at a time when surgical approaches differed compared to today. In this context, it should be mentioned that studies in other tumor entities have shown an improvement in the QoL

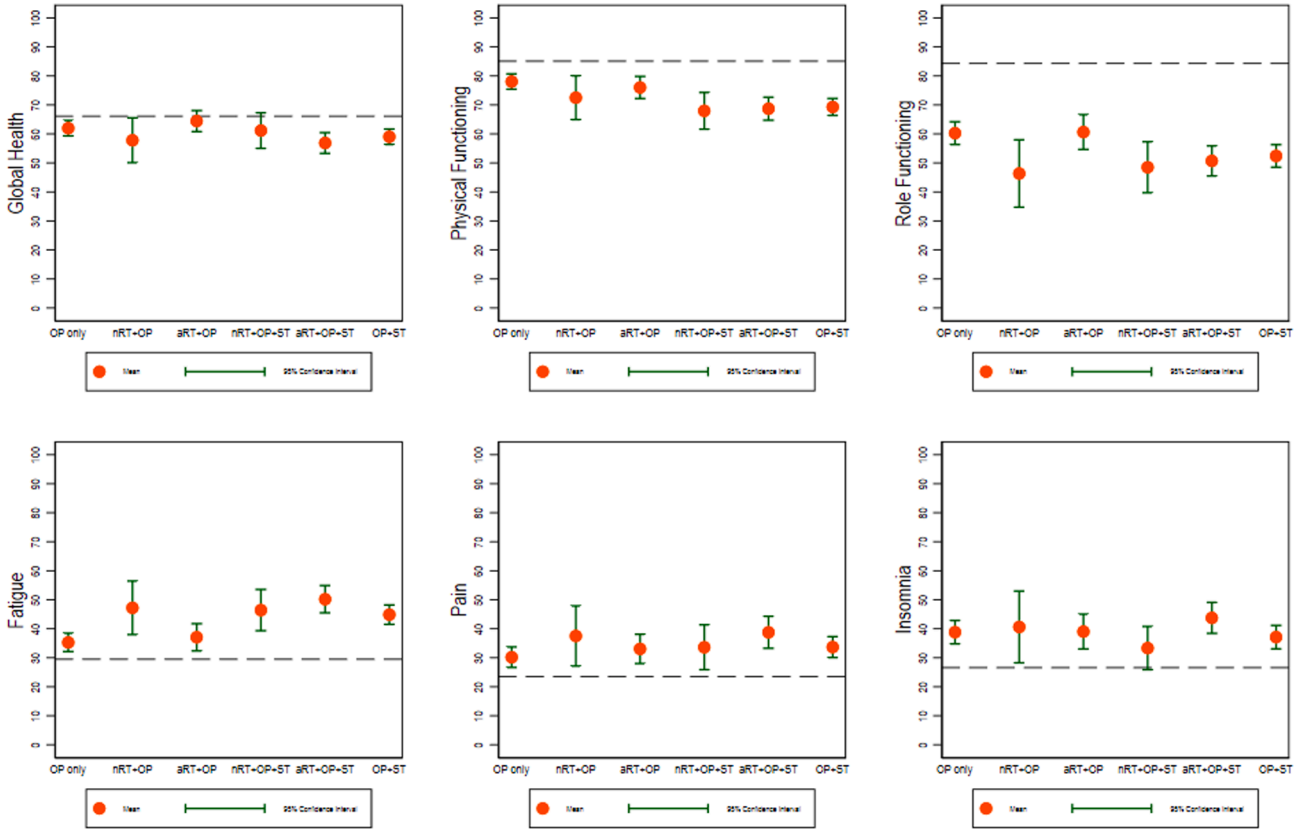

Fig. 3. Quality of life in sarcoma patients compared to the general population. The dashed lines represent the respective reference value from the general population. OP = surgery, nRT = neoadjuvant radiotherapy, aRT = adjuvant radiotherapy, ST = systemic therapy.

of survivors in recent decades [22], so it is important to keep collecting current data. This was done in the PROSa study, which reflects the contemporary treatment reality of a Western European country. Furthermore, it is possible that patients at that time had a different expectation of their QoL after treatment than they do today. Finally, it has been observed that cross-cultural differences in coping with illness lead to different ratings of QoL, so that the results of North American studies may not be applicable to Western Europe [23].

Our results show that, on the one hand, postoperatively irradiated patients report better role function and less pain than preoperatively irradiated patients. While differences were associated with a statistical uncertainty in the entire sample, in the group of patients without recurrence in follow-up we found medium and small differences that were statistically significant. It is noteworthy that the differences in this smaller group were more distinct, and statistically significant, than in the total sample, thus than in the larger group. As the p-value is a function of the sample size, this is unusual. One explanation is that the total sample was more heterogeneous than the smaller group, thereby creating statistical uncertainty. Another explanation, more clinical, would be that the effects of the timing of radiotherapy are only relevant until there is progression. From that point on, the QoL is determined more by the recurrence or metastases than by the type of radiotherapy. Role functioning means being able to "fulfill one's role" in work, leisure, school, etc., for example, going to work and pursuing one's hobbies. Poorer role functioning and pain can be due to both radiation therapy and surgery. Though it was not the purpose of this study to compare surgery and radiotherapy, it is important to keep that in mind. As both aspects of QoL are also very important for patients with soft tissue sarcoma [6,24–26], these domains should be considered in future QoL studies as relevant endpoint.

On the other hand, the postoperatively irradiated patients had more problems with insomnia. Sleep problems can have many causes, both physical and psychological (see below for more details). Other domains of QoL did not differ, which is largely consistent with the observations of the NCIC-SR2 study [2].

If we assume that the differences found are not due to residual confounding but reflect true dissimilarity, potential causes are still difficult to ascertain. It could be due to a different perception of the tumor disease. Patients with neoadjuvant therapy are confronted for a longer time with macroscopic disease, which for them is perceivably real. They accept the delay in resection in the hope of a higher chance to remain tumor-free for a longer time. The risk remains that the neoadjuvant therapy does not lead to the desired resection or that distant metastases do appear before resection. The delay of resection may be perceived by the patient as psychological stress that lingers [27].

This explanation may seem vague but it has been shown in "low risk" prostate cancer patients that the presence of a tumor may induce such a stressful situation that active surveillance or non-surgical approaches are rejected in favor of immediate radical resection despite the former having a better side-effect profile [28]. In contrast, however, women with breast cancer report comparable levels of distress after pre- and postoperative chemotherapy [29]. Little is known about the ongoing psychological burden after resection and its differences in primarily surgically and primarily conservatively treated patient groups, even among breast cancer patients. It is possible, however, that patients cope differently with their disease in the first two years after tumor treatment, which was the time span many patients took part in our survey, compared to afterwards.

Breast cancer patients are also vulnerable regarding their body image depending on their age and the extent of resection [30]. The issue of body image also plays a role in sarcoma patients and has been poorly addressed [24]. In addition, besides aesthetic features, functionality has a complex influence on body image and quality of life [31]. It is likely that patients who receive radiotherapy neoadjuvantly are among those who have more advanced tumors than those who receive radiation only postoperatively. This may include constellations involving contact with bones, vessels, and nerves. The commonly cited rationale for neoadjuvant use of radiation is to reduce the propensity for recurrence when resection margins are tight [32]. This necessitates more extensive resections and reconstructions, which may also cause differences in functionality and its perception. Although our statistical analysis adjusted for a wide variety of risk characteristics, such as tumor size, it was impossible to adjust for all potential confounders such as exact type of surgery, radiation dose, or fractionation. This is a clear limitation of the presented data.

In addition, no analyses could be performed on reconstruction, functionality, and the effects of wound healing disorders, since the primary focus was on the assessment of patient-relevant topics, i.e., their QoL. Nevertheless, it must be stated at present that patients who received neoadjuvant irradiation experience deficits in their role function, which must receive attention in the phase of physical rehabilitation and building of coping strategies.

Another key issue that needs to be addressed is the level of pain which is worse in preoperatively irradiated patients. This was consistently shown in both the PROSa and NCIC studies. However, we do not know yet what is causing this difference, especially given the smaller volumes and lower doses typically used in neoadjuvant radiotherapy. It might be due to residual confounding or to differences in the quality of the pain, warranting further research. Since pain, along with fatigue, can be a dominant trigger of emotional distress [33–36], it is important to treat pain not only from a somatic perspective but also for QoL reasons. For patients with sarcomas, Maggi et al. were able to confirm this [37]. As a recommendation that can be derived from the results of our study, the treatment of pain as well as the teaching of coping strategies should not only be focused on patients who develop a palliative situation, but also – and especially – on patients who remain without recurrence. This should take into account age- [38] and location-dependent QoL limitations as well [25,39]. However, although some underlying fear of recurrence remains in many patients [40], we also found that symptoms were less frequent on average two years after primary therapy. This has also been demonstrated by other researchers [41].

Finally, another very relevant point for people's well-being is healthy, restful sleep. Our results suggest that this is associated more frequently with neoadjuvant radiotherapy than with postoperative therapy. This does not imply that adjuvant therapy causes insomnia. Sleep problems can also be related to mental health conditions such as depression (difficulties falling asleep) or anxiety (waking up during the night or early in the morning), both known to be more common in patients with soft-tissue sarcoma compared to cancer-free controls [42]. Another explanation could be related to the fact that in the adjuvant therapy group there were more often patients with lower extremity sarcomas, perhaps leading to restless leg syndrome which can cause severe sleep problems, thereby reducing QoL [43]. Although we adjusted for tumor location in the statistical models, it is still possible that residual confounding played a role.

Conclusion

Potential differences in the QoL of patients undergoing neoadjuvant versus adjuvant radiotherapy identified in our study were in the domains role functioning, pain, and insomnia. Moreover, patients' QoL differed from that of the general population. It should be noted though that real-world data not allow conclusions to be drawn about causal relationships.

For radiotherapy, two tasks remain challenges in keeping QoL of sarcoma patients as high as possible; first, a strong focus on later functioning through target volumes that take into account functional structures even in adulthood, and second, the integration of QoL issues in the mandatory radiotherapy follow-up with initiation of long-term rehabilitation and self-help programs including referral to specialized services (e.g., cancer counseling centers). From the point of view of the question addressed here, the essential task remains to further investigate

the effect of different radiation techniques and timing on QoL.

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Author contributions

SSi and SSe wrote the paper.

MKS and ME developed questionnaires and study design.

JS and MKS developed the conception of the study and supervised with ME the work throughout the whole study.

SSi, SSe, HG, and ME developed the statistical analysis plan for this paper.

HG, KF, AK, SZ, RG, RF, TK, CJ, DA, and MKS were responsible for the enrolment of patients or enrolled patients directly.

All authors have revised the manuscript critically and approved the published version.

Conflicts of interest statements

SSi received lecture fees from Lilly and consulting fees from Content Ed Net, all outside of this work.

SSe received consultant honoraria from PharmaMar, not related to this work.

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Declaration of Competing Interest

The authors declare that they have no known competing financial interests or personal relationships that could have appeared to influence the work reported in this paper.

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