

Return to work and quality of life in disease-free adult patients with soft tissue and bone sarcoma of the extremity

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Abbreviations:

CES-D	Center for Epidemiologic Studies-Depression
CI	Confidence Interval
FoP-Q-SF	Fear of Progression Questionnaire-Short Form
GIST	Gastrointestinal Stroma Tumor
QoL	Quality of Life
RtW	Return to Work
SD	Standard Deviation
SF-36	Short-Form Health Survey
TESS	Toronto Extremity Salvage Score

Abstract

Treatment of extremital sarcoma patients may be associated with significant functional disabilities and psychosocial distress affecting return to work (RtW) and quality of life (QoL). In this exploratory study we prospectively investigated the RtW rate, explored biomedical and psychosocial predictors of RtW, and compared generic QoL with Swiss population norms. Forty people (89%) returned to work. Full-time employment before sarcoma diagnosis, high educational level, and low tumor grade showed an increased probability of RtW. The median age was lower in patients that returned to work, and they reported less fear of progression. Generic QoL (SF-36) was reduced in almost all dimensions when compared to a normative Swiss population. Physical functioning and fear of progression have to be addressed in the rehabilitation process.

Keywords: sarcoma, return to work, quality of life, fear of progression

Introduction

Sarcomas are a rare and heterogeneous group of malignant tumors of mesenchymal origin that comprise less than one percent of all adult malignancies and 12 percent of pediatric cancers.(1) Approximately 80 percent of sarcomas originate from soft tissue and the rest from bone. Sarcomas occur at all anatomic body sites, but the majority are in the extremities.(2) Wide surgical resection of the primary tumor is the essential component of treatment for virtually all patients, with the possible addition of adjuvant radiotherapy and/or chemotherapy. This treatment, however, may leave patients with significant functional disabilities. Functional disabilities may cause patients to suffer from persistent emotional and social distress with a reduced quality of life (QoL) and impact on the return to work (RtW) process.(3)

Employment status, *i.e.* the ability to find or maintain employment, is crucial for all cancer patients. Compared to healthy peer groups, adult childhood cancer survivors are approximately twice more prone to unemployment and are more likely to report that health problems prohibit employments.(4-6) Occupation of patients treated for sarcomas of the extremities has been reported in several studies with an unemployment rate between 11% and 47%.(7-10) In all of these reports the cohorts mainly consisted of children, adolescents and young adult patients.

There are many studies assessing physical functioning and psychosocial outcome in sarcoma patients.(11, 12) While it is evident that physical disability hampers the RtW process the impact of psychological factors on RtW outcome is less clear. (13-15) In order to study the relation between RtW, physical limitations and psychosocial distress it is worthy assessing both in this context. With this study, we aimed to investigate the RtW rate, predictors of RtW and evaluate QoL-related outcomes in adult disease-free sarcoma patients in order to improve post treatment care, support and rehabilitation.

Material and Methods

Study design, population and objectives

This study is based on a cross-sectional investigation. Patients with the diagnosis of a limb sarcoma of soft tissue and bone, surgically treated between 2000 and 2015 at the University Hospital Bern, age at diagnosis of ≥ 18 and < 65 (retirement age in Switzerland), alive and without evidence of sarcoma disease were eligible for the study. Patients affected at the trunk were excluded from this study.

The primary objective was to investigate the RtW rate and explore biomedical and social predictors of RtW. RtW was defined as return to the former activity. Secondary objectives were to assess QoL-related outcomes, to explore its association with RtW, and compare generic QoL to the Swiss population norms.

This study was approved by the ethics committee of Bern (No: 2016-01446) and was funded by Swiss Cancer League (KLS-3812-02-2016).

Procedures

Firstly, the clinical database of the Department of Orthopedics was screened for patients fulfilling the inclusion criteria. In case of missing data, the patient's general practitioner, external health institutions or the patient him or herself were contacted. Contact details of patients lost to follow-up were requested at the residents' registration office.

All identified patients were then contacted by post, some weeks later by phone and invited to participate in this study. Patients having consented to participate were interviewed in the outpatient clinic in order to assess educational and occupational details and subsequently completed the QoL questionnaires. All interviews were conducted by a trained study nurse who was familiar with the questionnaires.

Patient (age, gender) and disease specific data (date of diagnosis, tumor localization, sarcoma subtype, tumor size, - depth, and - differentiation, treatment details, comorbidities, disease status) were collected from the clinical database of the Department of orthopedics.

Interview and QoL questionnaires

First, the patients were interviewed in order to gather occupational history and socio-demographic data. They then were asked to complete the Toronto Extremity Salvage Score (TESS), Short-Form Health Survey (SF-36), Center for Epidemiologic Studies-Depression Scale (CES-D) and the Fear of Progression Questionnaire-Short Form (FoP-Q-SF) (see supplement text 1: questionnaires). With the exception of the Fear of Progression Questionnaire-Short Form (FoP-Q-SF), these measures have been used in different sarcoma populations.(16-22)

Statistical analysis

Baseline variables and predictors of RtW are presented by frequency and percentage for categorical variables and median and interquartile range for continuous variables. Secondary QoL-related outcomes are presented as mean and standard deviation. We originally planned to compare predictors of RtW and QoL-related outcomes between patients with and without

RtW in uni- and multivariable models. However, due to the low number of patients not returning to work ($n=5$), we decided to present these data in a purely descriptive way. Associations between baseline variables and QoL-related outcomes were analyzed using linear regression. Forward model selection was used to find optimal multivariable models based on the AIC. All analysis was performed in version 3.4.1 of the R statistical environment.

Results

Baseline characteristics

We identified 259 extremal sarcoma patients surgically treated in the Department of Orthopedics between 2000 and 2015 of whom 107 were eligible for the prospective study part. The participant flow and the reasons for not participating are illustrated in Figure 1. Forty-five patients (42%) agreed to participate. Median time from diagnosis to interview was 5.8 years. The patient and tumor characteristics of the participants and non-participants are summarized in Table 1. Participants underwent less amputations (2.2% vs. 12.9%) and more Whoops procedures (42.2% vs. 24.3%) when compared to the patients refusing study participation.

Return to work

Forty out of 45 (89%, 95%-CI: 76-96%) interviewed patients returned to work after sarcoma diagnosis and treatment. Out of these, seven patients (18%) reduced their work load from full to part-time. The educational and occupational details are illustrated in Supplement Table 1. Full-time employment before sarcoma diagnosis (77.5% vs 20%, respectively) and high educational level (70% vs. 20%) was more frequent in patients with as compared to patients without RtW. The proportion of high tumor grade (22.5% vs. 40% in G3, respectively) and the median age at time of diagnosis (44 vs. 63 years, respectively) was lower in patients with as compared to patients without RtW. The distribution of gender, type of sarcoma (soft tissue or bone), tumor site (upper or lower extremity), time since diagnosis, presence of Whoops procedure (incorrect initial diagnostic work-up and surgical treatment of soft tissue and bone lesion), civil status, and work area was not substantially different between both groups (Table 2).

Quality of life

The QoL-related outcomes are summarized in Table 3.

The majority of study participants indicated no or little difficulties at all regarding the activities assessed by the TESS (mean score 88.5, SD 12.9). 73.1% (median; range 33.3-100%) of

the assessed activities were answered with having “no difficulties at all”. According to the TESS, patients with RtW had a better physical function (mean 89.7 (SD 11.2) vs. 78.7 (22.0)) compared with patients without RtW.

The SF-36 profile scores were generally lower when compared to normative Swiss population (figure 2).(23) The SF-36 physical component summary score was better in patients that returned to work compared to patients that did not return to work (mean 43.3 (SD 4.4) vs. 38.2 (5.4), respectively).

In the total sample, fear of progression (FoP-Q-SF) was low (mean score 22.9, SD 8.0). Patients with no RtW expressed moderate fear (mean score 31.0, SD 14.1), according to reported cut-offs (i.e., mean scores between 26 - 44).The RtW cohort did experience lessFear of progression than the no RTW group (FoP-Q-SF score; mean 21.9 (SD 6.5) vs. 31.0 (14.1), respectively).

The CES-D score in the total sample (mean score 6.7, SD 6.7) corresponded to normative data; it was less than half of the cutoff score (≥ 16) for individuals at risk for clinical depression. There was no substantial difference for the CES-D score between patients going back to work or not (mean 6.1 (SD 5.8) vs. 11.0 (12.0)).

Discussion

This is the first exploratory study to investigate RtW and one of the very few reporting on the association of psychological QoL factors and RtW in adult only sarcoma patients. The main findings can be summarized as follows: (1) The RtW rate in adult extremital sarcoma patients was high. (2) Patients with full-time employment before sarcoma diagnosis, high education level and low-grade tumors have a higher probability of RtW. (3) Fear of progression (FoP-Q-SF) and to a lesser extent difficulties with activities (TESS) were lower in patients that returned to work. (4) Generic QoL (SF-36) was reduced in almost all dimensions when compared to a normative population.

The high RtW rate of adult sarcoma patients in our analysis is in the upper range of the extremity sarcoma literature revealing a RtW rate between 53% and 89%. (7-9, 24) To note, all of these reported cohorts mainly consisted of children and AYA's, whereas in our study children and adolescents were excluded. Therefore, our results surprise because occupation after cancer diagnosis and treatment seems to be reduced with age.(25) The high RtW rate in our cohort may have several reasons. Firstly, adults are often already involved in the working process and getting back to work is in the interest of the employee as well as the

employer. Secondly, the number of patients not returning to work might be higher than assessed in our trial, as 57% of the eligible patients declined study participation. Reduced physical and mental functioning cannot be excluded in the non-participants cohort, although there were only minor differences in patients and tumor characteristics between the participants and the non-interviewed cases (slightly less amputation and more Whoops procedures). Thirdly, one third of the participants was characterized by well-differentiated soft tissue and bone tumors assuming less radical tumor resections.

The degree of employment before cancer diagnosis is reported to represent only a moderate predictor of RtW.(26) In contrast to our study, this finding was based on trials assessing RtW mainly in a non-sarcoma population.(27-31) Notably, Parson and colleagues recently assessed the impact of cancer on work and education among adolescent and young adult cancer survivors including a few sarcoma patients, too. In this population more than 72% of patients working or in school full-time before diagnosis had returned to full-time work or school post-diagnosis compared with 34% of previously part-time workers/ students.(32) Our results support that the foregoing degree of employment is an important job-associated factor in the RtW process in patients suffering from extremity sarcomas as well. Possible explanations for our observation in adult patients may be the presence of other psychosocial factors before sarcoma disease influencing the rehabilitation outcome, like patient motivational or employer's reasons. The motivation of our sarcoma patients for RtW will be investigated in a supplementary study.

High educational level was strongly associated with improved RtW in Gragnano's review assessing the role of sociodemographic factors in the RtW process in cancer patients.(26) This is in line with our results.

Patients suffering from low-grade sarcomas tended to have a higher RtW rate. The most reasonable explanation for this observation is a less radical surgery performed in these tumors when compared to more aggressive ones. In particular, no difference was found comparing upper vs. lower extremity location. It has to be noted, that some subgroups were too small for an exploration, e.g. the impact of limb sparing surgery vs. amputation. In the literature limb sparing surgery results in significantly better functional outcomes compared to amputation.(8, 9, 19, 33). On the other hand, in a retrospective study, unemployment was not associated with poor functional outcome.(34)

Fear of progression is a highly relevant issue in cancer in general.(35, 36) Approximately one third of cancer survivors express difficulties in dealing with fear of progression after cancer

treatment.(37) Long-term cancer survivors are often still affected.(38) Fear of progression was not studied intensively in sarcoma patients. Patients suffering from gastrointestinal stromal tumors (N=28) were reported to suffer from high levels of fear of cancer recurrence/progression.(39) Our study highlights the importance of addressing fear of progression in patient care.

Employment is closely related to physical and mental QoL.(13) Our results of the TESS indicate a relatively high level of functioning in adult extremity sarcoma patients. Similar TESS scores were reported in adults following limb salvage surgery for lower-extremity soft tissue sarcoma (mean score 82.7).(16) The SF-36 physical component summary is in the same range as reported in adolescent and young adult survivors of low extremity bone tumors.(22) To note, lower-extremity soft tissue sarcoma were associated with worse physical functioning when compared to sarcomas located at the upper extremities.(40) Due to the limited patient number in our study no conclusion can be drawn in this regard.

Data on symptoms of depression in sarcoma patients is limited. Depression in sarcoma patients develops more often during the follow-up period.(41) Only one small trial (N=28) used the CES-D in sarcoma patients indicating a low level of depressive symptoms particularly in patients who had amputation compared to limb salvage.(21) In long-term survivors of pediatric sarcoma, four out of 32 patients were reported to suffer from a psychiatric disorder, including one patient with major depression.(20)

Apart from its prospective trial design, this study has several limitations. Our study is based on a single-center experience of a University Cancer Center. Fifty-eight percent of the individuals refused study participation due to different reasons which potentiate a selection bias. The sample size was too small to apply multivariable models and correct for potential confounders in terms of the primary outcome RtW. Still some of the factors investigated, especially the occupational situation before sarcoma diagnosis, physical functioning and fear of progression warrant for further investigation regarding the rehabilitation.

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Tables

Table 1: Patient and tumor characteristics

	Participants N = 45	Non-participants N = 62
Gender		
- Male (%)	26 (57.8)	36 (58.1)
- Female (%)	19 (42.2)	26 (41.9)
Age at the time of the diagnosis [years]		
- Median (IQR)	45.0 (34.5; 56.0)	50.0 (33.0; 59.0)
Type of sarcoma		
- Soft tissue sarcoma (%)	39 (86.7)	44 (71.0)
- Bone sarcoma (%)	6 (13.3)	18 (29.0)
Depth of tumor (soft tissue sarcoma subtype)		
- Deep (%)	36 (80)	42 (67.7)
- Superficial (%)	3 (6.7)	1 (1.6)
- Unknown	6 (13.3)	1 (1.6)
Tumor site		
- Upper extremity (%)	6 (13)	15 (24.2)
- Lower extremity (%)	39 (87)	47 (75.8)
Max. tumor size [cm]*		
- Median (IQR)	8.0 (5.0, 14.2)	8.0 (4.0, 10.0)
Grading		
- G1 (%)	15 (33.3)	17 (27.4)
- G2 (%)	12 (26.7)	17 (27.4)
- G3 (%)	11 (24.4)	14 (22.6)
- Unknown (%)*	7 (15.6)	14 (22.6)
Procedure in first surgical intervention		

- Limb salvage (%)	44 (97.8)	53 (85.5)
- Amputation (%)	1 (2.2)	9 (14.5)
Other therapies (mc)		
- Chemotherapy (%)	4 (8.8)	15 (24.2)
- Radiotherapy (%)	18 (40)	15 (24.2)
- No chemotherapy/ radiotherapy (%)	24 (53.3)	35 (56.5)
Whoops (%)	19 (42.2)	16 (25.8)
Major health problems at time of interview(mc)		
- No relevant comorbidities (%)	30 (66.7)	-
- Sarcoma-related comorbidities (%)	2 (4.4)	-
- Not sarcoma-related comorbidties (%)	13 (28.9)	-

mc (multiple choices)

* missing data in 44 patients for tumor size and 21 for grading; no missing data for the other parameters

Table 2: Predictors of return-to-work.

	All N = 45	Return to work N = 40	No return to work N = 5
Age at diagnosis [years]	45.0 (34.5; 56.0)	44.0 (34.3; 54.0)	63.0 (40.5; 64.0)
Female gender	19 (42.2%)	17 (42.5%)	2 (40.0%)
Bone sarcoma	6 (13.3%)	5 (12.5%)	1 (20.0%)
Upper extremity	6 (13.3%)	5 (12.5%)	1 (20.0%)
Grading			
G1	15 (33.3%)	15 (37.5%)	0 (0.0%)
G2	12 (26.7%)	10 (25.0%)	2 (40.0%)
G3	11 (24.4%)	9 (22.5%)	2 (40.0%)
unknown	7 (15.6%)	6 (15.0%)	1 (20.0%)
Diagnosis to interview [years]	5.8 (3.1; 10.3)	6.0 (3.1; 10.4)	3.1 (2.5; 8.8)
Whoops	19 (42.2%)	17 (42.5%)	2 (40.0%)
Married at diagnosis	29 (64.4%)	25 (62.5%)	4 (80.0%)
Higher education	29 (64.4%)	28 (70.0%)	1 (20.0%)
Working in service before diagnosis	29 (64.4%)	26 (65.0%)	3 (60.0%)
Working full time before diagnosis	32 (71.1%)	31 (77.5%)	1 (20.0%)

Table 3: Quality of life-related outcomes according to return to work status

	All (N = 45)	Return to work (N = 5)	No return to work (N = 40)
Toronto Extremity Salvage Score (TESS)			
- Mean (SD)	88.5 (12.9)	89.7 (11.2)	78.7 (22.0)
FoP-Q-SF			
- Mean (SD)	22.9 (8.0)	21.9 (6.5)	31.0 (14.1)
Center for Epidemiologic Studies-Depression Scale (CES-D)			
- Mean (SD)	6.7 (6.7)	6.1 (5.8)	11.0 (12.0)
SF-36			
Physical Component Summary			
- Mean (SD)	42.8 (4.7)	43.3 (4.4)	38.2 (5.4)
Mental Component Summary			
- Mean (SD)	58.9 (8.9)	59.4 (8.1)	55.2 (14.3)
General Health			
- Mean (SD)	54.4 (9.6)	55.3 (8.9)	47.1 (12.7)
Physical Functioning			
- Mean (SD)	29.5 (10.4)	29.1 (10.6)	32.3 (9.6)
Role Physical			
- Mean (SD)	50.6 (8.4)	51.6 (7.2)	42.8 (13.6)
Bodily Pain			
- Mean (SD)	53.6 (9.3)	54.8 (8.2)	43.9 (12.7)
Vitality			
- Mean (SD)	55.1 (8.3)	55.6 (8.0)	51.4 (10.4)
Social Functioning			
- Mean (SD)	53.8 (6.9)	53.7 (7.0)	54.3 (6.7)

	All (N = 45)	Return to work (N = 5)	No return to work (N = 40)
Role Emotional			
- Mean (SD)	52.5 (6.8)	53.3 (4.8)	45.7 (14.8)
Mental Health			
- Mean (SD)	52.9 (7.6)	53.3 (7.1)	49.8 (11.2)

Figure Legends

Figure 1: Patient flow and reasons for non-participation

Figure 2: Comparison of SF-36 scores with a healthy population