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Original Article

Patient and Diagnostic Intervals of Survivors of Sarcoma: Results From the SURVSARC Study

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BACKGROUND: Patients diagnosed with sarcoma are hypothesized to experience a prolonged route to a cancer diagnosis. This route, the total interval, can be divided into a patient interval (the time from the appearance of symptoms to physician consultation) and diagnostic interval (time from the first consultation to diagnosis). In the current study, the authors investigated these intervals among survivors of sarcoma and identified factors associated with prolonged intervals. **METHODS:** A cross-sectional study was conducted among adult patients with sarcoma 2 to 10 years after diagnosis. Patients completed a questionnaire regarding their total interval, which was linked to clinical data from the Netherlands Cancer Registry. Descriptive statistics were used to describe intervals. Based on Dutch clinical guidelines, a diagnostic interval ≥1 month was considered to be prolonged and an interval ≥3 months was considered as very long. Multivariable regression analyses investigated associations between patient and tumor characteristics and interval length. **RESULTS:** A total of 1099 participants were included (response rate, 58%); approximately 60% reported a patient interval ≥1 month and 36% reported a patient interval ≥3 months. Risk factors for a very long patient interval were sarcoma of the skin or pelvis, liposarcoma, or rhabdomyosarcoma. Stage III disease was associated with a shorter patient interval. The diagnostic interval length was ≥1 month in 55% of patients and ≥3 months in 28% of patients. Risk factors for a very long diagnostic interval were female sex, age <70 years, or having a synovial sarcoma or chordoma. **CONCLUSIONS:** The patient and diagnostic interval lengths were prolonged in a substantial percentage of this sarcoma survivorship population. Factors found to be associated with the length of the patient interval or the diagnostic interval differed. Creating awareness among (especially young) patients to consult a physician and awareness among physicians to consider a sarcoma diagnosis will contribute to optimization of the total interval. ***Cancer* 2020;126:5283-5292**. © *2020 American Cancer Society*.

KEYWORDS: cancer diagnosis, delay to diagnosis, diagnostic interval, diagnostic pathway, patient interval, sarcoma, survivorship.

INTRODUCTION

Sarcomas are a group of solid malignant mesenchymal tumors, of which there are >70 histological subtypes.[1] These tumors have considerable heterogeneity with respect to age of onset, anatomic location, speed of progression, and outcome. Approximately 80% of sarcomas originate in soft tissue (soft-tissue sarcoma [STS]) and 20% in bone (bone sarcoma [BS]). Sarcomas form a typical example of a rare cancer, with an estimated incidence of 4 to 5 cases per 100,000 population per year.[2] Patients with rare cancers have a higher mortality rate than those with common cancers. Delayed diagnostic pathways, a lack of expert pathologists, the absence of rare tumor–specific multidisciplinary meetings, cancer-specific therapies, and clinical trials often preclude patients with rare cancers from receiving proper, timely diagnosis and care.[3]

Patients with sarcoma may experience long intervals to diagnosis, and the time to diagnosis has been measured frequently.[4] Total intervals for patients with BS were 9 to 120.4 weeks, and were reported to be 4.3 to 614.9 weeks for patients with STS. However, these studies often described small cohorts and were heterogeneous with regard to inclusion criteria and study designs. Several theoretical models currently exist to describe time to a cancer diagnosis. For research purposes, it is important to work with a standardized framework with clear definitions of each event and the time interval within the diagnostic pathway. In the current study, we used the influential model developed by Olesen et al.[5] The time to diagnosis, the time between first symptoms and (histological) diagnosis, is known as

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the total interval, which can be divided into a patient interval and a diagnostic interval.[5,6]

The current interest in a prolonged interval in general is based mainly on the assumption that early diagnosis will lead to better survival. Because to our knowledge research regarding diagnostic intervals focuses mainly on patients who are newly diagnosed with sarcoma, no data currently are available regarding survivors and their recall from the total interval. In patients with other cancer diagnoses, prolonged total intervals lead to worse outcomes.[7] This knowledge led to the search for optimizing the diagnostic pathway for several types of cancer by, for example, introducing fast referral pathways or performing multiple additional investigations within 1 day. Therefore, it is important to identify risk groups for a prolonged interval to examine whether these strategies also would improve outcomes for patients with sarcoma. The objective of the current study was to describe the total interval and its components among survivors of sarcoma, and to identify patient and tumor characteristics with which to define risk groups for prolonged intervals.

MATERIALS AND METHODS

Study Design and Participants

The current population-based, cross-sectional study included sarcoma survivors aged ≥18 years who were registered in the Netherlands Cancer Registry (NCR) and who had been diagnosed with sarcoma between January 1, 2008, and December 31, 2016, at 1 of the 6 participating sarcoma expertise centers (Radboud University Medical Center [Nijmegen], The Netherlands Cancer Institute [Amsterdam], University Medical Center Groningen, Leiden University Medical Centre, Erasmus MC Cancer Institute [Rotterdam], and Maastricht University Medical Centre) regardless of their current disease status (the Supporting Information includes the selected morphology codes derived from the *International Classification of Diseases for Oncology, Third Edition* [ICD-O-3][8]). Exclusion criteria were cognitive impairment, too ill (as judged by their [ex-] treating physician) or dead at the time of the study, unverifiable address, or an inability to read and write in Dutch. Patients with desmoid fibromatosis, grade 1 chondrosarcoma, atypical lipomatous tumors, or giant cell tumors were excluded due to the indolent clinical behavior of and less aggressive treatment strategies for these histological subtypes. In addition, patients with gastrointestinal stromal tumors were excluded. The NCR compiles data from all individuals newly diagnosed with cancer in the Netherlands.[9] Data registration is performed by employees of the Netherlands Comprehensive Cancer Organization (IKNL) and includes patient and tumor characteristics. The main pathology source is the Nationwide Network and Registry of Histo- and Cytopathology in the Netherlands (PALGA).[10]

Ethical approval was provided by the medical ethical committee of Radboud University Medical Centre (2017-3944). According to Dutch law, approval of 1 ethical committee for questionnaire research is valid for all participating centers. The study was registered in the Dutch Trial Registry (NTR-7253).

Recruitment and Data Collection

Eligible patients received a letter from their (ex-)treating physician explaining the purpose of the study. Patients provided informed consent to participate and agreed to linkage of questionnaire data with their clinical data in the NCR. Data collection was conducted from October 2018 through June 2019 within Patient Reported Outcomes Following Initial treatment and Long-term Evaluation of Survivorship (PROFILES; www.profilesregistry.nl). PROFILES is a data management system for the study of the physical and psychosocial impact of cancer and its treatment. Questionnaires could be completed online or using pencil and paper upon request. Paper questionnaires were returned and then scanned to digitalize the data. Further details regarding the data collection method have been described previously.[11] Responders were compared with nonresponders: patient and clinical characteristics registered in the NCR were anonymously compared on a group level.

Study Measures

Although the study primarily was designed to examine health-related quality of life among survivors of sarcoma compared with an age-matched and sex-matched normative population (https://www.trialregister.nl/trial/7048; NTR-7253), the current study was a secondary analysis with the objective to describe the total interval and its components among survivors of sarcoma and to identify patient and tumor characteristics with which to define risk groups for prolonged intervals. Questions regarding patient and diagnostic intervals were designed by the study group to match time intervals and events as defined in our adapted version of the standardized definitions proposed by Olesen et al and Weller et al,[5,6] and as published before.[4] The

diagnostic interval can be divided further into a primary care, secondary care, and tertiary care interval. All interval lengths were categorical and patient reported (<2 weeks, 2 weeks-1 month, 1-3 months, 3-6 months, 6-12 months, and >12 months). A panel of patients provided feedback regarding relevance, comprehensibility, length of the questionnaire, and design of the questions.

Sociodemographic and Clinical Characteristics

Patient and tumor characteristics hypothesized to influence the total interval length were selected. Clinical data were derived from the NCR, which routinely collects data regarding patient and tumor characteristics including sex, age, socioeconomic status (SES), date of diagnosis, histological subtype, tumor grade, localization, and stage of disease at the time of diagnosis. Not all sarcomas are graded at the time of diagnosis, at which time if possible we added a grade according to the guideline at the time of the study.[1] Participants with missing grades were not excluded from further analyses. To report on clinically relevant subgroups, participants were divided into age categories at the time of diagnosis (age 18-39 years, age 40-70 years, and age ≥70 years). Time since diagnosis was calculated by subtracting the date of questionnaire completion from the date of diagnosis. Participants were divided into categories (<2 years, 2-5 years, and ≥5 years since diagnosis). SES was derived from zip codes, and was based on educational level, income, and employment status.[12] Marital status, educational level, employment status, and number of comorbidities were measured at the time of questionnaire completion and therefore were not included in the current analysis.

Statistical Analysis

Characteristics of the responders were compared with those of nonresponders using chi-square statistics for categorical variables and Student *t* tests for continuous variables. Descriptive statistics were used to describe the study population, their total interval, and its components. Categorical variables were presented as numbers or percentages, whereas means and standard deviations were reported for continuous variables.

The study population was grouped by length of the patient interval and diagnostic interval. Intervals were dichotomized into <1 month versus ≥1 month based on the previous literature and considering that campaigns regarding awareness of cancer symptoms usually use a cutoff of ≥3 weeks for the duration of new symptoms.[13-15] For the diagnostic interval, the Dutch SONCOS guideline (Stichting ONCologische Samenwerking; a foundation for multidisciplinary oncological collaboration) has stated that a period of 4 weeks between referral by the general practitioner and diagnosis is acceptable.[16] To identify risk factors for patients with a very long patient or diagnostic interval, the same analyses also were performed with a cutoff of 3 months based on previous literature regarding cancer intervals.[14,15,17] Missing items were assumed to be missing at random. Only available data were analyzed.

Multivariable logistic regression analyses were performed using a forced entry method. We built 4 models for 4 dependent variables: patient interval of ≥1 month and ≥3 months and a diagnostic interval of ≥1 month and ≥3 months. Based on a literature review, sex, age at diagnosis, SES, histology, stage of disease, tumor grade, and localization were selected as independent variables.[4] In the case of multicollinearity, we tried both factors in different models. The factor that resulted in the best model was chosen for further analysis. The calibration of final models was tested using the Hosmer-Lemeshow goodness-of-fit test. Odds ratios and 95% confidence intervals were reported. All statistical analyses were performed using IBM SPSS statistical software (version 25.0). Two-sided *P* values <.05 were considered to be statistically significant.

RESULTS

A total of 1887 (ex-) patients with sarcoma were approached to participate in the current study, 1099 of whom (58%) provided informed consent and completed the questionnaire. Figure 1 presents the flow chart.

Responders Versus Nonresponders

Comparative analysis of responders and nonresponders found no differences with regard to sex, time since diagnosis, and sarcoma subtype (BS vs STS) (Table 1). Nonresponders were diagnosed at a younger age (50.2 years vs 55.1 years; $P < .01$) and had a lower SES (all $P < .05$). Furthermore, their sarcomas less often were localized retroperitoneally, but more often were diagnosed in the skin or gynecological organs, and dermatofibrosarcoma protuberans occurred more frequently (all $P < .01$).

Characteristics of the Participants

Greater than one-half of the participants were male (54%) with a mean age at diagnosis of 55 years (Table 1). The mean time since diagnosis was 67 months, and 76% of patients had a STS, with 47% having disease localized in the extremities. Only 2% of patients were found to

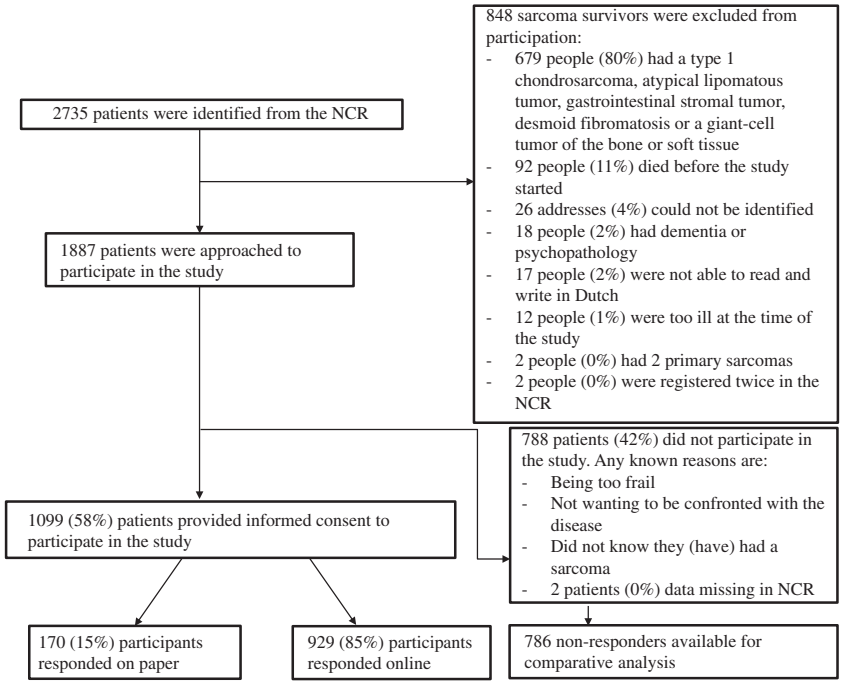

Figure 1. Flow chart. NCR indicates Netherlands Cancer Registry.

have stage IV (distant metastases) disease at the time of diagnosis.

Length of the Components of the Total Interval

Figure 2 shows the percentage of participants and their patient and diagnostic intervals. The patient interval (982 patients) lasted ≥1 month in 60% of patients. Many patients waited >3 months (36%), or even 12 months (15%) before consulting a physician, and approximately 10% of patients could not remember their patient interval length. The diagnostic interval (1035 patients) lasted ≥1 month in 55% of patients, and for 28% of patients it took ≥3 months with 9% of patients taking ≥12 months; approximately 5% of patients were unable to remember.

The diagnostic interval can be separated into primary (899 patients), secondary (964 patients), and tertiary (984 patients) care intervals. Approximately one-half of the patients were referred within 1 week (28%) or within 1 to 2 weeks (23%) by their general practitioner. Those who were not referred promptly had a very long primary care interval of 2 weeks to 1 month (18%), 1 to 3 months (15%), 3 to 6 months (6%), 6 to 12 months (4%), or ≥12 months (7%). Approximately 12% of patients reported consultation with a different physician first, whereas 4% were unable to remember their primary care interval length. The secondary care interval was <1 month in 64% of patients and 1 to 3 months in 23% of patients. Only a small percentage of patients had a longer interval of 3 to 6 months (7%), 6 to 12 months (3%), or ≥12 months (3%). Within the tertiary care interval, we observed a similar trend: 85% of patients were diagnosed within <1 month (35% even within 1 week) and 30% of patients were diagnosed within 1 to 2 weeks. Those patients who took longer to be diagnosed usually took 1 to 3 months (12%), with only a few participants reporting 3 to 6 months (2%), 6 to 12 months (1%), or ≥12 months (1%) (Fig. 2). Approximately 8% and 9% of patients, respectively, were unable to remember the length of their secondary and tertiary care intervals.

A diagnostic interval of ≥3 months was caused by lengthening of all components. Participants with a diagnostic interval of ≥3 months (28%) had a primary care interval of ≥3 months in 50% of cases; for secondary care and tertiary care, these percentages were 38% and 9%, respectively, versus 17%, 13%, and 4%, respectively, for all participants.

Association Between Patient Interval Length and Patient and Tumor Characteristics

Multivariable analyses demonstrated an association between age and having a patient interval of ≥1 month. Patients aged ≥70 years at diagnosis were found to be less likely to have a patient interval ≥1 month (Table 2). This

TABLE 1. Characteristics of Responders and Nonresponders

Characteristic	Responders N = 1099	Nonresponders N = 786	P^a
Sex, no. (%)			
Female	504 (46)	381 (49)	.24
Male	595 (54)	405 (51)	
Age at time of diagnosis, y			
Mean (SD)	55.1 (15.3)	50.2 (18.7)	<.01
Time since diagnosis, mo			
Mean (SD)	67.4 (30.3)	69.6 (30.9)	.12
Socioeconomic status, no. (%)			
Low	286 (26.1)	279 (35.6)	<.01
Intermediate	462 (42.1)	289 (36.8)	.02
High	349 (31.8)	217 (27.6)	.05
Current marital status, no. (%)			
Married, civil partnership, or cohabiting	857 (78)	NA	NA
Single, widowed, or divorced	242 (22)		
Current highest education, no. (%)			
No education, primary or secondary school	242 (22)	NA	NA
Vocational qualification	451 (41)		
College or university	406 (37)		
Current employment status, no. (%)			
Working full time or part time	451 (41)	NA	NA
(Partially) disabled	99 (9)		
Other	506 (46)		
Unknown	43 (4)		
Current comorbidities, no. (%)			
0	374 (34)	NA	NA
1	351 (32)		
≥2	374 (34)		
Histologic subtype, no. (%)			
Bone sarcoma	264 (24)	172 (22)	.29
Osteosarcoma	70 (6)	53 (7)	.75
Chondrosarcoma	130 (12)	72 (9)	.06
Chordoma	30 (3)	19 (2)	.76
Ewing sarcoma	28 (3)	21 (3)	.87
Other bone sarcomas	6 (1)	7 (1)	.38
Soft tissue sarcoma	835 (76)	614 (78)	.28
Liposarcoma	177 (16)	108 (14)	.15
Pleomorphic liposarcoma	10 (1)	9 (1)	.62
Myxoid liposarcoma	68 (6)	42 (5)	.43
Undifferentiated liposarcoma	64 (6)	33 (4)	.11
Other liposarcoma	35 (3)	24 (3)	.86
Myxofibrosarcoma	136 (12)	89 (11)	.48
Dermatofibrosarcoma protuberans	74 (7)	109 (14)	<.01
Leiomyosarcoma	114 (10)	82 (10)	.97
Rhabdomyosarcoma	15 (1)	11 (1)	.95
Malignant peripheral nerve sheath tumor	34 (3)	24 (3)	.96
Synovial sarcoma	35 (3)	25 (3)	.99
Vascular sarcoma	43 (4)	27 (3)	.59
Other soft tissue sarcoma	207 (19)	139 (17)	.55
Localization, no. (%)			
Head and neck	70 (6)	49 (6)	.96
Thoracic	81 (7)	42 (5)	.08
Abdominal excl urogenital organs	102 (9)	46 (6)	<.01
Intraperitoneal	39 (4)	19 (2)	.16
Retroperitoneal	63 (6)	27 (3)	.02
Gynecological	19 (2)	29 (3)	<.01
Urological	11 (1)	11 (1)	.43
Extremities	514 (47)	357 (45)	.55
Upper extremities	114 (10)	77 (10)	.67
Lower extremities	400 (36)	280 (36)	.72
Breast	24 (2)	18 (2)	.88
Pelvis	84 (8)	50 (6)	.31
Skin	121 (11)	146 (19)	<.01
Other localization	73 (7)	38 (5)	.10
TNM staging of disease, no. (%)			
IA	204 (19)	141 (18)	.75
IB	208 (19)	157 (20)	.59

TABLE 1. *Continued*

Characteristic	Responders N = 1099	Nonresponders N = 786	P^a
IIA	221 (20)	119 (15)	<.01
IIB	94 (9)	57 (7)	.30
III	134 (12)	68 (9)	.01
IV	24 (2)	14 (2)	.53
IVA	4 (0)	5 (1)	.40
IVB	4 (0)	5 (1)	.40
Unknown	206 (19)	220 (28)	<.01
Grade			
Low grade	615 (56)	NA	NA
Intermediate or high grade	407 (37)		
Unknown	77 (7)		

Abbreviations: excl, excluding; NA, not available for non-responders analysis.
Because of rounding, percentages may not add up to 100%.
[a]Differences in continuous variables were examined using the Student *t* test for unpaired data. For differences in categorical variables, chi-square statistics were used.

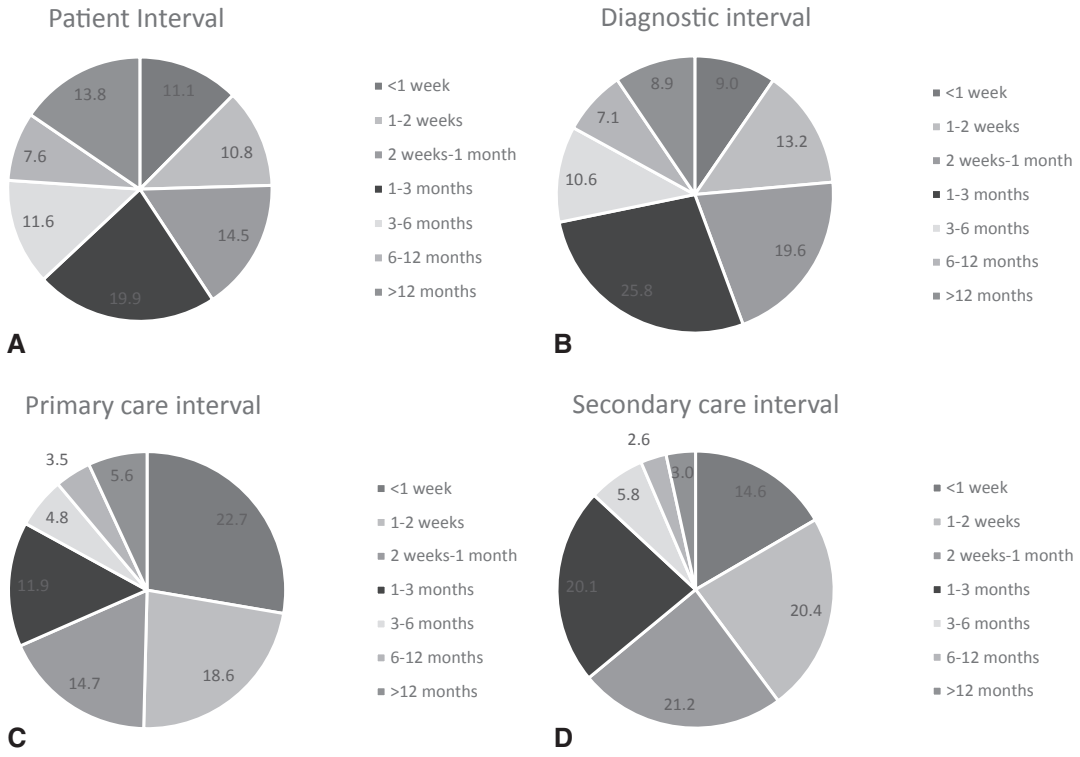

Figure 2. Percentages of participants per interval length.

relationship lost its significance at a cutoff of 3 months. Histology, stage of disease, and localization were found to be associated with a patient interval of ≥3 months.

Association Between Diagnostic Interval Length and Patient and Tumor Characteristics

Multivariable analysis demonstrated an association between age at diagnosis and a diagnostic interval of ≥1 month. Patients aged ≥70 years were found to be less likely to have a long diagnostic interval (Table 2). This association remained significant at a cutoff of 3 months. Patient sex also was found to be associated with a diagnostic interval ≥3 months, with female patients found to be more likely to experience a long diagnostic interval.

TABLE 2. Multiple Regression Analysis of Association Between Patient and Diagnostic Intervals and Clinical and Sociodemographic Factors

	Patient Interval ≥1 Month N = 872		Patient Interval ≥3 Months N = 872		Diagnostic Interval ≥1 Month N = 915		Diagnostic Interval ≥3 Months N = 915	
	OR	(95% CI)	OR	(95% CI)	OR	(95% CI)	OR	(95% CI)
Sex								
Male								
Female	1.2	0.9-1.6	1.0	0.7-1.3	1.3	1.0-1.7	1.4[a]	1.1-2.0
Age at diagnosis, y								
18-39								
40-69	0.8	0.5-1.2	1.1	0.7-1.6	0.8	0.5-1.1	0.7	0.5-1.0
≥70	0.5[a]	0.3-0.9	0.7	0.4-1.2	0.5[a]	0.3-0.8	0.5[a]	0.3-0.9
Socioeconomic status								
Low								
Intermediate	0.9	0.6-1.3	0.9	0.6-1.3	0.9	0.6-1.3	1.0	0.7-1.5
High	1.0	0.7-1.4	0.8	0.5-1.1	1.0	0.7-1.4	1.3	0.9-2.0
Histology								
Dermatofibrosarcoma protuberans								
Liposarcoma	0.3	0.1-1.0	0.3[a]	0.1-1.0	1.3	0.4-3.5	0.7	0.2-2.3
Myxofibrosarcoma	0.4	0.1-1.3	0.3[a]	0.1-1.0	1.4	0.5-4.0	0.8	0.2-2.8
Leiomyosarcoma	0.5	0.2-1.6	0.4	0.1-1.1	1.5	0.6-4.1	0.8	0.2-2.6
Rhabdomyosarcoma	0.2	0.0-1.1	0.1[a]	0.02-0.8	0.7	0.2-3.1	0.8	0.1-4.6
MPNST	0.5	0.1-2.4	0.5	0.1-2.5	1.1	0.2-5.1	1.0	0.2-5.2
Synovial sarcoma	1.4	0.3-6.1	0.5	0.1-1.9	3.4	0.9-13.4	2.5	0.6-10.5
Vascular sarcoma	[b]	[b]	[b]	[b]	[b]	[b]	[b]	[b]
Other soft tissue sarcoma	0.4	0.1-1.2	0.3[a]	0.1-0.8	1.5	0.6-4.0	0.9	0.3-2.8
Osteosarcoma	0.5	0.1-1.8	0.3	0.1-1.1	1.3	0.4-4.0	0.8	0.2-3.0
Chondrosarcoma	0.8	0.2-2.6	0.6	0.2-2.0	2.0	0.7-5.7	1.3	0.4-4.6
Chordoma	0.5	0.1-2.3	0.6	0.1-2.3	1.8	0.5-7.2	2.9	0.6-13.7
Ewing sarcoma	0.5	0.1-2.2	0.7	0.2-2.8	0.5	0.1-1.8	0.9	0.2-4.3
Other bone sarcoma	0.5	0.1-3.2	0.3	0.1-1.7	0.7	0.1-3.7	1.0	0.2-6.3
TNM Clinical staging								
I								
II	1.0	0.7-1.4	1.0	0.7-1.5	0.8	0.5-1.2	1.0	0.6-1.5
III	0.8	0.5-1.4	0.5[a]	0.3-0.9	0.6	0.4-1.0	0.9	0.5-1.7
IV	0.8	0.4-1.7	1.0	0.4-2.1	0.6	0.3-1.3	0.4	0.2-1.0
Grade								
Low grade								
Intermediate or high grade	1.1	0.7-1.6	1.3	0.8-2.0	1.2	0.8-1.7	0.8	0.5-1.3
Localization								
Head and neck								
Thoracic	1.5	0.7-3.3	1.7	0.7-3.9	1.4	0.7-3.2	0.8	0.3-1.8
Abdominal	1.0	0.5-2.2	1.4	0.6-3.4	0.6	0.3-1.2	0.9	0.4-2.2
Breast	[c]	[c]	[c]	[c]	[c]	[c]	[c]	[c]
Skin	2.2	0.8-6.5	3.3[a]	1.1-10.1	0.8	0.3-2.2	0.7	0.2-2.5
Pelvis	2.1	1.0-4.5	2.6[a]	1.2-6.0	0.6	0.3-1.3	0.8	0.3-1.8
Upper extremities	1.4	0.7-2.9	1.8	0.8-3.9	1.0	0.5-2.1	1.1	0.5-2.4
Lower extremities	1.7	0.9-3.2	1.8	0.9-3.7	0.8	0.4-1.4	1.0	0.5-1.9
Other	1.5	0.5-4.1	1.4	0.5-4.3	1.7	0.6-4.9	1.5	0.5-4.4

Abbreviations: MPNST, malignant peripheral nerve sheath tumor; OR, odds ratio.
The first category was the reference category.
[a]$P < .05$.
[b]Two patients for multivariable analysis; therefore the OR was unreliable (>10.000) as was the 95% CI (0.0-infinite).
[c]Seven patients for multivariable analysis; therefore the OR was unreliable. Chi-square statistic for model for patient interval of ≥1 month: 73.111 ($P = .000$); and ≥3 months: 84.146 ($P = .000$). The chi-square statistic for a diagnostic interval of ≥1 month: 55.122 ($P = .003$); and ≥3 months: 57.271 ($P = .002$).

DISCUSSION

In the current cross-sectional survivorship study, a total interval for adult patients with sarcoma was described as reported by survivors of sarcoma and factors were identified that were associated with the length of the patient and diagnostic intervals. To our knowledge, the current study is the largest to date to report on the route to diagnosis of adult patients with sarcoma.

We found the length of the total interval of adult patients with sarcoma to be highly variable due to different patient and diagnostic intervals, which is in keeping with the existing literature.

The patient interval was long (≥1 month) in 60% of patients, and very long (≥3 months) in 36% of patients. The hypothesis that low-stage, indolent sarcomas do not cause patients to seek help is supported by the current study findings due to our survivorship patient selection. Tumors located in the pelvis often cause nonspecific symptoms, causing patients to delay a visit to their general practitioner. Stage III tumors often grow rapidly, causing patients to seek help as soon as they experience symptoms. Similar results were found in a British adult sarcoma study.[17] A review among other patients with cancer, using mostly retrospective data, found contradictory results: older age was associated with patient delay for breast cancer, whereas there was inconclusive evidence or no impact on patient interval length in patients with upper gastrointestinal, gynecological, colorectal, urological, and lung cancers.[18] Similar to the findings in the current study, patient sex and SES were not found to be associated with patient interval length in the majority of cancers, although patients with a lower SES who had upper gastrointestinal or urological cancers waited longer.

The diagnostic interval was long (≥1 month) in 55% of patients, and very long (≥3 months) in 28% of patients. A long diagnostic interval was not based on 1 specific component but remarkably on all its components (primary, secondary, and tertiary care intervals). These are important findings because improving the patient, diagnostic, and referral pathways could be highly profitable in reducing the total interval length. It is difficult to compare the findings of the current study with those of other sarcoma studies because in general those studies included mainly children. However, the trend toward younger patients having longer diagnostic intervals also was noted in a British study of adult patients with sarcoma,[17] and generally is observed among other cancer subtypes such as breast, upper gastrointestinal, and pancreatic carcinoma, although the results appear contradictory for several other cancer types in different studies.[18,19] Furthermore, the latter study by Din et al[19] only included patients aged ≥40 years, and therefore these results are not directly comparable.

In the current study, the secondary care interval lasted <4 weeks in 57% of patients, although it lasted >1 month for 33% of patients. According to Dutch guidelines, the secondary interval should last no more than 4 weeks[16] unless a patient is being referred to a different health care facility, such as a sarcoma center, in which case an additional 3 weeks may be added to the interval. A significant number of patients therefore do not receive a diagnosis within this time limit. The tertiary care interval was <1 month for 78% of patients. This percentage may be overestimated due to a group of patients who were diagnosed with sarcoma at the referring hospital, and who thus received their diagnosis before or at the time of the first appointment (eg, within 1 week; 32% of patients).

The question arises whether the incidence of prolonged intervals found in the current study is due to health care system factors. The Dutch curative health care sector is financed by taxes and obligatory personal health care insurance, and therefore care by a general practitioner does not result in additional costs for the patient. Nearly all citizens are registered with a particular general practitioner, who they need to consult to be referred for hospital care. In the Netherlands, there is no private sector for sarcoma care. To our knowledge, literature regarding whether health care system factors influence total interval length is scarce and studies with direct comparisons are lacking. Future research ideally should have an international design, which would enable evaluation of the contribution of health care system factors to total interval length.

The current study had a response rate of 58%, which is high considering decreasing response rates reported in cross-sectional surveys.[20-23] Although nonresponders were slightly younger and had a lower SES compared with responders, they demonstrated an equal distribution with regard to sex, time since diagnosis, and rate of BS versus STS and therefore we believe the current study is representative of all patients with sarcoma experiencing a 2-year to 10-year survival after diagnosis. However, due to the survivorship nature of the current study, there was a selection bias in which elderly patients with significant comorbidities, patients with primary metastatic disease, and patients with low literacy most likely were underrepresented in this cohort.[24] Another part of this selection bias is that we invited patients who were diagnosed or treated at 6 sarcoma centers and may have missed patients treated in regional hospitals, who most likely had more superficial and low-grade sarcomas.

A second limitation of the current study was that the data were patient-reported and subject to recall bias. However, when given the choice to indicate whether they could or could not remember the time intervals, approximately 90% and 95%, respectively, of patients indicated they still remembered their patient and diagnostic interval length. Furthermore, time since diagnosis was not found to be associated with either length of the patient interval or diagnostic interval (data not shown). A generally consistent research finding is that as the recall time increases,

the ability to recall events begins to degrade.[25] However, significant events, such as a cancer diagnosis, are less likely to be forgotten.[25] Furthermore, estimation of the duration of an event is extremely stable.[26] To minimize the effect of recall bias in the current study, patients had to report the duration of the intervals instead of exact dates, questions were anchored to a life event (cancer diagnosis), history had to be recalled in a chronological fashion, and the comprehensibility of the questions was checked by patients.

Further research is needed to understand the exact reasons for and consequences of long diagnostic intervals. Our study group currently is conducting a prospective, longitudinal, international study called QUEST (QUality of life and Experiences of Sarcoma Trajectories) to investigate the total interval in more detail and to link its length with both clinical and patient-reported outcomes (clinical trials record 2017-3881). The international design of this study allows for comparison of health care system factors as well as patient and tumor characteristics. Its prospective design will enable us to include all patients, including those with incurable disease and aggressive subtypes. Furthermore, a better understanding of the consequences of long diagnostic intervals will enable the sarcoma community to develop strategies to reduce diagnostic delay, including creating awareness among the general population and physicians (such as the "On the Ball" campaign in the United Kingdom) and expert and fast comprehensive diagnostics at sarcoma centers.

Conclusions

The time to diagnosis in adult patients with sarcoma who have survived 2 to 10 years after diagnosis is highly variable, and both the patient and diagnostic intervals contribute to a long total interval. Greater than one-half of the current study participants had a patient and diagnostic interval of ≥1 month, or even ≥3 months in approximately one-third of cases. Risk factors for a very long patient interval were sarcomas in the skin or pelvis, whereas having a liposarcoma, myxofibrosarcoma, rhabdomyosarcoma, or other STS and stage III disease led to a shorter interval. Risk factors for a very long diagnostic interval were being female or aged 18 to 69 years. Because to the best of our knowledge the effect of a prolonged interval on outcomes remains unclear in terms of morbidity, health-related quality of life, and survival, we should prioritize in depth analysis of all contributing factors in patients and health care systems that are responsible for diagnostic delays. Analyzing this will result in recommendations that enable optimization of the total diagnostic trajectory for patients with sarcoma.

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CONFLICT OF INTEREST DISCLOSURES

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AUTHOR CONTRIBUTIONS

Olga Husson and **Winette T. A. van der Graaf** were responsible for the conceptualization. **Vicky L. M. N. Soomers**, **Olga Husson**, **Ingrid M. E. Desar**, **Winan J. van Houdt**, **Lonneke van de Poll-Franse**, and **Winette T. A. van der Graaf** designed the study. **Lonneke van de Poll-Franse** was responsible for use of the Patient Reported Outcomes Following Initial treatment and Long-term Evaluation of Survivorship (PROFILES) registry. **Vicky L. M. N. Soomers** was responsible for ethical approval, data curation, analysis, and writing the original draft. **Olga Husson** and **Winette T. A. van der Graaf** were responsible for supervision. All authors contributed to patient inclusion, writing, and editing.

REFERENCES

1. Fletcher C, Bridge J, Hogendoorn P, Mertens F, eds. WHO Classification of Tumours of Soft Tissue and Bone. 4th ed. World Health Organization; 2013.
2. Stiller CA, Trama A, Serraino D, et al. Descriptive epidemiology of sarcomas in Europe: report from the RARECARE project. *Eur J Cancer*. 2013;49:684-695.
3. Blay JY, Coindre JM, Ducimetiere F, Ray-Coquard I. The value of research collaborations and consortia in rare cancers. *Lancet Oncol*. 2016;17:e62-e69.
4. Soomers V, Husson O, Young R, Desar I, Van der Graaf W. The sarcoma diagnostic interval: a systematic review on length, contributing factors and patient outcomes. *ESMO Open*. 2020;5:e000592.
5. Olesen F, Hansen RP, Vedsted P. Delay in diagnosis: the experience in Denmark. *Br J Cancer*. 2009;101(suppl 2):S5-S8.
6. Weller D, Vedsted P, Rubin G, et al. The Aarhus statement: improving design and reporting of studies on early cancer diagnosis. *Br J Cancer*. 2012;106:1262-1267.
7. Neal RD, Tharmanathan P, France B, et al. Is increased time to diagnosis and treatment in symptomatic cancer associated with poorer outcomes? *Systematic review. Br J Cancer*. 2015;112(suppl 1):S92-S107.
8. Fritz A, Percy C, Jack A, et al. International Classification of Diseases for Oncology. 3rd ed. World Health Organization; 2013.
9. Netherlands Cancer Registry. https://www.iknl.nl/en. Accessed September 6, 2020.
10. Casparie M, Tiebosch AT, Burger G, et al. Pathology databanking and biobanking in The Netherlands, a central role for PALGA, the nationwide histopathology and cytopathology data network and archive. *Cell Oncol*. 2007;29:19-24.
11. van de Poll-Franse LV, Horevoorts N, van Eenbergen M, et al. The Patient Reported Outcomes Following Initial treatment and Long term Evaluation of Survivorship registry: scope, rationale and design of an

infrastructure for the study of physical and psychosocial outcomes in cancer survivorship cohorts. *Eur J Cancer*. 2011;47:2188-2194.
12. The Netherlands Institute for Social Research. https://english.scp.nl/ Accessed September 6, 2020.
13. Keeble S, Abel GA, Saunders CL, et al. Variation in promptness of presentation among 10,297 patients subsequently diagnosed with one of 18 cancers: evidence from a National Audit of Cancer Diagnosis in Primary Care. *Int J Cancer*. 2014;135:1220-1228.
14. Forbes LJ, Warburton F, Richards MA, Ramirez AJ. Risk factors for delay in symptomatic presentation: a survey of cancer patients. *Br J Cancer*. 2014;111:581-588.
15. Herbert A, Lyratzopoulos G, Whelan J, et al. Diagnostic timeliness in adolescents and young adults with cancer: a cross-sectional analysis of the BRIGHTLIGHT cohort. *Lancet Child Adolesc Health*. 2018;2:180-190.
16. SONCOS. Multidisciplinary guideline oncological care in the Netherlands. Published 2020. Accessed April 2020. https://www.soncos.org/kwaliteit/normeringsrapport/
17. Younger E, Husson O, Bennister L, et al. Age-related sarcoma patient experience: results from a national survey in England. *BMC Cancer*. 2018;18:991.
18. Macleod U, Mitchell ED, Burgess C, Macdonald S, Ramirez AJ. Risk factors for delayed presentation and referral of symptomatic cancer: evidence for common cancers. *Br J Cancer*. 2009;101(suppl 2):S92-S101.
19. Din NU, Ukoumunne OC, Rubin G, et al. Age and gender variations in cancer diagnostic intervals in 15 cancers: analysis of data from the UK Clinical Practice Research Datalink. *PLoS One*. 2015;10:e0127717.
20. Brick JM, Williams D. Explaining rising nonresponse rates in cross-sectional surveys. *Ann Am Acad Pol Soc Sci*. 2013;645:36-59.
21. Galea S, Tracy M. Participation rates in epidemiologic studies. *Ann Epidemiol*. 2007;17:643-653.
22. Morton LM, Cahill J, Hartge P. Reporting participation in epidemiologic studies: a survey of practice. *Am J Epidemiol*. 2005;163:197-203.
23. van Eenbergen MCHJ, Vromans RD, Boll D, et al. Changes in internet use and wishes of cancer survivors: a comparison between 2005 and 2017. *Cancer*. 2020;126:408-415.
24. Blay JY, van Glabbeke M, Verweij J, et al. Advanced soft-tissue sarcoma: a disease that is potentially curable for a subset of patients treated with chemotherapy. *Eur J Cancer*. 2003;39:64-69.
25. Stull DE, Leidy NK, Parasuraman B, Chassany O. Optimal recall periods for patient-reported outcomes: challenges and potential solutions. *Curr Med Res Opin*. 2009;25:929-942.
26. Burt CD, Kemp S, Conway M. What happens if you retest autobiographical memory 10 years on? *Mem Cognit*. 2001;29:127-136.