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Incidence, mortality, and survival trends of soft tissue and bone sarcoma in Switzerland between 1996 and 2015

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ABSTRACT

Background: Research on soft-tissue sarcoma (STS) and bone sarcoma (BS) is increasingly in the focus of physicians and pharmaceutical companies. Expanding knowledge has improved the management of sarcoma and possibly survival. Here we provide the first population-based data on time trends of incidence, mortality, and survival of STS and BS diagnosed in Switzerland between 1996 and 2015.

Methods: We performed a retrospective registry study with data from the National Institute for Cancer Epidemiology and Registration (NICER) database in Switzerland between 1996 and 2015.

Results: We identified 5384 STS patients and 940 BS patients. The three most common STS subtypes were undifferentiated/unclassified sarcoma (22.3%), liposarcoma (20.6%) and leiomyosarcoma (20.6%). Chondrosarcoma, osteosarcoma and Ewing sarcoma represented 40.4%, 27.0% and 15.2% of the BS group, respectively. The age-standardized incidence and mortality rates in 2011–2015 were 4.43 and 1.42 per 100,000 person-years for STS, and 0.91 and 0.42 for BS. Age-standardized incidence of STS in males was significantly higher during 1996–2000 than during 2001–2015; however, mortality rates did not change significantly over time. Five-year relative survival (RS) for STS improved significantly from 56.4% (95%CI 52.9–59.7 for 1996–2001) to 61.6% (95%CI 58.6–64.4 for 2011–2015) ($p = 0.025$). No improvement in 5-year RS for BS could be observed (RS 1996–2000: 69.6%, 95%CI 61.2–76.6; RS 2011–2015: 73.1%, 95%CI 66.6–78.6; $p = 0.479$).

Conclusion: Incidence rates of STS and BS have been stable since 2001. The longer RS in STS can be attributed to advances in sarcoma patient management.

1. Introduction

Sarcomas represent a rare group of malignant tumors arising from transformed cells of mesenchymal origin. They represent about 1% of all malignancies in adulthood and 12% in the pediatric cancer population [1–3]. Depending on the tissue of origin, approximately 80% of sarcomas originate in soft tissue and the rest in bone [2]. Of note, sarcomas are a heterogeneous tumor group comprising more than 80 subtypes. Based on their histological and molecular features they are currently classified according to the updated World Health Organization (WHO) classification published in 2013 [3]. It is evident that most of these subtypes differ in biology, clinical characteristics, treatment response and prognosis.

Epidemiological data on incidence, mortality and survival for sarcomas are sparse in the literature. The documentation in and analysis of registries are complicated by difficulties in classifying sarcomas. This fact also hampers comparison of published data. Recently, Toro and colleagues reported that less than half (47.9%) of all soft-tissue sarcoma (STS) cases arise from connective tissue; the other STS cases were found in many different organ systems (i.e. the digestive tract or respiratory

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system). Notably, sarcomas of the same histological subtype may occur at different primary sites [4].

The age-standardized incidence of STS (excluding gastrointestinal stromal tumors, GISTs) and bone sarcoma (BS) in Europe is reported to be 4.20–4.71 and around 0.8 per 100,000, respectively [5,6]. The 5-year relative survival rates of STS and BS in adulthood are reported as 59–60% and 53–55%, respectively [7,8]. Of note, in both studies STSs and BSs were defined by ICD code and therefore STSs of most organ-specific sites were excluded. These epidemiological benchmark data are expected to be similar in Switzerland. However, outcome parameters such as mortality rate and survival may differ due to differences in national healthcare systems. While care and treatment of sarcoma patients is centralized and provided in high-volume sarcoma centers in many bigger European countries (i.e. France and the United Kingdom), a structured sarcoma patient flow and centralization have only recently been well established in Switzerland. The Swiss National Sarcoma Advisory Board (SNSAB), a national interdisciplinary association of sarcoma experts, was initiated in 2013 in order to support the exchange among sarcoma experts in Switzerland, to define clinical practice guidelines for the treatment and work-up of sarcoma patients, and in particular to guide collaboration between sarcoma centers and other hospitals [9]. Networking has improved among sarcoma experts, yet discussion on highly specialized medicine and case load is currently still ongoing.

Here we provide the first population-based data on time trends of STS and BS incidence, mortality, and survival in patients diagnosed between 1996 and 2015 and reported to the Swiss Cantonal Cancer Registries (CCRs). Advancements in medical imaging technology, better understanding of tumor biology, recent developments with regard to systemic and radiation therapy, and first steps towards centralization of sarcoma patient care have improved the management of sarcomas. With this analysis we aim mainly to investigate whether all these improvements in sarcoma patient care and management are reflected in outcome data for the Swiss patient population.

2. Methods

2.1. Data sources and inclusion criteria

Primary STS and BS data from the years 1996–2015 and corresponding vital status information were extracted from the National Institute for Cancer Epidemiology and Registration (NICER) database. NICER is collecting and harmonizing data from the CCRs and provides a central national database of cancer registration data in Switzerland. At the time of data extraction in August 2018, 2015 was the latest available incidence year. We chose 1996 as the starting point. Subsequent to this year all major language regions of Switzerland have been covered by cancer registration, at least in part. In addition, basic obligatory health insurance was introduced in 1996; before this date, health insurance was predominantly voluntary.

All cancer cases collected by NICER were coded according to the third revision of the International Classification of Diseases for Oncology (ICD-O-3). Cancer cases diagnosed prior to the introduction of ICD-O-3 were recorded from ICD-O-2 to ICD-O-3 by the CCRs. Due to the gradual introduction of cantonal cancer registration, national population coverage for this study varied from 57.8% (1996–2000) to 79.4% (2011–2015). Both trend and overall analyses are based on the same dataset including the incidence years by canton presented in Supplementary Table S1.

Vital status information was collected by passive follow-up (linkage with federal mortality data) and active follow-up (verification of vital status with the cantonal registration offices). Overall, 97.2% of all cases were morphologically verified. The proportion of death-certificate-only (DCO) cases was 0.4%, indicating a high completeness of case ascertainment.

Mortality data (coded in ICD-10), mid-year population estimates, and cantonal death rates by age, sex and calendar year were obtained from the Swiss Federal Statistical Office (SFSO), referring to all persons with permanent residence status in Switzerland. For mortality analyses, we used national data for the entire study period.

The total person-years at risk for each calendar year of the study period for both incidence and mortality analyses are presented in Supplementary Figure S1.

2.2. Analytical methods

2.2.1. Classification in sarcoma subtypes

Histological subtypes of incident STS and BS were categorized according to Supplementary Tables S2 and S3. GISTs and Kaposi sarcomas were excluded from this study. Incident STSs were additionally grouped according to anatomical location as listed in Supplementary Table S4. Sarcoma deaths were identified by ICD-10 codes C40–C41 (BS) and C47–49 (STS).

2.2.2. Statistical analyses

We calculated 5-year age-specific crude and age-standardized incidence and mortality rates with corresponding 95% confidence intervals (95%CIs). To reduce random variation due to small numbers and to increase the precision of our estimates, we combined 5 calendar years for rate calculations resulting in four measurements for the period 1996–2015.

Age-standardized rates were calculated using the direct method and the European standard population as reference [10]. Case frequencies for the whole of Switzerland were obtained by applying the observed incidence rates (by age, sex and period) of the cantons covered by cancer registration to the cantons without registration, assuming homogeneity between cantons with and without cancer registration.

Relative survival (RS) was estimated using the Ederer II method [11]. We calculated OS and RS up to 5 years after diagnosis using period analysis for the period 2011–2015 and conventional cohort analysis for the prior periods [11]. RS estimates for all age groups combined were age-standardized applying the balanced method with five age groups as described by Gondos et al. [12]. Significance tests for RS were applied according to the method described by Parkin and Hakulinen, comparing 5-year RSs for the period 1996–2000 with those for 2011–2015 [13].

To assess whether increases in population coverage over time had an impact on observed trends, we performed sensitivity analyses excluding cancer registries implemented after 1996.

Statistical analyses were performed using Stata/MP version 15.0 (STAT Corp., TX, USA).

3. Results

3.1. Study population

Overall, 5384 patients with STS and 940 patients with BS were identified. A minor male predominance was found in both STS and BS (51.5% and 56%, respectively). The median age was 62 years for STS and 46 years for BS. The absolute number of documented sarcoma patients increased in the last analyzed 5-year period (2011–2015) when compared to the previous time periods. The three most common STS subtypes were undifferentiated/unclassified sarcoma (US) (1201 patients; 22.3%), liposarcoma (LS) (1108 patients; 20.6%) and leiomyosarcoma (LMS) (1107 patients; 20.6%); 32.3% of STS cases had an extremital origin. Chondrosarcoma, osteosarcoma and Ewing sarcoma represented 40.4%, 27% and 15.2% of the BS group, respectively. Detailed patient and tumor characteristics are depicted in Tables 1 and 2.

Table 1
Characteristics of soft-tissue sarcoma patients reported to Swiss cancer registries, 1996–2015.

	N	%	CR	ASR [95%CI]
Overall	5384	100.0	5.48	4.54 [4.41–4.66]
Sex				
Males	2774	51.5	5.77	5.02 [4.84–5.22]
Females	2610	48.5	5.20	4.18 [4.02–4.36]
Age (years)				
Median age	62			
Time period				
1996–2000	1261	23.4	6.13	5.22 [4.92–5.52]
2001–2005	1073	19.9	5.04	4.24 [3.98–4.51]
2006–2010	1290	24.0	5.31	4.37 [4.13–4.63]
2011–2015	1760	32.7	5.48	4.43 [4.21–4.65]
Histological group				
Undifferentiated/unclassified sarcoma	1201	22.3	1.22	0.93 [0.88–0.99]
Liposarcoma	1108	20.6	1.13	0.92 [0.86–0.97]
Others	*325*	*29.3*	*0.33*	*0.27 [0.24–0.30]*
Well differentiated	*296*	*26.7*	*0.30*	*0.24 [0.22–0.27]*
Myxoid–round cell	*230*	*20.7*	*0.23*	*0.21 [0.18–0.24]*
Dedifferentiated	*154*	*13.9*	*0.16*	*0.12 [0.10–0.14]*
Pleomorphic	*103*	*9.3*	*0.10*	*0.08 [0.07–0.10]*
Leiomyosarcoma	1107	20.6	1.13	0.90 [0.84–0.95]
Fibroblastic/myofibroblastic	700	13.0	0.71	0.63 [0.58–0.68]
Tumors of uncertain differentiation	397	7.4	0.40	0.37 [0.20–0.25]
Vascular sarcoma	298	5.5	0.30	0.23 [0.20–0.25]
Nerve sheath tumors	264	4.9	0.27	0.23 [0.20–0.26]
Rhabdomyosarcoma	184	3.4	0.19	0.22 [0.19–0.25]
Ewing sarcoma	80	1.5	0.08	0.08 [0.06–0.10]
Pericytic (perivascular) sarcoma	39	0.7	0.04	0.04 [0.03–0.05]
So-called fibrohistiocytic	6	0.1	0.01	0.01 [0.00–0.01]
Anatomical location				
Extremity	1742	32.3	1.77	1.48 [1.40–1.55]
Trunk	815	15.1	0.83	0.71 [0.66–0.76]
Head or neck	559	10.4	0.57	0.45 [0.41–0.49]
Retroperitoneal	451	8.4	0.46	0.37 [0.34–0.41]
Uterus	331	6.2	0.34	0.29 [0.26–0.32]
Others	314	5.8	0.32	0.27 [0.24–0.30]
Pelvis (non-visceral)	295	5.5	0.30	0.25 [0.22–0.28]
Gastrointestinal	259	4.8	0.26	0.21 [0.19–0.24]
Heart, mediastinum, lung or pleura	219	4.1	0.22	0.18 [0.15–0.20]
Genitourinary	185	3.4	0.19	0.16 [0.14–0.19]
Breast	93	1.7	0.09	0.07 [0.06–0.09]
Unknown	62	1.2	0.06	0.05 [0.04–0.06]
Gynecological (other than uterus)	59	1.1	0.06	0.05 [0.04–0.07]

Population covered by cancer registration: 57.8% in 1996–2000, 58.1% in 2001–2005, 63.5% in 2006–2010, and 79.4% in 2011–2015. CR, crude rate per 100,000 person-years; ASR, age-standardized rate per 100,000 person-years.

3.2. Incidence and mortality of soft-tissue and bone sarcoma in Switzerland

3.2.1. Soft-tissue sarcoma

Estimated annual case frequency varied between 366 (2001–2005) and 448 (2011–2015) cases. In 2011–2015, the age-standardized incidence and mortality rates were 4.43 (95%CI 4.21–4.65) and 1.42 (95%CI 1.32–1.53) per 100,000 py, respectively. A significantly higher age-standardized STS incidence in males was noted in the period 1996–2000 compared to later time periods, but since 2001 the incidence remained stable for both sexes (Table 3). The age-standardized incidence rate per 100,000 py in the four time periods was slightly higher in males than in females and ranged from 4.63 (95%CI 4.24–5.05) to 6.11 (95%CI 5.64–6.59) in males and 3.96 (95%CI 3.61–4.33) to 4.59 (95%CI 4.21–5.00) in females. The age-standardized mortality rates per 100,000 py were similar in males and females: 1.28 (95%CI 1.13–1.46) to 1.47 (95%CI 1.32–1.63) in males and 1.27 (95%CI 1.13–1.43) to 1.39 (95%CI 1.25–1.54) in females. Distribution of incidence up to the age of 69 and mortality over all ages stratified for sex and age classes were comparable over the earliest and latest 5-year periods studied (1996–2000 and 2011–2015). Age-specific (crude) incidence and mortality rates steadily increased up to the age of 89 (Table 3 and Fig. 1).

Table 2
Characteristics of bone sarcoma patients reported to Swiss cancer registries, 1996–2015.

	N	%	CR	ASR [95% CI]
Overall	940	100.0	0.96	0.34 [0.92–0.86]
Sex				
Males	526	56.0	1.09	1.05 [0.96–1.15]
Females	414	44.0	0.82	0.80 [0.72–0.89]
Age (years)				
Median age	46			
Time period				
1996–2000	181	19.3	0.88	0.86 [0.74–1.00]
2001–2005	225	23.9	1.06	1.03 [0.89–1.17]
2006–2010	228	24.3	0.94	0.88 [0.77–1.01]
2011–2015	306	32.6	0.95	0.91 [0.81–1.02]
Histological group				
Chondrosarcoma	380	40.4	0.39	0.34 [0.30–0.37]
Conventional	*353*	*92.9*	*0.36*	*0.31 [0.28–0.35]*
Mesenchymal	*16*	*4.2*	*0.02*	*0.02 [0.01–0.03]*
Dedifferentiated	*11*	*2.9*	*0.01*	*0.31 [0.28–0.35]*
Osteosarcoma	254	27.0	0.26	0.27 [0.24–0.31]
Conventional	*240*	*94.5*	*0.24*	*0.26 [0.22–0.29]*
Others	*14*	*5.5*	*0.01*	*0.01 [0.00–0.02]*
Others	163	17.3	0.17	0.14 [0.12–0.17]
Ewing sarcoma	143	15.2	0.15	0.17 [0.14–0.20]

Population covered by cancer registration: 57.8% in 1996–2000, 58.1% in 2001–2005, 63.5% in 2006–2010, and 79.4% in 2011–2015. CR, crude rate per 100,000 person-years; ASR, age-standardized rate per 100,000 person-years.

The age-standardized incidence rate of US decreased from 1.25 (95%CI 1.11–1.40) in the initial time period (1996–2000) to 0.83 (95%CI 0.74–0.92) in the last period (2011–2015). The age-adjusted incidence of LMS was similar and decreased from 1.28 (95%CI 1.14–1.43) to 0.78 (95%CI 0.70–0.88) when comparing the two time periods. In contrast, an increasing incidence was documented in the LS subgroup: 0.80 (95%CI 0.69–0.93) versus 1.04 (95%CI 0.94–1.15) in the latter period of time (Supplementary Table S5). In respect to the different LS subtypes an increasing age-adjusted incidence can be found particularly in the dedifferentiated subtype (Supplementary Table S6). The incidence outcomes with regard to anatomical location are illustrated in Supplementary Table S7. Whereas a decrease in age-adjusted incidence rate was detected in head-and-neck and gastrointestinal STSs, the incidence rate of STS at other sites remained rather stable.

3.2.2. Bone sarcoma

Estimated annual case frequency of BS varied between 63 and 78 cases per year. Age-standardized incidence rates ranged from 0.86 (95%CI 0.74–1.00) to 1.03 (95%CI 0.89–1.17) (Table 3). No significant differences in the predefined time periods were found. In contrast, 33–43 BS-related deaths per year for each time period were documented. Again, mortality rate did not change significantly over time. Age-standardized mortality rate ranged from 0.37 (95%CI 0.32–0.44) to 0.48 (95%CI 0.41–0.56). The age-standardized (adjusted) incidence rates per 100,000 py was slightly higher in males than in females and ranged from 0.96 (95%CI 0.81–1.12) to 1.18 (95%CI 0.98–1.41) in males and 0.70 (95%CI 0.56–0.87) to 0.89 (95%CI 0.72–1.10) in females. The age-standardized (adjusted) mortality rate per 100,000 py was also slightly higher in males, ranging from 0.45 (95%CI 0.36–0.56) to 0.59 (95%CI 0.48–0.72), than in females, 0.28 (95%CI 0.22–0.36) to 0.39 (95%CI 0.31–0.49). The corresponding crude and age-standardized (adjusted) incidence and mortality rates are summarized in Table 3. Age-specific crude incidence and mortality rates are illustrated in Fig. 3. Expectedly, age-specific incidence in BS was characterized by two peaks, one in the adolescent and young adult period and the other in the age group > 60 years. By contrast, age-specific mortality increased relevantly in patients > 60 years.

The age-adjusted incidences of chondrosarcoma, osteosarcoma and Ewing sarcoma between 2011 and 2015 were 0.43 (95%CI 0.34–0.54),

Table 3
Incidence and mortality of sarcoma by type, sex and time period.

	Soft tissue sarcoma			Bone sarcoma		
	Annual cases*	CR	ASR [95% CI]	Annual cases*	CR	ASR [95% CI]
INCIDENCE						
Males						
1996–2000	228	6.62	6.11 [5.64–6.59]	36	1.03	1.02 [0.83–1.24]
2001–2005	184	5.15	4.63 [4.24–5.05]	43	1.21	1.18 [0.98–1.41]
2006–2010	206	5.47	4.67 [4.31–5.06]	43	1.14	1.08 [0.90–1.28]
2011–2015	237	5.86	4.89 [4.57–5.22]	41	1.03	0.96 [0.81–1.12]
Females						
1996–2000	204	5.67	4.59 [4.21–5.00]	27	0.74	0.71 [0.56–0.90]
2001–2005	183	4.92	3.96 [3.61–4.33]	34	0.91	0.89 [0.72–1.10]
2006–2010	201	5.16	4.19 [3.85–4.55]	29	0.75	0.70 [0.56–0.87]
2011–2015	211	5.11	4.07 [3.78–4.37]	36	0.88	0.87 [0.73–1.03]
Both sexes						
1996–2000	431	6.13	5.22 [4.92–5.52]	63	0.88	0.86 [0.74–1.00]
2001–2005	366	5.04	4.24 [3.98–4.51]	78	1.06	1.03 [0.89–1.17]
2006–2010	407	5.31	4.37 [4.13–4.63]	72	0.94	0.88 [0.77–1.01]
2011–2015	448	5.48	4.43 [4.21–4.65]	77	0.95	0.91 [0.81–1.02]
MORTALITY						
Males						
1996–2000	48	1.39	1.28 [1.13–1.46]	21	0.62	0.59 [0.48–0.72]
2001–2005	60	1.67	1.45 [1.29–1.63]	18	0.49	0.45 [0.36–0.56]
2006–2010	63	1.67	1.34 [1.19–1.50]	22	0.58	0.50 [0.41–0.60]
2011–2015	75	1.87	1.47 [1.32–1.63]	25	0.62	0.52 [0.43–0.62]
Females						
1996–2000	68	1.86	1.30 [1.15–1.46]	18	0.51	0.39 [0.31–0.49]
2001–2005	70	1.86	1.27 [1.13–1.43]	15	0.41	0.30 [0.23–0.38]
2006–2010	77	1.97	1.35 [1.21–1.50]	15	0.39	0.28 [0.22–0.36]
2011–2015	87	2.13	1.39 [1.25–1.54]	19	0.46	0.33 [0.26–0.41]
Both sexes						
1996–2000	116	1.63	1.29 [1.19–1.41]	40	0.56	0.48 [0.41–0.56]
2001–2005	130	1.77	1.36 [1.25–1.47]	33	0.45	0.37 [0.32–0.44]
2006–2010	139	1.82	1.32 [1.22–1.43]	37	0.48	0.38 [0.33–0.45]
2011–2015	162	2	1.42 [1.32–1.53]	43	0.54	0.42 [0.36–0.48]

* Incidence: mean annual case frequency extrapolated to the whole Swiss population from cases observed in the cancer registries. Discrepancies between the sum and total number of expected cases are caused by rounding errors. Mortality: mean annual case frequency derived from nationwide cause of death statistics. CR, crude incidence-rates per 100'000 person-years; ASR, age-standardized incidence-rates per 100,000 person-years (old European standard).

0.26 (95%CI 0.19–0.36) and 0.14 (95%CI 0.08–0.22), respectively. No relevant change over the decades could be noticed. The age-adjusted chondrosarcoma incidence was consistently higher in the male cohort than in females: 0.43 (95%CI 0.34–0.54) versus 0.30 (95%CI 0.22–0.39) in 2011–2015 (Supplementary Table S8). Incidence rates for different subtypes of osteosarcoma (conventional versus others) and chondrosarcoma (conventional, mesenchymal and dedifferentiated) are illustrated in Supplementary Tables S9 and S10.

3.3. Observed and relative survival

3.3.1. Soft-tissue sarcoma

Including all age groups, the 5-year OS of STS patients was 56.5% in the time period 2011–2015 (Supplementary Table S11). The RS improved significantly from the initial time period compared to the latest period and was 56.4% (95%CI 52.9%–59.7%) and 61.6% (95%CI 58.6%–64.4%) (p = 0.025), respectively (Fig. 4a, Supplementary Table S11). RSs for the five most common histological categories are presented in Supplementary Table S12. When compared to the earliest time period, an increased RS for LMS and sarcoma of uncertain differentiation and a trend to decreased survival for US and sarcoma of (myo-)fibroblastic origin was observed in the latest period.

3.3.2. Bone sarcoma

In the most recent time period (2011–2015) OS and RS were 69.7% and 73.1% (95%CI 66.6–78.6), respectively (Fig. 4b, Supplementary Table S11). When compared to the earliest period (1996–2000) no significant difference in RS could be found in the overall population (p = 0.479) (Fig. 4b).

3.4. Sensitivity analyses

The sensitivity analyses excluding all cancer registries implemented after 1996 showed similar results compared to our main analyses for both incidence and survival (data not presented).

4. Discussion

Here we provide the first population-based epidemiological analysis of STS and BS patients in Switzerland from 1996 to 2015. The analysis focused on descriptions of trends in annual case frequency, morphological classification, incidence, mortality and survival. The main findings of this study can be summarized as follows: (a) the RS of STS improved significantly from the initial time period to the latest period; (b) the age-adjusted incidence in females and mortality in STS and BS overall and the RS in BS remained stable during the last 20 years; (c) age-specific (crude) incidence and mortality rates steadily increased with age in STS and were characterized by two peaks in BS; (d) the three most common STSs and BSs were US, LS and LMS and chondrosarcoma, osteosarcoma and Ewing sarcoma, respectively; and (e) incidence of US and LMS decreased and that of LS increased.

4.1. Epidemiological data of STS

The age-standardized incidence and mortality rates in our study were 4.47 (95%CI 4.26–4.69) and 1.42 (95%CI 1.32–1.53) per 100,000 py from 2011 to 2015, respectively. These numbers are comparable to findings reported by other national, European and United States registries [14–17]. In general, the results of studies investigating the

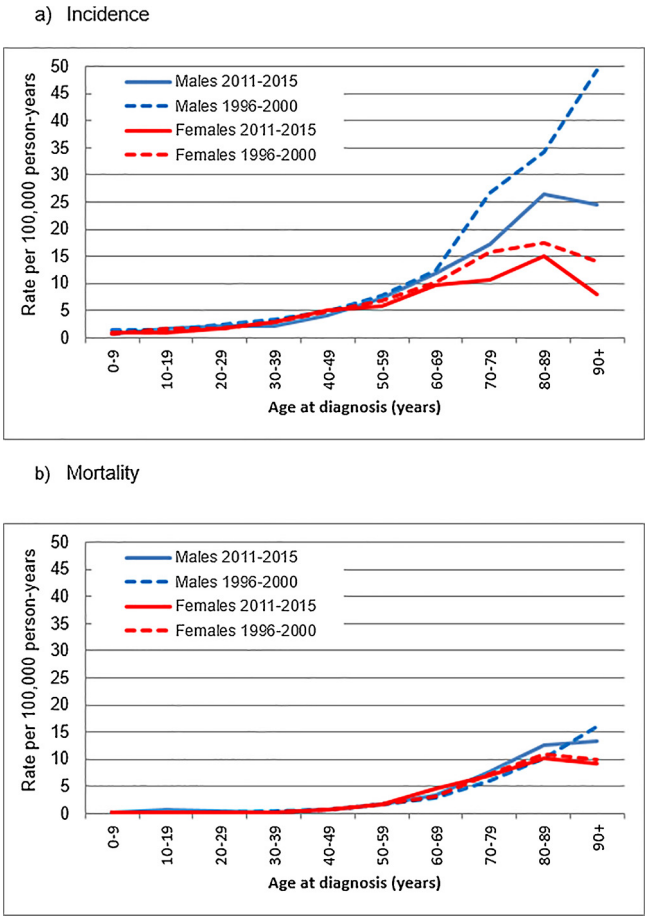

Fig. 1. Age-specific incidence and mortality of soft-tissue sarcoma (STS), 1996–2000 and 2011–2015. (a) Incidence. (b) Mortality.
The incidence rates for the five most common histological STS categories are depicted in Fig. 2.

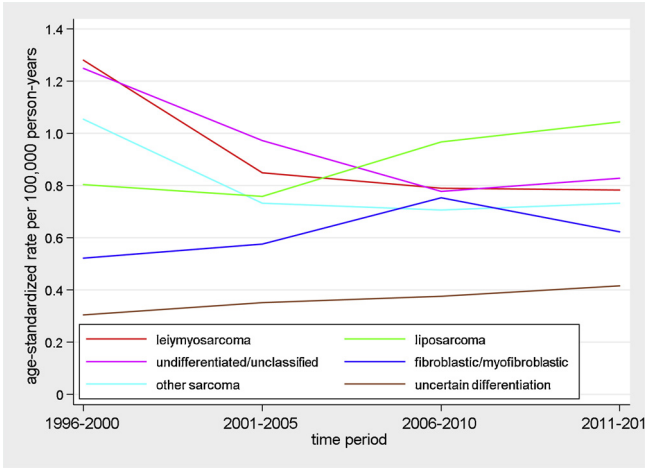

Fig. 2. Incidence rates for the five most common histological categories of soft-tissue sarcomas. PYs, person-years.

epidemiology of STS are difficult to compare. The studies usually differ in assessment methods used to identify patients, and they use varying inclusion criteria with regards to sarcoma types, patient age, analyzed time period, tumor stage and endpoints.

Some of these reports suggest an increasing incidence rate in the last decades [18]. Levi and colleagues collected and studied epidemiological STS data in Vaud, a single Swiss canton. They reported an increase

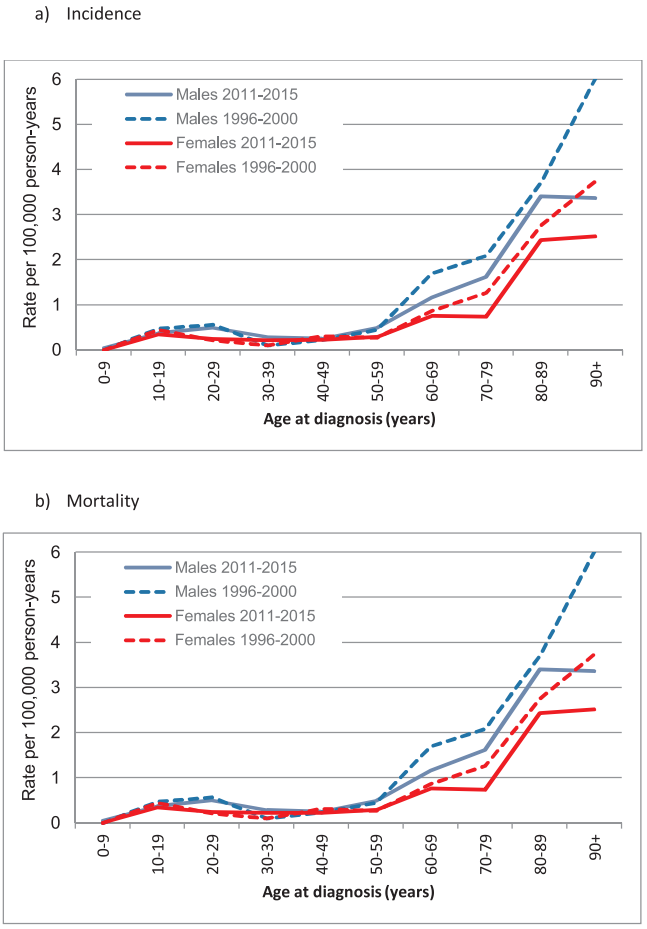

Fig. 3. Age-specific incidence and mortality of bone sarcoma, 1996–2000 and 2011–2015. (a) Incidence. (b) Mortality.

in overall STS incidence rates from 2.68/100,000 males in 1974–1979 to 6.86/100,000 males in 1990–1994, and from 3.61 to 4.27/100,000 females, respectively. However, after excluding Kaposi's sarcoma, no consistent trend over time was observed [19].

Toro and colleagues reported on the incidence patterns of STS in the Surveillance, Epidemiology and End Results (SEER) program of the United States, 1978–2001, notably excluding bone tumors. Although they included more or less the same morphology codes, a strict comparison with our data is difficult. Whereas their grouping was based on the former WHO classification of 2002, there was a significant shift in sarcoma diagnostic criteria and classification in the new WHO classification of 2013 which we used for our analysis. The incidence rate in the SEER analysis was 4.60–6.26/100,000 and therefore slightly higher. One reason among others might be the inclusion of GIST in the era before 1990 [4].

The slight male predominance with regards to incidence rate reflects current knowledge [3]. Analysis of pooled data from the German Centre for Cancer Registry revealed an age-adjusted incidence for STS (including GIST) of 6.2 and 5.9 per 100,000 for males and females, respectively [20]. As there is a significant relationship between sarcoma subtype and patient gender we cannot exclude that the case mix between males and females might impact on the observed differences. The decline in age-standardized STS incidence rate in males in our analysis from the earliest time period to the latter periods remains unclear.

Incidence rates of STS subtypes and potential changes over time are only rarely reported in the literature. US, LMS and LS represent the three most common STS subtypes to date. The incidence rates of these entities are in line with current data reported from Ducimetière et al. [21]. While we observed a decrease in the US and LMS incidence rates,

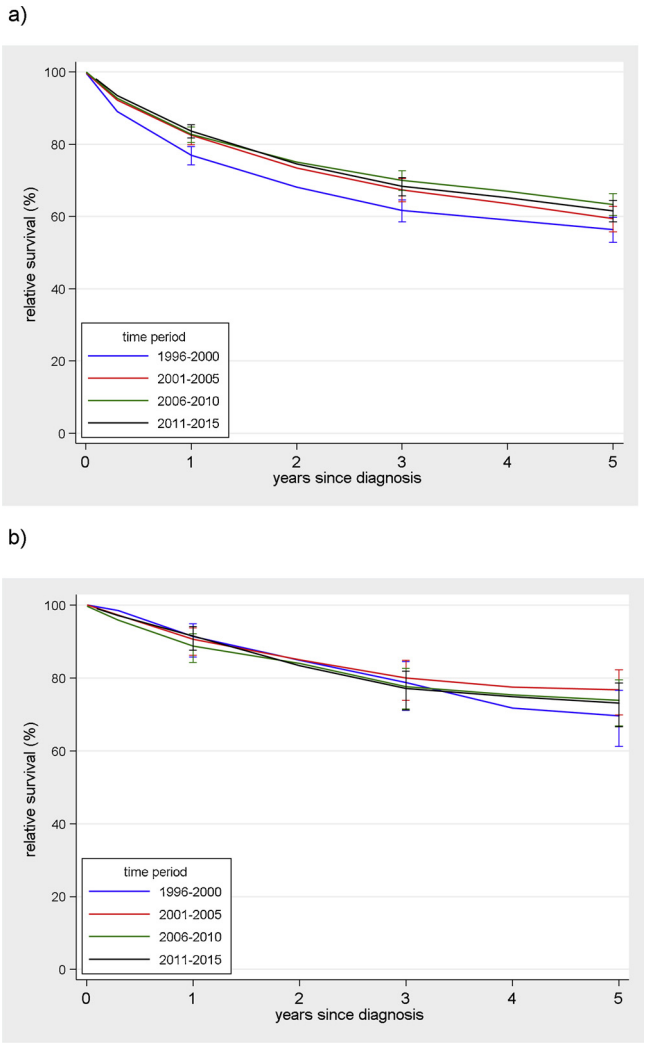

Fig. 4. Age-standardized survival for soft-tissue sarcoma (STS) and bone sarcoma (BS). (a) Relative survival for STS. (b) Relative survival for BS.

an increasing LS incidence could be identified, notably exceeding the incidence of US. The reason for this observation is likely due to the refinement of histological diagnosis by the WHO classification system, which included in its last version the steadily increasing knowledge on molecular diagnostics [3]. For example, fluorescence in-situ hybridization testing of MDM2 (mouse double minute 2 homolog) might reclassify US as LS. The decrease in LMS incidence, and notably of STS of gastrointestinal origin, also has its origin in improved diagnostic tools in the last decades. In the past GIST might have been misdiagnosed as LMS [22]. The incidence rates of other STS subtypes reported in our study were all far below 1 per 100,000, hampering profound interpretation.

4.2. Outcome data for STS

The most noteworthy finding of this analysis is the significantly improved RS of STS during the period 2011–2015 when compared to the earliest time period. Owing to the low incidence and heterogeneity, STSs were and are still prone to misrecognition, misdiagnosis, and consequently inadequate treatment. Yet there are several explanations for the above observation [23].

Possibly the most relevant reason for the improved survival lies in the refinement of surgical techniques and recent developments with regards to systemic and radiation therapy [24,25]. In addition, networks of experts and hospitals have been established in the last years in many European countries in order to improve the management and outcome of sarcoma patients. Treating sarcoma patients within specialized, high-volume centers has an impact on outcome [26–28]. Recently, an improved survival was reported by Blay et al. for sarcoma patients presented at specialized multidisciplinary tumor boards [29]. All seven Swiss sarcoma centers run interdisciplinary sarcoma boards and discuss diagnostic findings and the optimal treatment strategy on a regular basis. Notably, adherence to consensus-based diagnosis and treatment guidelines in adult STS patients has been shown to improve long-term outcome [26,30].

Improvements in histological and imaging technologies may furthermore allow an earlier and more accurate diagnosis of sarcoma leading to a more tailored management strategy [31,32]. The RS trends in the different STS groups and their impact on the RS of the whole cohort should be interpreted with caution. In most of the categories there seems to be a difference in RS over time, mainly in the last two periods (since 2006). The main explanation for this observation might be the fact that many subsets of tumors have been moved into new sections over time. This is reflected within the new 2013 WHO classification which includes current advances in molecular and genetic studies. It also recognized some new entities. As the STS incidence overall was not subject to changes during the last decades, we suggest a rather stable case mix in this Swiss cohort. Nevertheless, we cannot completely exclude that a different case mix might have an impact on our survival results. For example, the incidence of US decreased and concurrently the RS of US. Again, the diagnostic refinement in recent years has clearly reduced the cohort diagnosed with US. This subentity usually represents a rather poor prognostic histology, which explains the worsening RS. Although the incidence of liposarcoma has increased in the last decade (mainly the dedifferentiated variant) the age-adjusted RS of liposarcoma did not change relevantly. The intensified research focus on LS and LMS, and consequently optimized treatment, might support the improvement of RS in these two cohorts on the one hand and in the whole STS group on the other hand.

The 5-year STS survival rate including all age groups in the time period 2011–2015 was 56.5% in our study. This result mirrors the 5-year survival reported by Saltus and colleagues from a German registry-based analysis, also excluding GIST [15]. The improved survival in the last decade is supported by the results of an analysis based on a large cancer registry from Florida. In an STS cohort including 8249 patients from 1981 and 2004 a 5-year overall survival of 23.6% was documented at that time [17].

A possible explanation for the increase in survival rates for STS while both incidence and mortality have remained more or less constant might be that mortality rates rely on the quality of the cause-of-death information on the death certificate, whereas relative survival rates are independent of the cause-of-death information. As a consequence, potential misclassification of the underlying cause of death may result in discrepant results when trends in mortality and relative survival are compared. In addition, there might have been insufficient time for increase in survival to lead to decrease in mortality because many of the avoided deaths would have occurred after the end of the study period.

4.3. Epidemiological and outcome data of BS

The BS incidence and mortality rates assessed in our study are in line with those in the current literature [21]. In contrast to STS, survival analysis for BS does not reveal a significant improvement in the last decades. Surgical and radiation therapy techniques in STS and BS have been optimized in recent years. However, while the treatment sequence remained mostly unchanged, the impact of newer local treatment techniques is rather limited in many sarcoma subtypes regarding outcome. Ewing sarcomas and osteosarcomas represent more than half of all BS cases and are characterized by a high frequency of synchronous and metachronous hematogenous metastases. Therefore, the impact of

systemic therapy on outcome is significant. However, different treatment strategies studied in the last years—including chemotherapy intensification for poor-risk patients and immunotherapeutic approaches—have not led to a survival improvement for these two BS entities [33–35]. Molecular diagnostics and novel treatment approaches will hopefully change this in the future.

4.4. Implications for health care

Our results confirm an improvement in STS survival even in a small country like Switzerland with limited health policy interventions on a national level and difficulties in coordinating the management of orphan diseases. Current internationally elaborated strategies for an optimal management of sarcoma patients have entered into daily clinical practice and are a key factor for better outcomes. In order to keep pace with the increasing knowledge, national and international collaboration is of utmost importance. Further efforts should be made to provide access for all patients to high-volume centers, to address clinical trial participation, and to optimize post-treatment rehabilitation programs and follow-up strategies in order to further improve outcomes.

4.5. Strengths and limitations

The strength of our study is based on the high quality and high completeness of data assessment within the NICER database [36]. The proportion of patients with DCO reported here was only 0.4%, and 97.2% of cases were microscopically verified without relevant changes during the observation time. Despite the rarity and heterogeneity of this disease, epidemiological data of several STS and BS subtypes—in particular LS—are provided in this analysis.

A potential limitation of our study might be that cancer registration in Switzerland is organized on a cantonal level, and not all CCRs covered the entire study period. Although our data provide useful insight in the epidemiology of sarcoma, including incidence, mortality and survival data, data on patient and tumor characteristics (i.e. comorbidities, tumor stage) and on treatment details are lacking. Due to the low number of observed cases in a few STS and BS subtypes, the data should be interpreted with caution. Additionally, the assessment of incidence rate and mortality rate were incongruent. This methodological difference may have overestimated the difference between incidence and mortality rates mainly in STS.

5. Conclusions

The incidence and mortality rates of STS and BS did not change during the last decades. Although some predisposing factors have been identified—including genetic predisposition and exposure to radiotherapy—most cases have no clearly defined etiology. The longer relative survival in STS can presumably be attributed to improvements in treatment techniques and a growing systemic treatment armamentarium, and to a lesser extent to advances in sarcoma patient management in Switzerland. However, efforts to structure the management of sarcoma patients, to offer access to multidisciplinary tumor board discussions, and to foster guideline-conforming therapy and participation in national and international clinical trials should be continued and intensified.

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Authors' contributions

AK: initiation, conception and design, analysis and interpretation of data, drafting, final approval.

CR: conception and design, analysis and interpretation of data, drafting, final approval.

FK: initiation, revision, final approval.

BB: analysis, interpretation of data, manuscript revision, approval of revision.

DB: analysis, interpretation of data, manuscript revision, approval of revision.

VA: conception and design, analysis and interpretation of data, revision, final approval.

AF: statistical analysis, analysis and interpretation of data, drafting, final approval.

Declaration of Competing Interest

None declared.

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Appendix A. Supplementary data

Supplementary material related to this article can be found, in the online version, at doi:https://doi.org/10.1016/j.canep.2019.101596.

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