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Research Paper

Clinical epidemiology and treatment outcomes of spindle cell non-osteogenic bone sarcomas – A nationwide population-based study

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ABSTRACT

Purpose: To describe epidemiological and clinical characteristics, as well as long-term treatment outcomes of spindle cell non-osteogenic bone sarcomas (SCS), comprising leiomyosarcoma, fibrosarcoma and undifferentiated pleomorphic sarcoma in bone.

Method: We have analysed a nationwide cohort of 104 patients with histologically verified SCS diagnosed between 1975 and 2009, based on registry sources supplemented with clinical records from Norwegian hospitals involved in sarcoma management.

Results: In this unselected cohort, a stable annual incidence for SCS patients of slightly below 0.6 per million was observed, with a dominant peak among elderly patients. SCS is mostly a high-grade malignancy (92%) with a male to female ratio of 1.6 for all patients. The axial to appendicular ratio was 0.7, seemingly independent of age. More than one fourth of the patients (29%) had primary metastatic disease. Another 32 patients (46%) developed metastases during follow-up and 12 (17%) experienced local relapses. The five-year sarcoma-specific survival rate was 37%, with no documented improvement over time. Primary metastatic disease was an adverse prognostic factor for survival. Predisposing factors were documented in 19 patients (18%). Negative prognostic factors for overall survival were tumour size >9 cm, age > 40 years, axial tumour localization, FS as subtype and pathologic fracture at time of diagnoses. As expected, patients who received both surgery and chemotherapy as their primary treatment for high-grade SCS (25%) significantly had best sarcoma specific five years survival (62%).

Conclusion: We confirm SCS as a rare high-grade bone sarcoma entity, mostly among elderly patients and with a poor overall outcome. The combined treatment of surgery and chemotherapy is essential to achieve optimal long-term survival of SCS.

1. Introduction

Spindle cell non-osteogenic bone sarcomas (SCS) comprises a small and heterogeneous group of malignant tumours including fibrosarcomas (FS), leiomyosarcomas (LMS), angiosarcoma and malignant fibrous histiocytoma, the latter currently classified as undifferentiated pleomorphic sarcoma (UPS) [1–3]. SCS share several common features with osteosarcoma (OS) [4,5], but with an even greater span in tumour biology and prognosis [4,6]. So far, only small series of patients with SCS have been reported [2–4,7]. The currently recommended management of high-grade SCS involves neoadjuvant chemotherapy followed by surgical removal of all detectable disease and postoperative chemotherapy [1], in line with the existing protocols for OS [1,8,9]. UPS and OS seemingly show similar survival and chemosensitivity [7].

The purpose of this study was to describe the epidemiological and clinical characteristics related to treatment outcomes of FS, LMS and UPS in bone in an unselected Norwegian cohort diagnosed between 1975 and 2009. To our knowledge, no nationwide study on SCS has previously been published.

2. Patients and methods

2.1. Patient cohort

The patient material here studied is based on multiple sources of information, including data from the Norwegian Cancer Registry (NCR) [10]. The reporting of malignant neoplasms to the NCR has been

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Table 1
Characteristics of patients with spindle cell non-osteogenic bone sarcoma.

	All patients (%)	UPS (%)	FS (%)	LMS (%)
All patients	104	65	25	14
Gender				
Female	40 (38)	26 (40)	7 (32)	7 (50)
Male	64 (62)	39 (60)	18 (68)	7 (50)
Axial versus extremity				
Extremity	62 (60)	45 (69)	12 (48)	5 (36)
Axial	42 (40)	20 (31)	13 (52)	9 (64)
Age				
≤ 40 years	20 (19)	9 (14)	8 (32)	3 (21)
> 40 years	84 (81)	56 (86)	17 (68)	11 (79)
Primary metastatic disease[a]	28 (29)	19 (31)	6 (27)	3 (21)
Malignancy grade				
Low-grade	8 (8)	3 (5)	3 (12)[c]	2 (14)
High-grade	96 (92)	62 (95)	22 (88)	12 (86)
Tumour size[b]				
≤9 cm	38 (58)	27 (59)	8 (73)	3 (37)
>9 cm	27 (42)	19 (41)	3 (27)	5 (63)
Median/mean size in cm	8/9	8/9	6/8	9/8
Range in cm	3–25	3–25	3–20	3–13
Duration of symptoms[b]				
≤6 months	53 (60)	36 (69)	9 (40)	8 (57)
>6 months	35 (40)	16 (31)	13 (59)	6 (43)
Median/mean length in months	4/6	3/5	7/9	5/6
Range in months	0–36	0–36	0–24	0–24
Pathologic fracture	23 (22)	13 (20)	7 (28)	3 (21)
Predisposing factors	19 (18)	16 (25)	2 (8)	1 (7)
Previous radiation	14 (13)	13 (20)		1 (7)
Other	5 (5)	3 (5)	2 (8)	
Years of diagnosis				
1975–1979	12 (11)	3 (5)	8 (32)	1 (7)
1980–1989	28 (27)	18 (28)	7 (28)	3 (21)
1990–1999	30 (29)	22 (33)	3 (12)	5 (36)
2000–2009	34 (33)	22 (33)	7 (28)	5 (36)

[a] Seven cases had missing information regarding primary metastatic disease and were not included.
[b] Missing values equal the difference between the summarized numbers in the second column and the total patients in the study.
[c] Two cases underwent transformation from low to high-grade FS during follow-up.

compulsory since 1953, and the completeness has been reported to be higher than 95% [11]. 104 cases of SCS, embracing FS, LMS and UPS were identified based on histological reports from a gross study material that amounted to 702 patients with SCS and OS [12–14] between 1975 and 2009, including patients with sarcoma predisposing factor [10]. All questionable cases were histologically re-examined as part of this work, including immunohistology of these tumours in relevant cases [10]. The database is located at the NCR.

2.2. Demographic and tumour related variables

The characteristics of patients with SCS are presented in Table 1. We did not identify any primary angiosarcoma in bone in the present study, related to the selection criteria applied in the entire spindle cell sarcoma cohort in bone [10]. Most patients were treated at the Norwegian Radium Hospital. As expected, we have not reached full completeness regarding clinical information for all patients in the study.

All tumours were graded according to a four-grade malignancy scale [15] and classified according to current WHO criteria [2]. Malignancy grade was dichotomised between low-grade (grades I and II) and high-grade (grades III and IV) tumours [2,15]. Duration of symptoms was defined as the interval in months between first symptoms and time of biopsy. Tumour size was measured at the maximum length of the tumour in cm, either radiography or surgery/histology. We defined metastasis that evident within six weeks of primary diagnosis as primary metastatic disease [10]. Information regarding development of metastasis and/or local recurrence during follow-up, was based on radiographic images, biopsy or fine needle aspiration cytology in most cases [10]. Date and cause of death was primarily retrieved from the Cause of Death Registry (CDR).

2.3. Treatment variables

Surgery. Surgical treatment was classified between amputation, surgical excision and stabilizing osteosynthesis. The latter was a treatment option in a few cases due to high age and/or disseminated disease at time of diagnosis. Best local margins were evaluated as free or positive. The former implied surgical removal of the primary tumour with wide or marginal margins as described by Enneking et al. [16] while an intralesional margin [16] and/or residual macroscopic tumour were categorized as positive margins. We have regarded marginal margin as "adequate" taking into consideration that this is a nation-wide cohort with patients treated at several institutions and over a long time-frame, despite this is not the "gold standard" in sarcoma surgery. Our goal was to rule out patients with no surgery and/or clearly positive histological margins or remaining macroscopic tumour tissue left behind. Patients with metastatic disease at the time of diagnosis must have achieved complete surgical remission with free margins for both their primary tumour and metastasis in order to be classified as having received adequate surgery.

Chemotherapy. Patients received chemotherapy either at primary diagnosis and/or due to metastasis or local recurrence during follow-up. Most patients were treated according to the CYVADIC [17] regime or seven other consecutive chemotherapy protocols running during the study period; i.e. SSG II [18], SSG VIII [19], SSG XIV [20], ISG/SSG I [21], Euroboss I [22] or EURAMOS-I [23,24]. Patients not treated according to the protocols were considered for individualized chemotherapy, adjusted for age and toxicity. In the current study, it was neither possible to report cumulative doses of chemotherapy nor to study any impact dose-intensity might have had on outcome, as previously reported for osteosarcoma [12].

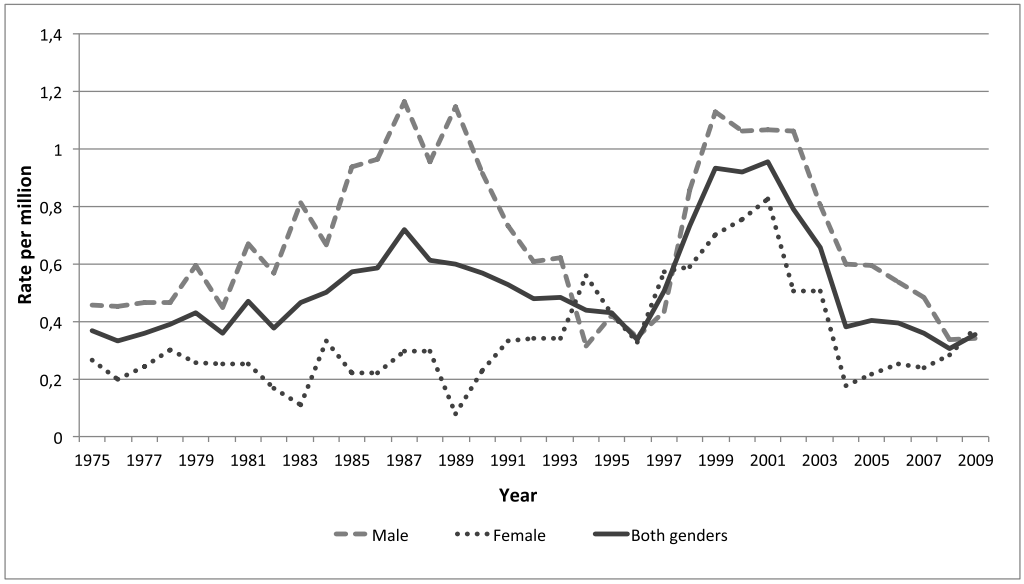
Radiotherapy. A curative treatment intent was defined as fractionated radiotherapy or brachytherapy following surgery, for either the treatment of a primary tumour or a local recurrence, otherwise considered as palliative treatment.

2.4. Statistical analyses

The incidence calculations were based on WHO-age standard incidence rate per million per year, and the results were presented as five-years moving average. Chi square analyses (χ^2) or Fisher´s exact tests (F) were used to compare unrelated samples when appropriate. Survival analyses using Kaplan–Meier estimates, log-rank test and Cox regression were used to analyse overall survival and sarcoma specific survival (SSS). To identify the interactions between different prognostic factors, both univariate and multivariate Cox regression were applied.

Overall survival was calculated from date of diagnosis until death from any cause, while sarcoma specific death or treatment-related death was the endpoint of SSS. The endpoint for all follow-up in this study was set to January 2018 using updated registries, to prevent bias due to non-identical follow up of patients with few or frequent appointments. The mean and median follow up time for survivors were 19 and 18 years, respectively, range 8–34 years. All clinical follow-up data were updated as close to the closing date as possible.

Statistically significant prognostic variables in univariate analysis were included into multivariate backward Cox-regression analyses. The Cox proportion hazard assumption was evaluated using Kaplan–Meier plots. The statistical analyses were conducted using SPSS version 21 (SPSS Inc., Chicago, IL) and Stata version 13.1 (Stata corporation, College Station, TX).



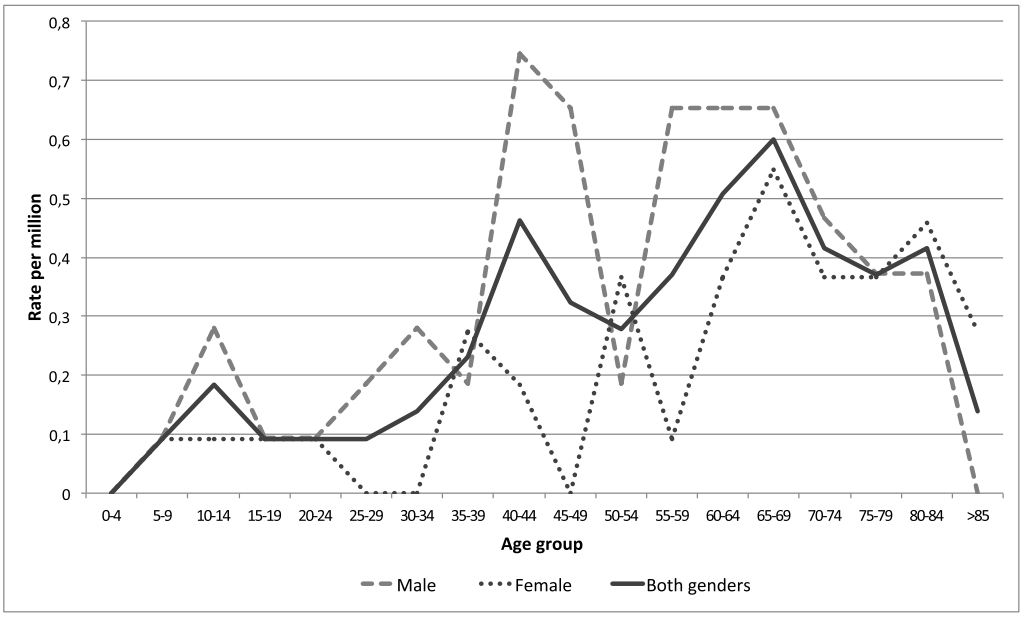


Fig. 1. Five-year moving average of age-standardised incidence rate of spindle cell non-osteogenic bone sarcomas (males, females and both genders) in Norway, 1975–2009 (A). Age-specific incidence rates of spindle cell non-osteogenic bone sarcomas (males, females and both genders), 1975–2009 (B).

2.5. Ethical approval

The Regional Ethical Committee was informed, although the study did not require a formal ethical approval since the data registration was in line with the legitimate mandate of the NCR.

3. Results

3.1. Incidence

The average incidence rate for SCS in both genders was slightly below 0.6 per million for the period 1975–2009. The male to female ratio was 1.6 for all patients; 1.9 for age under 40 years and 1.5 for elderly patients. Age standardized incidence rate fluctuated within a range of about 0.3 to 1.2 per million over the period in males, and about 0.1 to 0.8 per million in females with no clear time-trends (Fig. 1(a)). A dominant peak of SCS among elderly patients was observed (Fig. 1(b)). Mean and median age was 56 and 60 years for all patients, respectively (range 9–92 years).

3.2. Malignancy grade

The present cohort comprises eight cases of low-grade SCS (Table 1), were two of these, both FS, underwent subsequent transformation from low to high-grade SCS during follow-up. Only one of these eight patients is still a longtime survivor. Three patients died of SCS due to metastatic disease, including one in primary metastatic setting (range 2.6–6.1 years), while another three patients died of other diseases, i.e. one for gynecological cancer and two due to acute heart disease. Lastly, one patient died of a low-grade FS in the skull one year after primary diagnosis.

3.3. Secondary sarcoma

Nearly one fifth of all patients in the present cohort (19 cases) had a predisposing factor for SCS (Table 1). 14 cases were classified as

Table 2
Distribution of spindle cell non-osteogenic bone sarcoma according to primary site of disease.

	All patients (%)	UPS (%)	FS (%)	LMS (%)
Mandible/maxilla	6 (6)	2 (2)	4 (4)	
Skull/facial bone	4 (4)	3 (3)	1 (1)	
Costa/scapula	2 (2)	1 (1)	1 (1)	
Humerus	6 (6)	4 (4)	2 (2)	
Radius and handbound	2 (2)	1 (1)	1 (1)	
Columna vertebralis	5 (5)		1 (1)	4 (4)
Pelvis, sacrum	24 (23)	14 (13)	6 (6)	4 (4)
Femur	37 (36)	28 (27)	7 (7)	2 (2)
Fibula	4 (3)	1 (1)	2 (1)	1 (1)
Tibia	13 (13)	11 (11)		2 (2)
Origo incerta	1 (1)			1 (1)

secondary sarcoma due to previous radiotherapy, including three cases with previous diagnosis of retinoblastoma. Another three cases were arising from giant cell bone tumour and one from previous fibrous dysplasia. In one case, we just had an anamnestic indication of a familiar predisposition for SCS.

3.4. Clinicopathological data

The UPS group comprised 65 patients, making it the largest subgroup in the present cohort (Table 1). Of these cases, 45 (69%) had tumours located in long bones while the remaining 20 cases had tumours in the axial skeleton (Table 2). In the FS group the axial to appendicular ratio, was 1.1 (25 cases) and 1.8 among the LMS patients (14 cases), respectively (Tables 1 and 2). The axial tumour rate was independent of age in the present cohort (Fig. 2). We also observed an equal axial to appendicular ratio among the eight patients with low-grade tumours at diagnosis (Table 1).

In the present cohort 28 patients (29%) had metastases at time of diagnosis (Table 1), most commonly in the lungs only (29%), otherwise diagnosed in bone only (25%), in lungs and bone (14%) or other combinations. We identified no significant difference in the percentage of patients with primary metastatic disease, neither in relation to SCS in the axial versus appendicular skeleton ($p = 0.366$, χ^2) nor to age ($p = 0.258$, F). Nevertheless, 89% of all patients with primary metastatic disease (25 cases) were > 40 years at primary diagnosis.

Mean tumour size was nine cm in the entire cohort, approximately the same for the three subgroups of SCS (Table 1). Furthermore, the average symptom length before biopsy was approximately six months for all SCS, but the FS group had a longer time from symptoms to diagnoses (nine months in average) compared to the other two subgroups (Table 1).

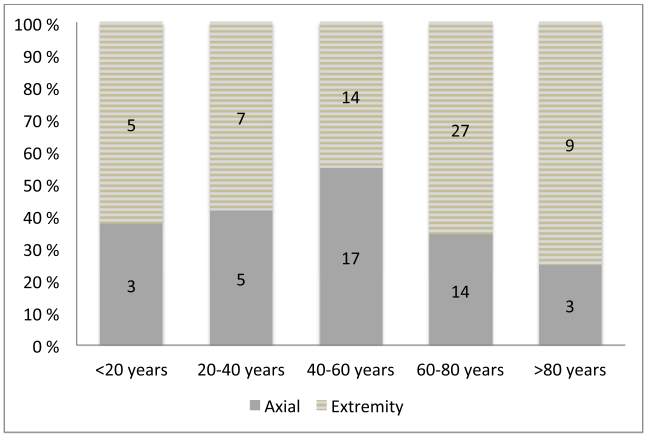


Fig. 2. Distribution of age and primary site of non-osteogenic spindle cell bone sarcoma, 1975–2009.

More than one fifth of the patients in the present cohort (23 cases) had pathologic fracture at time of diagnoses (Table 1), relatively equally distributed between the three subgroups of SCS (Table 1). Not surprisingly, nearly all these cases (78%) were in a weight-bearing extremity (17 cases in femur and one in fibula, respectively) in addition to two cases in columna/pelvis (extremity versus axial tumour localisation; $p = 0.003$, F). We neither identified increased risk of a pathologic fracture related to age </> 40 years ($p = 0.344$, χ^2), tumour size </> 9 cm ($p = 0.772$, χ^2), nor to gender ($p = 0.370$, χ^2).

3.5. Metastatic relapse or local recurrence during follow-up

Among patients without primary metastatic disease, 13 of the axial SCS (43%) and 19 with extremity SCS (46%) developed metastases from SCS during follow-up ($p = 0.826$, χ^2). Approximately three quarters developed lung metastases (first metastatic relapse). In addition, six patients developed metastases from another primary malignancy during follow up; one oesophageal cancer, two melanomas, one gynaecological cancer, one prostate cancer in addition to one with acute leukaemia. Another 11 patients died of SCS according to the CDR but without proven metastases at time of death (median 1.4 years, range 0.2–4.2 years). Unfortunately, autopsies were not performed in these latter cases. Among patients with axial SCS and no primary metastatic disease, eight patients (27%) experienced local relapse during follow-up compared to four patients (10%) among extremity SCS ($p = 0.105$, F). The median time to first metastatic event, or local recurrence were 1.3 years (range 0.2–10.7 years) and two years (range 0.7–5.1 years) from diagnosis, respectively.

3.6. Treatment

Table 3 outlines the extent of treatment administered to SCS patients and is further presented below.

Surgery. 73 patients underwent at least one operation at primary diagnosis, and 47 patients received adequate surgical treatment

Table 3
Summary of treatment for spindle cell non-osteogenic bone sarcoma.

	All patients[a] (%)	Local only[b] (%)	Local and systemic primary treatment[c] (%)
Surgery	76	28	26
At primary diagnosis			
Surgical procedure[d]	73	27	26
Amputation	31 (42)	14 (52)	8 (31)
Excision	35 (48)	10 (37)	18 (69)
Osteosynthesis	7 (10)	3 (11)	
Surgical margins[d]	67	26	22
Free margin	47 (70)	17 (65)	20 (91)
Positive margin	20 (30)	9 (35)	2 (9)
Later relapses/metastases	15	4	3
Radiotherapy	52	17	11
Curative treatment intention[e]	11	1	8
Chemotherapy	59		26
At primary diagnosis	44		26
Formal inclusion in trial	5		4

[a] The difference between the summarized number from each subgroup in the third and fourth column and all patients in column two equals the other combination of treatment during primary treatment or follow-up.
[b] Cohort of patients not receiving chemotherapy during primary treatment or follow-up, including six cases of low-grade SCS at primary diagnosis.
[c] Chemotherapy and surgery as primary treatment for high-grade SCS.
[d] Missing cases equals the difference between surgical procedures and surgical margins in column two to four.
[e] Fractionated radiotherapy or brachytherapy following marginal or intralesional surgery, for either the treatment of primary tumour or a local recurrence.

(Table 3). Interestingly, 28 patients received only local treatment without additional chemotherapy during primary treatment or follow-up (Table 3), and six of these cases had low-grade SCS at time of diagnosis. Hence, they were treated according to standard guidelines [1], while the remaining two cases of low-grade SCS (Table 1) underwent no operations. Another six of these 28 patients received only palliative local treatment at diagnosis; including three cases with osteosynthesis to stabilize a pathologic femur fracture.

Chemotherapy. 44 patients received chemotherapy with curative treatment intention at primary diagnosis in line with various consecutive trials (Table 3); i.e. SSG II (four cases), SSG VIII (four cases), SSG XIV (six cases), ISG/SSG I (two cases), Euroboss I (five cases), EURAMOS-I (one case). The CYVADIC combination (12 cases) or individualized chemotherapy regimens were given to the remaining cases. Only, five patients were formally included in the clinical trials, i.e. three in Euroboss I, one in SSG VIII and one in SSG XIV.

Just one low-grade SCS patient received chemotherapy at primary diagnosis due to primary metastatic disease. However, another two patients received chemotherapy at time of transformation from low to high-grade SCS during follow-up.

Adequate primary treatment. About a quarter of all high-grade SCS (26 cases) received both chemotherapy and surgery as part of primary treatment (Table 3), all treated between 1980 and 2009. Information regarding surgical margins after resection of primary tumour was available in 22 of these cases (Table 3). Both patients that were left with positive surgical margins after resection of their primary tumour developed recurrent disease during follow up and succumbed to their disease, i.e. 1.4 and 6.7 years after their diagnosis, respectively.

Among the remaining high-grade SCS (70 cases) 18 patients received surgery and chemotherapy during primary treatment or follow-up. However, half of these patients received only insufficient surgery at time of diagnosis, while the other half first received chemotherapy at time of metastatic relapse or local recurrence. The remaining reasons for inadequacy during primary treatment or follow-up were lack of surgery (13 cases), lack of chemotherapy (24 cases) or lack of both surgery and chemotherapy (11 cases).

Radiotherapy. Eleven patients received fractionated postoperative radiotherapy with curative intent as part of their multimodal primary treatment, and in ten of these cases neither metastatic disease nor local relapse were confirmed (Table 3). Only three of these patients are still longtime survivors, including a girl diagnosed with secondary UPS at an age of eight years due to previous radiotherapy for bilateral retinoblastoma. Five patients died of local and/or metastatic relapses of SCS (mean 3 years, range 1–6.7 years) while another three patients died of other diseases, i.e. one for oesophageal cancer, one for acute leukemia and another due to a heart attack, respectively.

3.7. Cause of death

A total of 69 died due to sarcoma or treatment-related death according to CDR, i.e. 78% of all deaths in the cohort updated by April 2018. However, when other available clinical information was scrutinized we found that additional six died of sarcoma while another three patients were incorrectly reported to have died of SCS while they actually died of a second primary malignancy. Hence, 72 died of SCS, i.e. 81% of all deaths, and this number was used in the calculations regarding SSS.

3.8. Survival analyses

We found a dismal longtime SSS for SCS as presented in Fig. 3(a). Five year SSS and overall survival for SCS was 37% (95%, CI = 27–46%) and 32% (95%, CI = 23–41%), respectively. Table 4 presents the results of univariate analyses as five year SSS and overall survival according to different characteristics of SCS. Patients with FS had inferior survival compared to the other subgroups of SCS (Fig. 3(b),

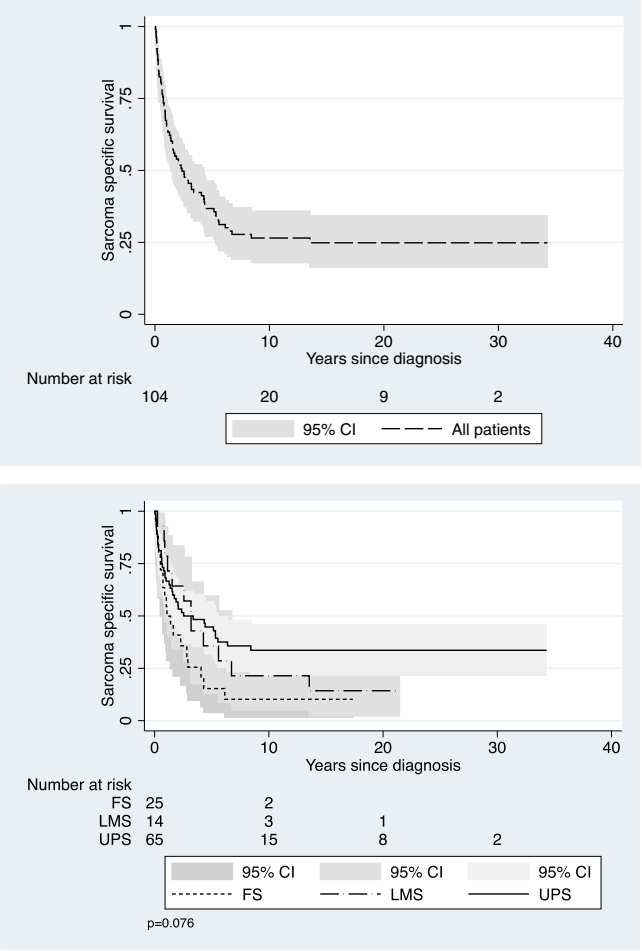


Fig. 3. Sarcoma-specific survival for all spindle cell non-osteogenic bone sarcomas (a) and dependent of histological subtype (b), 1975–2009.

Table 4). High age, primary metastatic disease and axial primary tumour all predicted poor outcome (Table 4 and Fig. 4(a)–(c)). Pathologic fracture and large tumour size were also associated with poor prognosis (Table 4).

We found no trend to improvement in survival since the 1970s in the present cohort of SCS patients (Table 4). As expected, patients who received both surgery and chemotherapy as primary treatment had significantly better survival than the remaining SCS patients (Tables 4 and 5). Twelve of the 15 survivors in the present cohort did receive both multi-agent chemotherapy and adequate surgery, either as primary treatment (10 cases) or in the metastatic setting (two cases). Further, one patient received adequate surgery for a low-grade SCS and two patients for high-grade SCS, respectively. It is known from the pre-chemotherapy era for OS, that up to 20% of all high-grade patients were cured by surgery and/or radiotherapy [25–27].

3.9. Prognostic factors

Multivariate analyses of the prognostic factors significant by univariate analysis in Table 4 are presented in Table 5. Primary metastatic disease was an adverse prognostic factor for survival while tumour size > 9 cm, age > 40 years, tumour in the axial skeleton, FS as subtype and pathologic fracture all resulted in inferior overall survival. As expected, patients who received adequate primary treatment significantly had best survival.

Table 4
Univariate Kaplan–Meier and Cox regression analyses of five-year sarcoma specific and overall survival according to different characteristics of all spindle cell non-osteogenic bone sarcoma.

	Patients (%)	Sarcoma specific survival			Overall survival		
		5 years in % (95% CI[a] in %)	RR[b] (95% CI[a])	*P*[c]	5 years in % (95% CI[a] in %)	RR[b] (95% CI[a])	*P*[c]
Gender				0.267			0.323
Female	40 (38)	*43 (27–58)*	*1*		*28 (18–39)*	*1*	
Male	64 (62)	*33 (21–45)*	*1.3 (0.8–2.1)*		*38 (23–52)*	*1.2 (0.8–1.9)*	
Axial versus extremity				0.066			0.039
Extremity	62 (60)	*44 (32–57)*	*1*		*40 (28–52)*	*1*	
Axial	42 (40)	*25 (12–39)*	*1.5 (1.0–2.5)*		*19 (9–32)*	*1.6 (1.0–2.4)*	
Age				0.011			0.001
≤ 40 years	20 (19)	65 (40–82)	1		65 (39–82)	1	
> 40 years	84 (81)	29 (20–40)	2.3 (1.2–4.3)		24 (15–33)	2.8 (1.5–5.1)	
Primary metastatic disease[e]				<0.001			<0.001
No	69 (71)	47 (35–59)	1		41 (30–53)	1	
Yes	28 (29)	11 (3–27)	4.7 (2.9–7.8)		11 (3–30)	3.8 (2.4–6.1)	
Malignancy grade				0.131			0.333
Low-grade	8 (8)	60 (20–85)	1		50 (15–76)	1	
High-grade	96 (92)	35 (25–45)	2.2 (0.8–6.0)		30 (21–40)	1.5 (0.7–3.2)	
Histological subtype				0.076			0.037
UPS	65	45 (32–57)	0.8 (0.4–1.6)		39 (27–50)	1.0 (0.5–1.9)	
FS	25	15 (4–38)	1.5 (0.7–3.1)		12 (3–28)	1.9 (0.9–3.8)	
LMS	14	36 (13–59)	1		36 (13–59)	1	
Tumour size[e]				0.012			0.013
≤ 9 cm	38 (58)	59 (41–73)	1		53 (36–67)	1	
> 9 cm	27 (62)	32 (15–50)	2.2 (1.2–4.1)		26 (36–67)	2.0 (1.1–3.5)	
Duration of symptoms[e]				0.868			0.279
≤ 6 months	53 (60)	41 (27–54)	1		34 (22–47)	1	
> 6 months	35 (40)	30 (16–46)	1.0 (0.6–1.7)		29 (15–44)	1.3 (0.8–2.1)	
Pathologic fracture				0.001			0.011
No	81 (78)	42 (31–53)	1		36 (26–46)	1	
Yes	23 (22)	19 (6–38)	2.3 (1.4–3.8)		17 (6–35)	1.9 (1.1–3.0)	
Predisposing factors				0.586			0.805
No	85 (82)	37 (27–47)	1		33 (23–43)	1	
Yes	19 (18)	35 (13–57)	1.2 (0.6–2.2)		26 (10–47)	1.1 (0.6–1.8)	
Years of diagnosis				0.321			0.592
1975–1979	12 (11)	29 (7–56)	1.2 (0.5–2.7)		25 (6–51)	1.4 (0.7–2.7)	
1980–1989	28 (27)	26 (12–43)	1.6 (0.9–2.8)		25 (11–42)	1.3 (0.7–2.3)	
1990–1999	30 (29)	46 (27–63)	1 (0.9–2.8)		37 (20–53)	1 (0.6–1.7)	
2000–2009	34 (33)	41 (24–57)	1		35 (20–51)	1	
Adequate primary treatment[d,e]				<0.001			<0.001
Yes[f]	32 (32)	62 (42–76)	1		53 (35–69)	1	
No	68 (68)	26 (16–40)	2.9 (1.6–5.2)		24 (14–34)	2.5 (1.5–4.1)	
Formal inclusion in trial				0.767			0.426
Yes	5 (5)	40 (5–75)	1		40 (5–75)	1	
No	99 (95)	37 (27–46)	1.2 (0.4–3.8)		31 (22–41)	1.6 (0.5–5.0)	

[a] Confidence interval.
[b] relative risk.
[c] Log rank.
[d] Surgery towards low-grade spindle cell sarcoma (6 cases) and surgery and chemotherapy towards high-grade spindle cell sarcoma (26 cases).
[e] Missing values equals the difference between the summarized number from each subgroup in the second column and the total number of patients in the study.

4. Discussion

The patient material here studied is based on an unselected cohort comprising all Norwegian SCS patients within a time frame of 3–4 decades. To our knowledge, no previous nationwide study has addressed clinical epidemiology and treatment result of the SCS entity.

The mean annual age-standard incidence of SCS amounted to slightly below 0.6 per million with no clear time trends, that is about one fifth of all skeletal OS cases in Norway during 1975 and 2009 [10]. Males are more frequently affected than females in line with previous reports [4,28,29] although another study has reported the opposite [30]. We confirm that SCS mainly affect an older age group than OS [2,4,28,30]. Age > 40 years at diagnosis was a significant adverse factor for overall survival in the present cohort (Table 5).

UPS was the largest subgroup in the present cohort and this entity predominantly affects the long bones of the lower extremities (Table 2) in line with the literature [2,4,29,31]. In contrast, the anatomical distribution of FS and LMS (Table 2) both showed increased axial to appendicular ratio as compared to previous published studies where distal femur was reported to be the most common site [2,28,30]. This discrepancy may be due to chance, partly as a result of the relatively small sample size. It is well established that axial localisation results in worse outcome than primary disease arising in the appendicular skeleton for OS [8] also confirmed in the present study for overall survival (Table 5).

SCS is typically a group of high-grade malignancies with high risk of early dissemination [4,32]. More than one quarter had primary metastatic disease in the present study, slightly higher than reported in a previous review article for OS [8]. Metastatic disease at presentation was a negative prognostic factor for survival (Table 5, Fig. 4(a)), in line with the literature [4,30,33]. A large part of the cases experienced local recurrences and/or distant metastases during follow-up, as previously reported [4,30,34].

Previous therapeutic radiation is well known to be a predisposing factor to development of sarcoma [35,36], as confirmed in the present cohort. We also confirm that SCS might develop secondary to other pre-

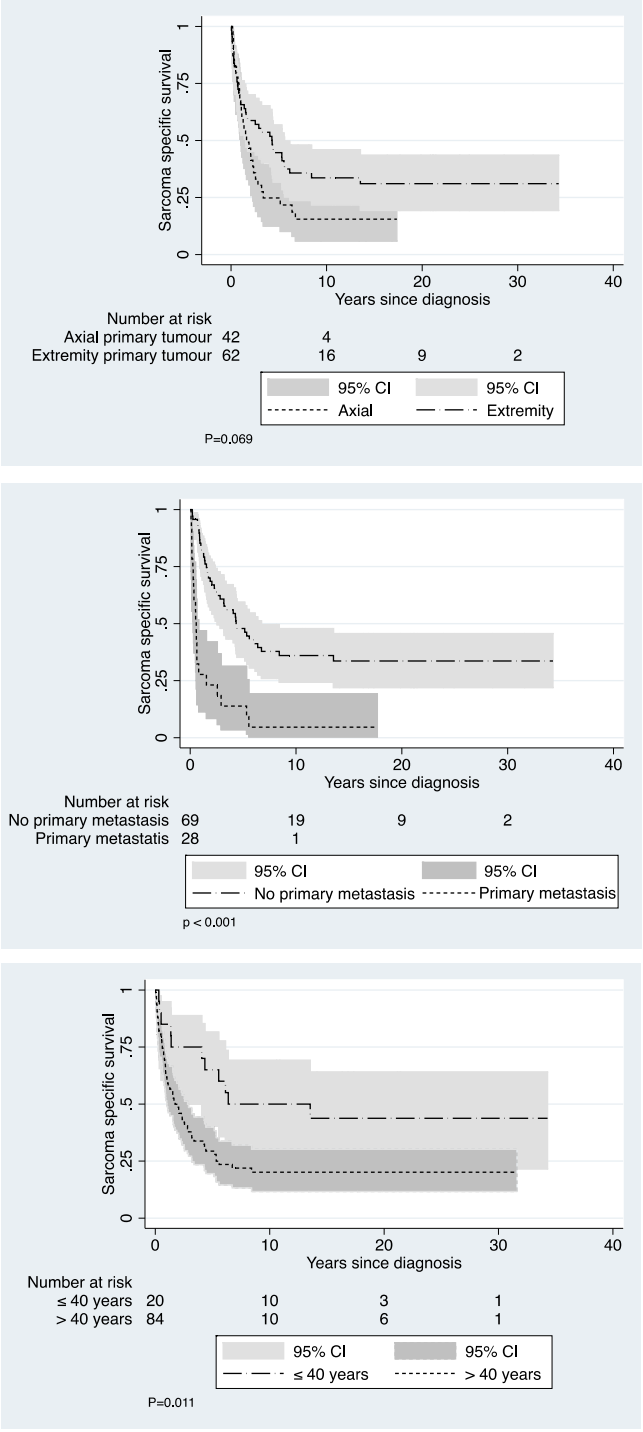


Fig. 4. Sarcoma specific survival of spindle cell non-osteogenic bone sarcoma (SCS) 1975–2009 (a) patients with and without metastasis at diagnosis, (b) extremity versus non-extremity SCS and (c) patients below and above 40 years of age at time of diagnosis.

existing bone conditions [2,31]. Interestingly, the presence of a pathologic fracture, typically in a weight-bearing extremity, was significantly higher in the present cohort as compared with the available literature for SCS [4,31]. Osteoporosis may be one contributing factor in this regard since the present cohort is dominated by elderly patients (Fig. 2). Pathologic fracture was a poor prognostic factor for survivor (Table 4, 5) in line with a previous report for OS [37]. Median tumour size was slightly smaller than in a corresponding report regarding all Norwegian high-grade OS patients during the past three to four decades

Table 5
Multivariate Cox-regression analysis of prognostic factors and treatment-related variables for sarcoma specific survival and overall survival. Spindle cell non-osteogenic bone sarcoma.

Variables[a]	Sarcoma specific survival		Overall survival	
	RR[b] (95% CI[c])	*P*	RR[b] (95% CI[c])	*P*
Adequate primary treatment				
Yes	1		1	
No	2.2 (1.0–4.8)	0.050	3.4 (1.7–7.1)	0.001
Age > 40 years	2.5 (1.0–6.6)	0.063	4.4 (2.0–9.4)	<0.001
Primary metastatic disease	3.6 (1.7–7.8)	0.001	5.1 (2.2–11.6)	<0.001
Tumour size > 9 cm	1.8 (0.9–3.5)	0.114	2.8 (1.4–5–7)	0.003
Axial primary tumour			4.4 (2.0–9.4)	<0.001
Pathological fracture	2.1 (0.9–4.6)	0.069	2.6 (1.2–5.8)	0.021
Histological subtype				0.003
UPS			1.2 (0.4–3.2)	0.756
FS			5.1 (1.6–16.7)	0.006

[a] Reference values in line with Table 4.
[b] Relative risk.
[c] Confidence interval.

[12]. Tumour size above median value of 9 cm was a negative prognostic factor in our study (Tables 4 and 5).

We found a dismal longtime survival among SCS (Fig. 3(a), Table 4) compared to a corresponding OS population for Norway [10] and with the poorest result among the FS subgroup (Fig. 3(b), Table 4). A previous report from the Mayo Clinic [31] has also documented a poor survival result for UPS, although later studies have shown similar survival for UPS and OS [7,34]. The two bone sarcoma entities have similar prognoses when treated with neoadjuvant chemotherapy regimens based on high-dose methotrexate, cisplatin, doxorubicin and ifosfamide in addition by wide excision of all malignant foci [7,34]. Adequate primary treatment, regarding both surgery and chemotherapy, had a positive prognostic impact on survival in the present study (Tables 4 and 5).

As mentioned above, several negative prognostic factors for survival were identified (Tables 4 and 5). Nevertheless, the poor prognoses of SCS in the present cohort are, in our opinion, mainly due to insufficient primary treatment in far too many cases (Tabled 3 and 4). The treatment provided may have been influenced by high age, poor general condition and/or co-morbidity at time of diagnosis for several SCS patients in the present cohort. Further, we have probably not been sufficiently alert to the role of (neo)adjuvant chemotherapy for SCS during this time period, as several patients in the present cohort first received chemotherapy at time of metastatic relapse/local recurrence. About three quarter of all patients in the present study did not receive either complete surgery of all (macroscopic) malignant foci at primary diagnosis and/or poly-drug chemotherapy based on standard guidelines [1,8].

Twelve of the 15 long-term survivors in the present cohort received both adequate chemotherapy and surgery. The dismal outcome in the present study confirms that micrometastases are present in the majority of SCS patients at primary diagnosis like described for OS [26,38–40]. Therefore, the combined treatment of surgery and chemotherapy is essential to achieve optimal long-term survival of SCS.

Primary malignant bone tumours like SCS are rare, and over the years most previous studies were likely to be confounded with some tumours that at present could fall under other categories, due to strict and relatively new diagnostic criteria based on immunohistochemistry and molecular tests in selected cases [2,5,41]. Both FS and UPS are currently diagnoses of exclusion [2]. Small patient cohorts, partly due to strict diagnostic criteria, make it challenging to learn more about rare histologic subgroups like SCS, including clinicopathological characteristic but also prognosis related to different treatment approaches.

We appreciate that the data quality of the present study might have been better with a uniform and formal histological re-examination of all 702 cases in the gross study material analysed [10], including immunohistochemical analyses as well as a retrospective review of the radiographic images in relevant cases. Nevertheless, a significant disadvantage of such an approach is the lack of available tissue specimens or radiographic images available for re-examination. This might be an even larger problem in nationwide studies than in studies based on, for example, institutional series. In addition, immunohistochemical analyses are also vulnerable to potential damage of tissue blocs due to e.g. the decalcification. Furthermore, most cases in the present cohort were already examined by at least one sarcoma pathologist at a University Hospital at time of diagnosis. Hence, we believe the potential disadvantage will exceed the potential gain of such an approach and that our key variables are valid in order to expand our knowledge regarding these rare SCS entities. Lastly, information on histologic response to preoperative chemotherapy [33,34,42–44] might have affected the prognostic factors in Table 5. However, the multidrug combinations have changed considerably during this time-period [26].

5. Conclusion

To our knowledge, this is the first study addressing clinical epidemiology and treatment outcome of SCS in a nationwide setting. We confirm SCS arising in the skeleton as mainly a high-grade malignancy among elderly patients. The poor prognoses of SCS in this report are in our opinion, mainly due to insufficient primary treatment in about three quarter of all high-grade patients. Hence, the combined treatment of surgery and chemotherapy is essential to achieve optimal long-term survival of SCS. The unfavourable prognosis, due to frequent metastases or local recurrences, may also relate to decreased tolerance for chemotherapy, especially among elderly patients.

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Disclosure

The NCR has approved the use of these data for international publishing.

Disclaimer

The authors alone are responsible for the content and writing of the paper.

References

[1] P.C. Hogendoorn, N. Athanasou, S. Bielack, E. De Alava, A.P. Dei Tos, S. Ferrari, et al., Bone sarcomas: ESMO clinical practice guidelines for diagnosis, treatment and follow-up, Ann. Oncol. 21 (Suppl 5) (2010) v204–v213.
[2] C.D.M. Fletcher, J.A. Bridge, P.C.W. Hogendoorn, F. Mertens, WHO Classification of Tumours of Soft Tissue and Bone, fourth ed., International Agency for Research on Cancer, Lyon, 2013.
[3] I. Matushansky, E. Charytonowicz, J. Mills, S. Siddiqi, T. Hricik, C. Cordon-Cardo, MFH classification: differentiating undifferentiated pleomorphic sarcoma in the 21st century, Exp. Rev. Anticancer Therapy 9 (8) (2009) 1135–1144.
[4] S.S. Bielack, A. Schroeders, N. Fuchs, G. Bacci, H.C. Bauer, S. Mapeli, et al., Malignant fibrous histiocytoma of bone: a retrospective EMSOS study of 125 cases. European Musculo-Skeletal Oncology Society, Acta Orthop. Scand. 70 (4) (1999) 353–360.
[5] C.M. Hattinger, M. Tarkkanen, S. Benini, M. Pasello, G. Stoico, P. Bacchini, et al., Genetic analysis of fibrosarcoma of bone, a rare tumour entity closely related to osteosarcoma and malignant fibrous histiocytoma of bone, Eur. J. Cell Biol. 83 (9) (2004) 483–491.
[6] D. Carrle, S.S. Bielack, Current strategies of chemotherapy in osteosarcoma, Int. Orthop. 30 (6) (2006) 445–451.
[7] D.G. Jeon, W.S. Song, C.B. Kong, J.R. Kim, S.Y. Lee, MFH of bone and osteosarcoma show similar survival and chemosensitivity, Clin. Orthop. Rel. Res. 469 (2) (2011) 584–590.
[8] A. Luetke, P.A. Meyers, I. Lewis, H. Juergens, Osteosarcoma treatment – where do we stand? A state of the art review, Cancer Treat. Rev. 40 (4) (2014) 523–532.
[9] C.M. Hattinger, M. Fanelli, E. Tavanti, S. Vella, S. Ferrari, P. Picci, et al., Advances in emerging drugs for osteosarcoma, Exp. Opin. Emerging Drugs 20 (3) (2015) 495–514.
[10] K. Berner, T.B. Johannesen, A. Berner, H.K. Haugland, B. Bjerkehagen, P.J. Bohler, et al., Time-trends on incidence and survival in a nationwide and unselected cohort of patients with skeletal osteosarcoma, Acta Oncol. 54 (1) (2015) 25–33.
[11] S. Tingulstad, T. Halvorsen, J. Norstein, B. Hagen, F.E. Skjeldestad, Completeness and accuracy of registration of ovarian cancer in the cancer registry of Norway, Int. J. Cancer 98 (6) (2002) 907–911.
[12] K. Berner, K.S. Hall, O.R. Monge, H. Weedon-Fekjaer, O. Zaikova, O.S. Bruland, Prognostic factors and treatment results of high-grade osteosarcoma in Norway: a scope beyond the "classical" patient, Sarcoma 2015 (2015) 516843.
[13] K. Berner, T.B. Johannesen, O.S. Bruland, Clinical epidemiology of low-grade and dedifferentiated osteosarcoma in Norway during 1975 and 2009, Sarcoma 2015 (2015) 917679.
[14] K. Berner, B. Bjerkehagen, O.S. Bruland, A. Berner, Extraskeletal osteosarcoma in Norway, between 1975 and 2009, and a brief review of the literature, Anticancer Res. 35 (4) (2015) 2129–2140.
[15] B. Bjerkehagen, J. Wejde, M. Hansson, H. Domanski, T. Bohling, SSG pathology review experiences and histological grading of malignancy in sarcomas. Acta Orthop. 80 (2009) 31–36.
[16] W.F. Enneking, S.S. Spanier, M.A. Goodman, A system for the surgical staging of musculoskeletal sarcoma, Clin. Orthop. Rel. Res. (153) (1980) 106–120.
[17] V. Bramwell, J. Rouesse, W. Steward, A. Santoro, H. Schraffordt-Koops, J. Buesa, et al., Adjuvant CYVADIC chemotherapy for adult soft tissue sarcoma–reduced local recurrence but no improvement in survival: a study of the European Organization for Research and Treatment of Cancer Soft Tissue and Bone Sarcoma Group, J. Clin. Oncol. 12 (6) (1994) 1137–1149.
[18] G. Saeter, T.A. Alvegard, I. Elomaa, A.E. Stenwig, T. Holmstrom, O.P. Solheim, Treatment of osteosarcoma of the extremities with the T-10 protocol, with emphasis on the effects of preoperative chemotherapy with single-agent high-dose methotrexate: a Scandinavian Sarcoma Group study, J. Clin. Oncol. 9 (10) (1991) 1766–1775.
[19] S. Smeland, C. Muller, T.A. Alvegard, T. Wiklund, T. Wiebe, O. Bjork, et al., Scandinavian Sarcoma Group Osteosarcoma Study SSG VIII: prognostic factors for outcome and the role of replacement salvage chemotherapy for poor histological responders, Eur. J. Cancer 39 (4) (2003) 488–494.
[20] S. Smeland, O.S. Bruland, L. Hjorth, O. Brosjo, B. Bjerkehagen, G. Osterlundh, et al., Results of the Scandinavian Sarcoma Group XIV protocol for classical osteosarcoma: 63 patients with a minimum follow-up of 4 years, Acta Orthop. 82 (2) (2011) 211–216.
[21] S. Ferrari, S. Smeland, M. Mercuri, F. Bertoni, A. Longhi, P. Ruggieri, et al., Neoadjuvant chemotherapy with high-dose Ifosfamide, high-dose methotrexate, cisplatin, and doxorubicin for patients with localized osteosarcoma of the extremity: a joint study by the Italian and Scandinavian Sarcoma Groups, J. Clin. Oncol. 23 (34) (2005) 8845–8852.
[22] S. Ferrari, S.S. Bielack, S. Smeland, A. Longhi, G. Egerer, K. Sundby Hall, et al., EURO-B.O.S.S.: a European study on chemotherapy in bone-sarcoma patients aged over 40: outcome in primary high-grade osteosarcoma, Tumori 104 (1) (2018) 30–36.
[23] S.S. Bielack, S. Smeland, J.S. Whelan, N. Marina, G. Jovic, J.M. Hook, et al., Methotrexate, doxorubicin, and cisplatin (MAP) plus maintenance PEGylated interferon Alfa-2b versus MAP alone in patients with resectable high-grade osteosarcoma and good histologic response to preoperative MAP: first results of the EURAMOS-1 good response randomized controlled trial, J. Clin. Oncol. 33 (20) (2015) 2279–2287.
[24] N.M. Marina, S. Smeland, S.S. Bielack, M. Bernstein, G. Jovic, M.D. Krailo, et al., Comparison of MAPIE versus MAP in patients with a poor response to preoperative chemotherapy for newly diagnosed high-grade osteosarcoma (EURAMOS-1): an open-label, international, randomised controlled trial, Lancet Oncol. 17 (10) (2016) 1396–1408.
[25] M.S. Weinfeld, H.R. Dudley Jr., Osteogenic sarcoma. A follow-up study of the ninety-four cases observed at the Massachusetts General Hospital from 1920 to 1960, J. Bone Joint Surg. Am. 44-a (1962) 269–276.
[26] O.S. Bruland, A. Pihl, On the current management of osteosarcoma. A critical evaluation and a proposal for a modified treatment strategy, Eur. J. Cancer 33 (11) (1997) 1725–1731.
[27] S. Harvei, O. Solheim, The prognosis in osteosarcoma: Norwegian National Data, Cancer 48 (8) (1981) 1719–1723.
[28] A.G. Huvos, N.L. Higinbotham, Primary fibrosarcoma of bone. A clinicopathologic study of 130 patients, Cancer 35 (3) (1975) 837–847.
[29] E.F. McCarthy, T. Matsuno, H.D. Dorfman, Malignant fibrous histiocytoma of bone: a study of 35 cases, Hum. Pathol 10 (1) (1979) 57–70.
[30] P. Brewer, V. Sumathi, R.J. Grimer, S.R. Carter, R.M. Tillman, A. Abudu, et al., Primary leiomyosarcoma of bone: analysis of prognosis, Sarcoma 2012 (2012) 636849.
[31] J. Nishida, F.H. Sim, D.E. Wenger, K.K. Unni, Malignant fibrous histiocytoma of bone. A clinicopathologic study of 81 patients, Cancer 79 (3) (1997) 482–493.
[32] L.A. Doyle, Sarcoma classification: an update based on the 2013 World Health Organization classification of tumors of soft tissue and bone, Cancer 120 (12) (2014) 1763–1774.
[33] G. Bacci, P. Picci, M. Mercuri, F. Bertoni, S. Ferrari, Neoadjuvant chemotherapy for

high grade malignant fibrous histiocytoma of bone, Clin. Orthop. Rel. Res. (346) (1998) 178–189.
[34] P. Picci, G. Bacci, S. Ferrari, M. Mercuri, Neoadjuvant chemotherapy in malignant fibrous histiocytoma of bone and in osteosarcoma located in the extremities: analogies and differences between the two tumors, Ann. Oncol. 8 (11) (1997) 1107–1115.
[35] A.G. Huvos, H.Q. Woodard, W.G. Cahan, N.L. Higinbotham, F.W. Stewart, A. Butler, et al., Postradiation osteogenic sarcoma of bone and soft tissues. A clinicopathologic study of 66 patients, Cancer 55 (6) (1985) 1244–1255.
[36] B. Bjerkehagen, S. Smeland, L. Walberg, S. Skjeldal, K.S. Hall, J.M. Nesland, et al., Radiation-induced sarcoma: 25-year experience from the Norwegian Radium Hospital, Acta Oncol. 47 (8) (2008) 1475–1482.
[37] L. Sun, Y. Li, J. Zhang, H. Li, B. Li, Z. Ye, Prognostic value of pathologic fracture in patients with high grade localized osteosarcoma: a systemic review and meta-analysis of cohort studies, J. Orthop. Res. 33 (1) (2015) 131–139.
[38] R.C. Marcove, V. Mike, J.V. Hajek, A.G. Levin, R.V. Hutter, Osteogenic sarcoma under the age of twenty-one. A review of one hundred and forty-five operative cases, J. Bone Joint Surg. Am. 52 (3) (1970) 411–423.
[39] O.S. Bruland, H. Hoifodt, G. Saeter, S. Smeland, O. Fodstad, Hematogenous micrometastases in osteosarcoma patients, Clin. Cancer Res. 11 (13) (2005) 4666–4673.
[40] N. Jaffe, D. Traggis, J.R. Cassady, R.M. Filler, H. Watts, E. Frei, Multidisciplinary treatment for macrometastatic osteogenic sarcoma, Br. Med. J. 2 (6043) (1976) 1039–1041.
[41] F.L. Chang, A.L. Folpe, C.Y. Inwards, 25 primary fibrosarcoma of bone: a re-evaluation of cases seen at a single institution for the period 1913–2009. Mod. Pathol. 25 (Suppl 2) (2012) 9A (25, Supplement 2, 9A).
[42] G. Rosen, A. Nirenberg, Neoadjuvant chemotherapy for osteogenic sarcoma: a five year follow-up (T-10) and preliminary report of new studies (T-12), Progr. Clin. Biol. Res. 201 (1985) 39–51.
[43] S.S. Bielack, B. Kempf-Bielack, G. Delling, G.U. Exner, S. Flege, K. Helmke, et al., Prognostic factors in high-grade osteosarcoma of the extremities or trunk: an analysis of 1,702 patients treated on neoadjuvant cooperative osteosarcoma study group protocols, J. Clin. Oncol. 20 (3) (2002) 776–790.
[44] J.C. Friebele, J. Peck, X. Pan, M. Abdel-Rasoul, J.L. Mayerson, Osteosarcoma: a meta-analysis and review of the literature, Am. J. Orthop. 44 (12) (2015) 547–553.