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Bone sarcoma incidence in the Netherlands

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ABSTRACT

Aims: Chondrosarcoma, osteosarcoma and Ewing sarcoma form the majority of malignant primary tumours of bone. High-grade bone sarcomas require intensive treatment due to their rapid and invasive growth pattern and metastasising capabilities. This nationwide study covers overall incidence, treatment and survival patterns of bone sarcomas in a 15-year period (2000–2014) in the total population of the Netherlands.

Patients and methods: Data for this study were derived from the Netherlands Cancer Registry, which receives primary notification from the national pathology database. Classification and categorisation was based on the ICD-O-3 classification and the WHO classification 2013 applied according to our clinicopathological expertise. Overall incidence over the 15-year-period was calculated as a rate per 100,000 person-years (using the European Standardised Rate, ESR). Survival was analysed with Kaplan-Meier curves and Cox proportional hazards regression.

Results: Incidence for high-grade chondrosarcoma (n = 429) was estimated at 0.15 per 100,000 ESR, and 5-year overall survival at 65.9% (95% confidence interval (CI): 61.0%–70.4%). Incidence for high-grade central osteosarcoma (n = 605) was estimated at 0.25 per 100,000 ESR and 5-year survival at 53.9% (95%CI: 49.7%–58.0%). Ewing sarcoma incidence (n = 334) was estimated at 0.15 per 100,000 ESR and 5-year survival at 59.3% (95%CI: 53.5%–64.6%). For high-grade central osteosarcoma, treatment at a bone tumour centre was associated with better survival (HR 0.593).

Conclusions: This study provides comprehensive incidence estimates for all the main primary bone sarcomas over a 15-year time period in a Northern European country with little migration. Centralisation of bone sarcoma care improves the clinical outcome in osteosarcoma.

1. Introduction

Chondrosarcoma, osteosarcoma and Ewing sarcoma are defined as primary malignant sarcomas of bone. High-grade central osteosarcoma and grade 2/3/dedifferentiated chondrosarcoma are defined as high-grade bone sarcomas according to the World Health Organization grading system [1]. High-grade bone sarcomas require intensive treatment due to their rapid and invasive growth pattern and metastasising capabilities. The addition of chemotherapy to the treatment regimen contributes to significantly increased survival in osteosarcoma and Ewing sarcoma patients [2–4]. However, survival in these patients did not seem to increase significantly since the routine introduction of chemotherapy in 1983, as was reported in 2011 [5,6].

Incidence figures, prognostic factors and survival rates for chondrosarcoma, osteosarcoma and Ewing sarcoma have been defined based on a large series [7–15]. These series are based on cohorts from several

Abbreviations: PALGA, Dutch pathology network; NCR, Netherlands cancer registry; ICD-O-3, international classification of diseases for oncology; ACT, atypical cartilaginous tumour; NOS, not otherwise specified; CBS, Central Bureau of Statistics Netherlands; ESR, European standardised rates; EAPC, estimated annual percentage change; CTC, chemotherapy; RT, radiotherapy; HR, hazard ratio

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hospitals in various countries and regions, with different treatment regimens. Several single-institution cohorts have also been described in the Netherlands [16,17]. Importantly, diagnosis and treatment of bone sarcomas have become increasingly centralised in four cooperating bone tumour centres in the past two decades in order to optimise treatment strategies and survival.

To evaluate the impact of centralised bone sarcoma care on a national level, more recent population-based incidence estimates and information on treatment and survival patterns may prove invaluable. The Netherlands is a relatively small and economically developed country with a steady population without significant migration in our study period. [18] Furthermore, high-quality databases are available to allow a comprehensive assessment. Information on histological material after a biopsy or resection of a bone sarcoma is centrally stored in the database of the Dutch Pathology Network (PALGA), and clinical information obtained after histological confirmation is collected in the Netherlands Cancer Registry (NCR).

2. Patients and methods

In the Netherlands, biopsy and treatment of bone sarcomas is centralised in four hospitals. All cases for this study were retrieved from the NCR, which receives primary notification from PALGA. Additional clinical information (on patient and tumour characteristics and on treatment regimens) was collected by data managers of the NCR from hospitals' patient records. The NCR is a population-based registry that covers the total population of the Netherlands since 1989 (approximately 17 million inhabitants in 2017). At present, about 96% of records concerns morphologically verified cases, with the majority of remaining cases representing clinical diagnoses. Unlike most cancer registries, the NCR has no access to death certificates, which impedes reporting on the proportion of Death Certificate Initiated as well as Death Certificate Only cases.

For this study, we focused on high-grade bone sarcomas. All patients diagnosed with chondrosarcoma, osteosarcoma and Ewing sarcoma in the Netherlands between 2000 and 2014 were selected. Classification and categorisation of sarcoma in terms of localisation and histology were based on the International Classification of Diseases for Oncology (ICD-O-3) and the WHO classification 2013 applied according to our clinicopathological expertise (see Appendix A). The Institutional Review Board approved this study (M18.226571), therefore patient informed consent was not required.

Chondrosarcoma was included as high-grade chondrosarcoma (grade 2, 3 and dedifferentiated chondrosarcoma). Survival was described separately for each of these histological grades. Clear cell chondrosarcoma and juxtacortical/periosteal chondrosarcoma were maintained as separate entities.

For osteosarcoma, allocation was based on localisation in the bone. Osteosarcoma was categorised into surface osteosarcoma grades 1, 2 or 3. Central osteosarcoma was categorised into low-grade and high-grade. Angiosarcoma of bone and sarcoma Not Otherwise Specified (NOS) were also included to determine a relative frequency for these infrequent lesions. For this study, we excluded 1311 patients with chondrosarcoma grade 1 / atypical cartilaginous tumour (ACT). An additional total of 65 patients were excluded from this study because of mismatches between the NCR dataset and the definitive classification as described above.

Overall incidence was defined as an annual rate per 100,000 person-years using the average annual population provided by Central Bureau of Statistics Netherlands (CBS), and standardised according to the European Standardised Rate (ESR). Calculations of incidence trends using annual percentage changes (by fitting a least squares regression line to the natural logarithm of the age-standardized rates, using calendar year as a regressor variable, in accordance with the methods described by the SEER) were programmed in Stata 14.0.

Furthermore, In analysing trends in treatment, the following regimens were distinguished: resection only, resection + chemotherapy (CT), resection + radiotherapy (RT), resection + CT + RT, CT/RT only, and biopsy without treatment.

For overall survival analyses, information on patients' vital status was obtained through linkage with the Municipal Personal Records Database. Univariable analyses were performed for all entities using Kaplan-Meier curves. Multivariable analyses were performed with Cox proportional hazards regression models for high-grade chondrosarcoma, high-grade central osteosarcoma and Ewing sarcoma to determine impact of treatment in a bone tumour centre. Patients' age, tumour localisation (long bones/axial skeleton), extent of disease at diagnosis (localised/metastasised), and type of hospital where the biopsy was taken (tumour centre/general hospital) were included in all models as potential explanatory factors. All tests were two-sided and p-values < 0.05 were considered statistically significant. Statistical analyses were performed using Stata 14.0 and SPSS Statistics 23.

3. Results

3.1. Incidence

A total of 1549 bone sarcoma patients with a median age of 32 years were included in this study. For high-grade chondrosarcoma (n = 429; 27.7%), this comprised in 324 patients with grade 2 chondrosarcoma, 60 patients with grade 3 chondrosarcoma and 45 patients with dedifferentiated chondrosarcoma. Juxtacortical/periosteal chondrosarcoma was diagnosed in 26 patients and 10 patients had clear cell chondrosarcoma. For osteosarcoma, 40 patients were diagnosed with grade 1 surface osteosarcoma (6.1% of osteogenic tumours), 10 with grade 2 surface osteosarcoma (1.5%), and four patients (0.6%) with grade 3 surface osteosarcoma. A single patient was identified with low-grade central osteosarcoma; 605 patients had high-grade central osteosarcoma (91.7%). A total of 334 patients with Ewing sarcoma were included, as well as 28 patients with angiosarcoma of bone and 62 patients with sarcoma of bone NOS (malignant fibrous histiocytoma). For high-grade chondrosarcoma, high-grade central osteosarcoma and Ewing sarcoma, clinicopathological characteristics are displayed in Table 1 and age distribution in Fig. 1.

Incidence estimates and incidence changes over time for bone sarcomas between 2000 and 2014 are displayed in Table 2.

3.2. Centralisation of care in terms of biopsy and treatment

Centralisation of tumour biopsy and treatment during our study period was displayed in Table 3. From the 147 tumour biopsies in a general hospital between 2010–2014, 36 patients (24.5%) were diagnosed with grade 2 chondrosarcoma, 7 patients (4.8%) with grade 3 chondrosarcoma and 11 patients (7.5%) with dedifferentiated chondrosarcoma. Furthermore, 49 patients (33.3%) with high-grade central osteosarcoma and 21 patients (14.3%) with Ewing sarcoma were diagnosed. With respect to treatment, the centre of treatment was unclear in 77 patients (22.8%) between 2000–2004. From 32 surgeries performed in a general hospital in 2010–2014, 17 patients (53.1%) were treated for chondrosarcoma grade 2, one patient (3.1%) for chondrosarcoma grade 3, five patients (15.6%) with high-grade central osteosarcoma and two patients (6.3%) with Ewing sarcoma. Patients with a dedifferentiated chondrosarcoma were not treated in a general hospital between 2010–2014.

3.3. Treatment

Treatment regimens between the years 2000 and 2014 for high-grade chondrosarcoma, high-grade central osteosarcoma and Ewing sarcoma are displayed in Fig. 2.

From 2000–2004, 4.9% of 121 patients with high-grade chondrosarcoma were administered chemotherapy (grade 2 (n = 1); grade 3

Table 1
Clinicopathological characteristics for low-grade chondrosarcoma, high-grade chondrosarcoma, high-grade central osteosarcoma and Ewing sarcoma.

	High-grade chondrosarcoma (grade 2/3/ddif) n = 429	High-grade central osteosarcoma n = 605	Ewing sarcoma n = 334
Gender (%)			
Male	244 (56.9)	325 (53.7)	189 (56.6)
Female	185 (43.1)	280 (46.3)	145 (43.4)
Median age at diagnosis in years (range)	57 (14-92)	21 (2-95)	15 (0-83)
Localization (%)			
Long bones	218 (50.8)	453 (74.9)	144 (43.1)
Axial skeleton	211 (49.2)	152 (25.1)	190 (56.9)
Period of diagnosis (%)			
2000-2004	121 (28.2)	177 (29.3)	100 (29.9)
2005-2009	150 (35.0)	206 (34.0)	117 (35.0)
2010-2014	158 (36.8)	222 (36.7)	117 (35.0)
Diagnosis at bone tumor centre (%)	231 (53.8)	392 (64.8)	196 (58.7)
Extent of disease at time of diagnosis (%)			
Localized	385 (89.7)	457 (75.5)	222 (66.5)
Metastasized	43 (10.0)	144 (23.8)	107 (32.0)
Unknown	1 (0.2)	4 (0.7)	5 (1.5)
Treatment (%)			
Resection only	321 (74.8)	51 (8.4)	6 (1.8)
Resection + CT	6 (1.4)	418 (69.1)	109 (32.6)
Resection + RT	40 (9.3)	7 (1.2)	0
Resection + CT + RT	0	16 (2.6)	92 (27.5)
CT/RT only	16 (3.7)	75 (12.4)	117 (35.0)
Biopsy without treatment	46 (10.7)	38 (6.3)	10 (3.0)
Surgery performed at bone tumor centre (%)			
Yes	247 (57.6)	408 (67.4)	157 (47.0)
No	120 (28.0)	84 (13.9)	50 (15.0)
Missing	62 (14.5)	113 (18.7)	127 (38.0)

ddif = dedifferentiated; n = number, CT = chemotherapy, RT = radiotherapy.

(n = 4); dedifferentiated (n = 1)). This percentage diminished towards zero percent during 2010–2014. Considering the treatment modalities (neo-adjuvant chemotherapy, surgery, radiotherapy and adjuvant chemotherapy) for patients with central high-grade osteosarcoma, no trends were seen over the years. By contrast, for patients with Ewing sarcoma resection alone without any form adjuvant/neoadjuvant therapy decreased from 3.0% in 2000–2004 to 0.9% in 2010-2014.

3.4. Survival

Median, 2-year and 5-year overall survival rates per entity are displayed in Table 4a.

Cox regressional hazard proportions in terms of survival for high-grade chondrosarcoma, high-grade central osteosarcoma and Ewing sarcoma was displayed in Table 4b. For all three entities, metastasis at diagnosis was a strong predictor for death of disease. For high-grade central osteosarcoma, treatment in a bone tumour centre was associated with better survival (HR 0.593; 95%CI: 0.414 − 0.850; p = 0.004).

For survival over time, we compared survival for the three different time periods. For high-grade chondrosarcoma as a group 5-year overall survival improved non-significantly from 57.0% in the years 2000–2004 to 66.9% in 2010–2014 (p = 0.096). No improvement was seen in 5-year overall survival for patients with central high-grade osteosarcoma. In 2000–2004 survival was 51.8%, compared to 51.3% in 2010–2014. In patients with Ewing sarcoma 5-year overall survival improved non-significantly from 56.8% in 2000–2004 to 62.6% in 2010–2014 (p = 0.124). Ten-year overall survival for high-grade chondrosarcoma, high-grade central osteosarcoma and Ewing sarcoma is illustrated in Fig. 3.

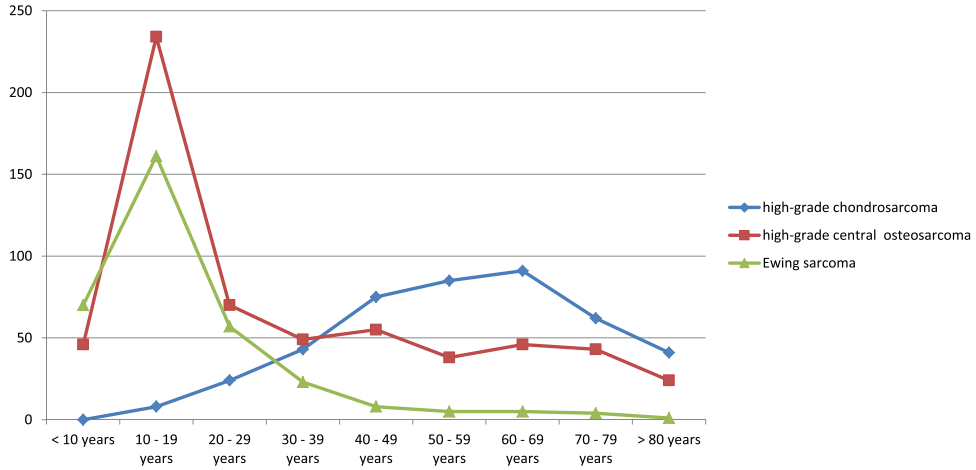

Fig. 1. Age distribution for high-grade chondrosarcoma, high-grade central osteosarcoma and Ewing sarcoma.
N = numbers of patients

Table 2
Incidence estimates with changes over time.

WHO	N	Overall Incidence (ESR)	Incidence 2000-2004	Incidence 2005-2009	Incidence 2010-2014	EAPC	95%CI low	95%CI high
Clear cell chondrosarcoma	10	0,00	0,00	0,01	0,01	5,59%	1,99%	9,32%
Periosteal/juxtacortical chondrosarcoma	26	0,01	0,01	0,01	0,02	8,04%	4,75%	11,43%
Chondrosarcoma (high-grade, 2/3/ddif)	429	0,15	0,13	0,16	0,16	2,99%	1,21%	4,81%
Surface osteosarcoma (grades 1-3)	54	0,02	0,03	0,02	0,02	1,62%	−1,46%	4,80%
Central osteosarcoma (high-grade)	605	0,25	0,22	0,26	0,27	1,68%	0,53%	2,85%
Ewing sarcoma	334	0,15	0,14	0,16	0,16	1,78%	1,18%	2,38%
Angiosarcoma	28	0,01	0,01	0,01	0,01	2,06%	−3,46%	3,62%
Sarcoma NOS (malignant fibrous histiocytoma)	62	0,02	0,01	0,03	0,03	9,61%	6,38%	12,94%

N = number; Overall incidence = rate per 100,000 person-years; ESR = European Standardised Rates; EAPC = Estimated Annual Percentage Change; CI = Confidence Interval; ddif = dedifferentiated; NOS = Not Otherwise Specified.

Table 3
Centralisation of care in terms of biopsy and treatment.

	Total (%)	2000-2004 (%)	2005-2009 (%)	2010-2014 (%)
Tumour Biopsy	476 (30.8)	171 (38.3)	158 (30.2)	147 (24.5)
General hospital				
University hospital	142 (9.2)	43 (9.6)	57 (10.9)	42 (7.3)
Bone tumour centre	927 (60.0)	233 (52.1)	309 (59.0)	385 (66.6)
Treatment	104 (9.3)	38 (11.3)	34 (8.0)	32 (7.2)
General hospital				
University hospital	106 (9.4)	26 (7.7)	50 (11.8)	30 (6.8)
Bone tumour centre	912 (81.2)	196 (58.2)	337 (79.5)	379 (85.4)

4. Discussion

Our study demonstrated clear differences in incidence, treatment patterns and survival between different primary bone sarcomas.

For high-grade chondrosarcoma, the incidence rate of 0.15 per 100,000 persons (n = 429) in our study was comparable with the incidence described in literature. Dorfman et al. displayed an incidence of 0.2 per 100,000 persons (n = 677) between 1973–1987 in the United States [13]. Whelan et al. displayed an incidence of 1.7 towards 2.0 per 1 million persons between 1979–2007 in England, Stiller et al. displayed an incidence of 0.2 per 100,000 persons (n = 1965) between 1995–2002 in Europe [19,20]. The incidence of chondrosarcoma in Taiwan was lower with 1.2 per million persons (n = 244) between 2003–2010 [21].

The incidence rate of 0.25 per 100,000 persons (n = 605) for central high-grade osteosarcoma in our study was also comparable with literature. Mirabello et al. display an incidence rate of 3.1 per million persons (n = 2336) for all osteosarcoma subtypes in the United States between 1973 – 2004. [15] Duong et al. found an incidence rate of 2.71 per million persons (n = 7.104) for malignant primary osteosarcoma in the United States between 1999 and 2008 [14]. Dorfman et al. displayed an incidence rate for osteosarcoma of 0.3 per 100,000 persons (n = 922) between 1973–1987 in the United States [13].

An interesting finding in our study population is the absence of a second age peak for osteosarcoma. Based on the available literature, the second age peak for osteosarcoma is most common in the United Kingdom, Australia and Canada followed by Europe and the United States [22]. For Latin America and Asia the available literature is limited, although Hung et al. published incidences for osteosarcoma showing a small second age peak [21,22].

With the inclusion of surface osteosarcoma (n = 54), we are aware that only 14 of these patients were diagnosed with high-grade surface osteosarcoma. However, we believe that epidemiological identification and quantification of this rare entity is relevant.

For Ewing sarcoma patients the incidence rate of 0.15 per 100,000 persons (n = 334) in our publication concurs with existing data. Dorfman et al. display an incidence rate for Ewing sarcoma of 0.1 per 100,000 persons (n = 420) [13].

Similar incidences of 0.1 per 100,000 persons were reported by Stiller et al. (n = 1046) [20]. A slightly lower incidence for Ewing sarcoma was seen in Taiwan with 0.89 per million persons [21].

The centralisation of care towards bone tumour centres in the Netherlands, which was introduced 25 years ago, is an interesting benchmark for investigating quality of care.

Centralisation of patients towards expert bone tumour centres was initiated by the Dutch Orthopaedic Society and supported by the government. Furthermore, the Netherlands is a relatively small and densely populated country with a centrally governed health care system. Despite this centralisation, tumour biopsies were performed outside a bone tumour centre in 33.3% of patients in our study population between 2010 and 2014. Apparently, most of these lesions were not recognized as primary bone sarcomas (e.g. metastasis, osteomyelitis) given the fact that patient referral after biopsy to a bone tumour centre resulted in an increase of centralisation towards 85.4% after surgery.

Survival analysis in our study population shows that the 5-year overall survival rates for high-grade chondrosarcoma (65.9%), high-grade central osteosarcoma (53.9%) and Ewing sarcoma (59.3%) are comparable with existing large series [23–26]. Hung et al displayed a 5-year overall survival rate of 72.6% for high-grade osteosarcoma between 2004 and 2011 in Taiwan (n = 125) [27]. As identified earlier in several publications and concordant with our study, metastasis at diagnosis proved to be a prognostic factor for high-grade chondrosarcoma, high-grade central osteosarcoma and Ewing sarcoma [7,8,12,23,24,27–29].

In our analysis, treatment at a bone tumour centre was associated with better survival in patients with high-grade central osteosarcoma. Based on our data, no specification was possible for the different treatment modalities. Treatment is therefore defined as multidisciplinary surgical and systemic treatment. The chemotherapeutic agents used in the Netherlands are standardized and did not change over the period reported. Therefore, we did not address this issue. Hoekstra et al. emphasized the importance of centralised care for soft tissue sarcoma [30]. Furthermore, a Dutch group as well as a Scandinavian group mentioned that the prognosis of chondrosarcoma is dependent on whether diagnosis and treatment are conducted by an experienced team [31,32]. Bone sarcoma care by an experienced team can only achieved by centralisation given the low incidence rates. We believe that the effect of centralisation could even be greater if we manage to further improve the concentration of both diagnosis and treatment towards a bone tumour centre.

A limitation of this study is its retrospective nature. However, the registration of histological data in PALGA is prospective, which makes the data more reliable. The overall survival figures presented for clear cell chondrosarcoma, periosteal chondrosarcoma, surface osteosarcoma, angiosarcoma and sarcoma NOS are difficult to interpret in a clinical setting due to low frequencies. We nonetheless believe that it is

Fig. 2. Treatment regimens for high-grade chondrosarcoma, high-grade central osteosarcoma and Ewing sarcoma.

relevant to describe these incidence and survival figures in order to support clinicians when they are confronted with rare pathological diagnoses. For this study, we excluded 1311 patients with chondrosarcoma grade 1/ACT due to potential bias. The incidence figures for chondrosarcoma grade 1/ACT have been published recently by van Praag et al. [33]

In our study period between 2000 and 2014, the Netherlands consisted of a steady population without significant migration. [18] Therefore, we believe that this nationwide publication provides comprehensive, reliable and valuable incidence numbers for all the main primary bone sarcomas in a 15-year period for a single country in Europe. Survival rates did not significantly improve between the years 2000 and 2014 for high-grade chondrosarcoma, central high-grade osteosarcoma and Ewing sarcoma. However, centralisation of bone sarcoma improves the clinical outcome in osteosarcoma.

Additional information

Cancer Epidemiology.

Ethical approval for research

The need for ethical approval was waived by the ethics committee from University Medical Center Groningen. Reference number

Table 4a
Median, 2-year and 5-year overall survival for bone sarcoma.

WHO	N	median survival (months)	95%CI low	95%CI high	2-year survival (%)	95%CI low	95%CI high	5-year survival (%)	95%CI low	95%CI high
Chondrosarcoma (high-grade, grade 2/3/ddif)	429	–	–	–	77.6	73.3	81.2	65.9	61.0	70.4
Surface osteosarcoma (grade 1-3)	54	–	–	–	96.2	85.5	99.0	91.7	79.1	96.8
Central osteosarcoma (high-grade)	605	87.6	56.9	–	66.6	62.6	70.2	53.9	49.7	58.0
Ewing sarcoma	334	140.1	73.1	–	73.2	67.9	77.7	59.3	53.5	64.6
Angiosarcoma	28	12.1	3.6	–	34.6	17.7	52.3	34.6	17.7	52.3
Sarcoma NOS (Malignant fibrous histiocytoma)	62	27.0	13.5	89.3	50.0	36.8	61.9	38.5	25.9	50.9
Total	**1.512**	**138.8**	**98.2**	–	**71.0**	**68.6**	**73.2**	**58.9**	**56.3**	**61.5**

WHO = World Health Organization.

Table 4b
Cox regressional hazard proportions in terms of survival for high-grade chondrosarcoma, high-grade central osteosarcoma and Ewing sarcoma.

	Chondrosarcoma (high-grade, 2/3/ddif) n = 429	p	Central osteosarcoma (high-grade) n = 605	p	Ewing sarcoma n = 334	p
Age < 18 years	–	–	0.478 (CI: 0.319-0.718)	0.000*	0.131 (CI: 0.042-0.411)	0.000*
Age 18-49 years	0.450 (CI: 0.287-0.707)	0.001*	0.515 (CI: 0.344-0.772)	0.001*	0.234 (CI: 0.075-0.731)	0.012*
Localisation: Axial skeleton vs long bones	1.099 (CI: 0.754-1.602)	Ns	1.007 (CI: 0.679-1.495)	Ns	1.040 (CI: 0.631-1.713)	Ns
Extent of disease: metastasised vs localised	4.144 (CI: 2.201-7.801)	0.000*	2.596 (CI: 1.838-3.667)	0.000*	4.792 (CI: 2.863-8.020)	0.000*
Hospital of treatment: bone tumour centre vs other	1.005 (CI: 0.677-1.493)	Ns	0.593 (CI: 0.414-0.850)	0.004*	1.072 (CI: 0.584-1.967)	Ns

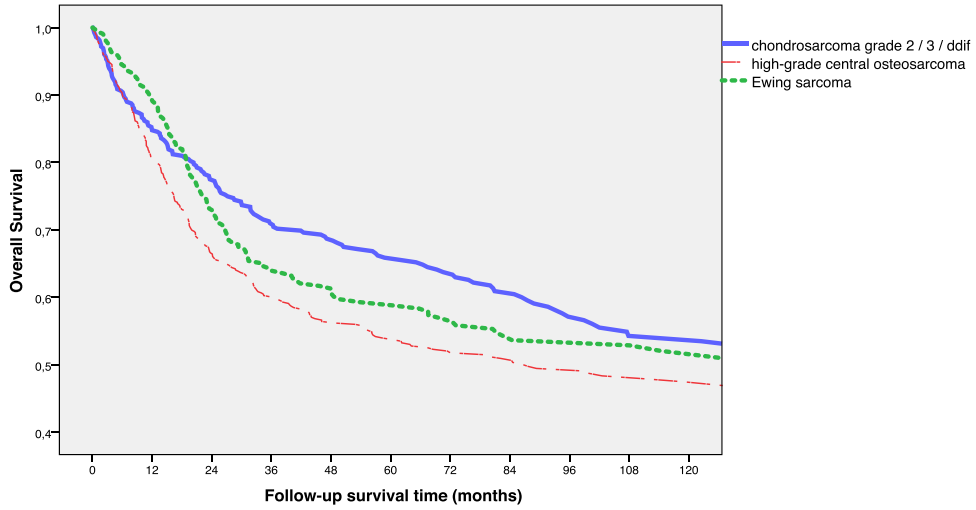

Fig. 3. Ten-year overall survival for high-grade chondrosarcoma, high-grade central osteosarcoma and Ewing sarcoma.

M18.226571.

This study was performed in accordance with the Declaration of Helsinki.

Consent for publication

Does not apply for this study.

Availability of data and material

The dataset generated during and analysed during this current study are available from the corresponding author on reasonable request.

Conflict of interest

None for this study.

Funding

There was no external funding.

Authors' contributions

Study concepts: PC Jutte.

Study design: LM Goedhart, VKY Ho, PC Jutte.

Data acquisition: VKY Ho.

Quality control of data and algorithms: LM Goedhart, VKY Ho, AJH Suurmeijer.

Data analysis and interpretation: LM Goedhart.

Statistical analysis: LM Goedhart, VKY Ho.

Manuscript preparation: LM Goedhart.

Manuscript editing: LM Goedhart, VKY Ho, PC Jutte.

Manuscript review: PDS Dijkstra, HWB Schreuder, GR Schaap, AJH Suurmeijer, MSA van de Sande, JJW Ploegmakers, ICM van der Geest, JA Bramer, PC Jutte.

Declaration of interest

None.

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Appendix A

Classification of sarcoma of bone based on the International Classification of Diseases for Oncology (ICD-O-3) and the World Health Organization (WHO) classification 2013 combined with clinicopathological expertise.

Sarcoma subtype (WHO 2013)	Morphology code	Grade
Low-grade chondrosarcoma, including ACT and chondrosarcoma NOS	9220/2	low
High-grade (2/3) chondrosarcoma		
Chrondrosarcoma NOS	9220/3 + 9231/3	high
Dedifferentiated chondrosarcoma	9243/3	high
Separate entities		
Clear-cell chondrosarcoma	9242/3	low
Juxtacortical/periosteal chondrosarcoma	9221/3	low
Surface osteosarcoma		
Juxtacortical/parosteal osteosarcoma	9190/3 + 9192/3	low
Periosteal osteosarcoma	9193/3	intermediate
High-grade surface osteosarcoma	9194/3	high
Central low-grade osteosarcoma		
Intraosseous well-differentiated osteosarcoma	9187/3	low
Central high-grade osteosarcoma		
Osteosarcoma NOS	9180/3	high
Chondroblastic osteosarcoma	9181/3	high
Fibroblastic osteosarcoma	9182/3	high
Teleangiectatic osteosarcoma	9183/3	high

Osteosarcoma in Paget's disease	9184/3	high
Small-cell osteosarcoma	9185/3	high
Central osteosarcoma	9186/3	high
Intracortical osteosarcoma	9195/3	high
Ewing sarcoma	9260/3	high
Angiosarcoma of bone		
Epithelioid hemangioendothelioma NOS	9133/3	intermediate
Hemangiosarcoma	9120/3	high
Sarcoma of bone NOS		
Sarcoma	8800/3	high
Splindle cell sarcoma	8801/3	high
Small-cell sarcoma	8803/3	high

Grades: 1 = low, 2 = intermediate, 3 = high

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