Clinical approach towards bone sarcoma care

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The impact of centralisation

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Colofon

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The sailboats on the cover represent the five bone sarcoma centers in the Netherlands. As a result of centralisation and collaboration, they are sailing in the same direction to optimize bone sarcoma care.

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Contents

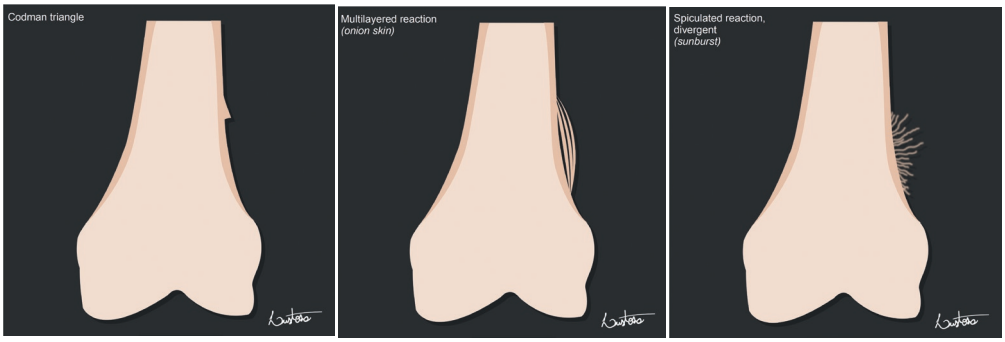
CHAPTER 1

General introduction

General Introduction

Sarcomas of the bone are considered a rare malignant entity expanding destructively from bone into soft tissue. Bone sarcomas have a primarily mesenchymal origin and occur in younger age groups compared to osseous metastasis. High-grade chondrosarcoma, osteosarcoma and Ewing sarcoma are all defined as high-grade bone sarcomas. These entities are rare neoplasms with incidences ranging from 1.5 to 4.6 per millions persons. Historically, the first case of a bone sarcoma was described around 800 BC. A metaphyseal aggressive humeral lesion was seen in a Celtic individual. (1) Fast-growing lesions, such as osteosarcoma and Ewing sarcoma, can provoke a periosteal reaction of the bone. Typical radiological signs of aggressive periosteal reaction are Codman's triangle, onion skinning and sunburst phenomenon on conventional radiographs. Historically, a periosteal reaction caused by tumour growth, later defined as sunburst phenomenon, was discovered on a native Peruvian around 900 years ago. (1) Popcorn calcifications or rings and arcs are seen in chondromatous lesions like chondrosarcoma on conventional radiographs.

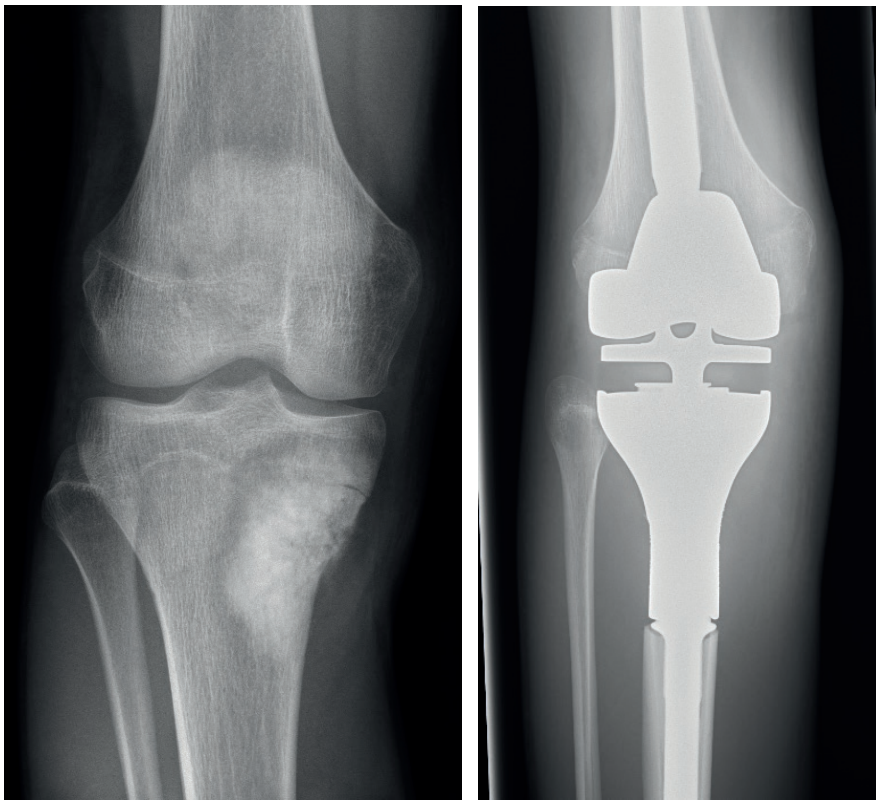
Figure 1. Radiological signs of aggressive periosteal reaction



Case courtesy of Leonardo Lustosa, Radiopaedia.org, rID: 97282

Clinical presentation varies upon localisation of the tumour. Pain is common in patients with long bone lesions and is usually caused by local bone destruction with fracturing/microfracturing or compression of adjacent soft tissue. Bone sarcomas rarely occur in the spine. In patients with a pelvic lesion, the tumour has the potential to grow substantially without symptoms. This often results in patient and doctor delays, which could affect survival due to metastasised disease at presentation. Given the malignant nature and metastasising capabilities of high-grade bone sarcomas, radical treatment is required. Both surgical and medicinal treatment have evolved in the last 30 years. Although amputation yields a maximal oncological result, functional impairment and phantom pain are significant downsides. The development of effective chemotherapy has allowed surgeons to perform limb-salvage procedures with the use of modular tumour prostheses or biological reconstructions. (2,3)

Figure 2. Radiological example of patient with osteosarcoma of the proximal tibia at presentation and after radical resection followed by reconstruction with a tumour prosthesis.

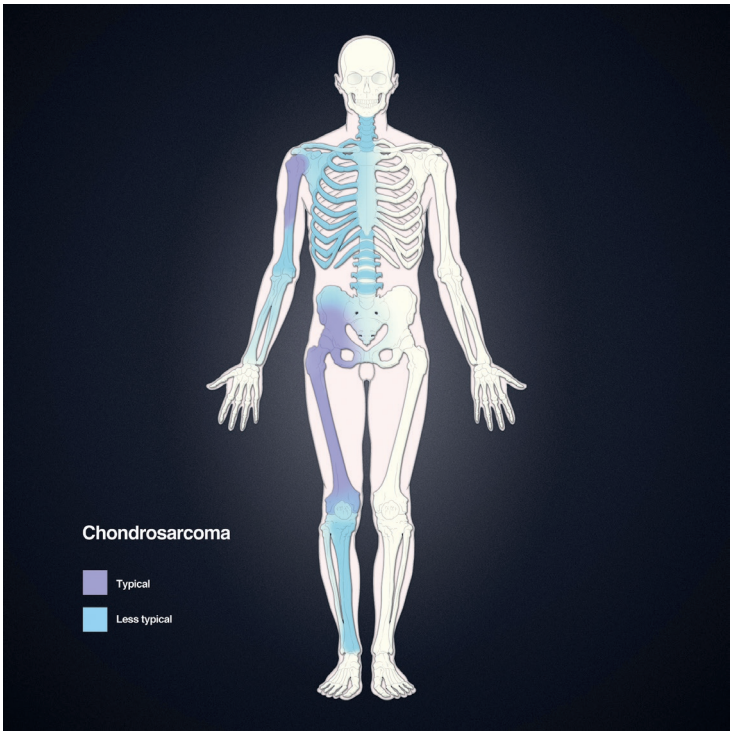


High-grade bone sarcomas

High-grade chondrosarcoma is a cartilage-forming malignant bone tumour, usually diagnosed over the age of 40. (4–6) The femur and pelvis are the most commonly affected sites. Pulmonary and osseous lesions are most seen in metastasised cases. Low-grade chondrosarcoma is described as an atypical cartilaginous tumour. Atypical cartilaginous tumours tend to grow at a slow pace, and rarely metastasise. Dedifferentiated chondrosarcoma is a histological variant with more aggressive behaviour, and thus lower survival rates, than conventional high-grade chondrosarcoma. (7) Pulmonary and osseous metastases are most frequently seen in high-grade chondrosarcoma. Chondrosarcoma is resistant to chemotherapy and radiotherapy, making wide surgical resection the preferred treatment. Due to the resistance to chemotherapy and radiotherapy, recurrent and metastatic chondrosarcoma cases are difficult to treat. Through extensive basic research, the molecular footprint of chondrosarcoma has become clearer (8,9) and several novel

molecular targeted therapies with immunotherapy are currently under development and investigation.

Figure 3. Localisations for chondrosarcoma

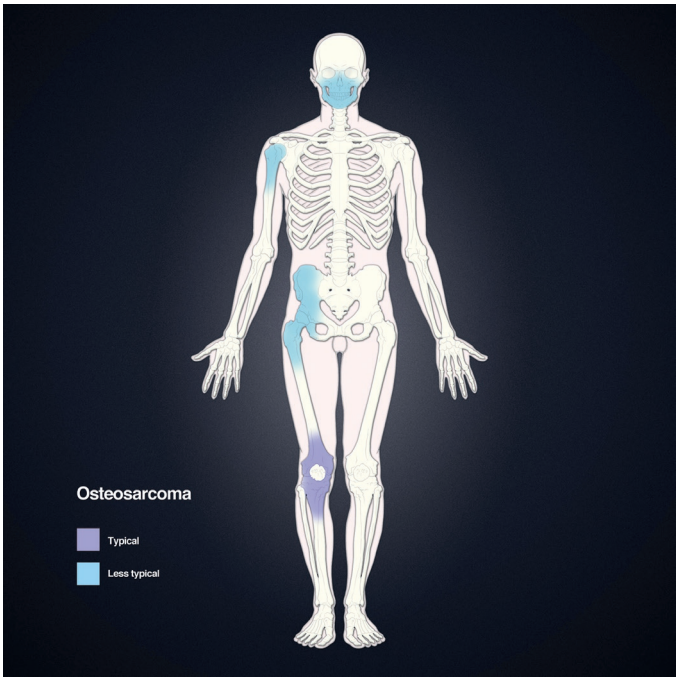


Case courtesy of Assoc Prof Frank Gaillard, Radiopaedia.org, rID: 7529

Osteosarcoma is the most common high-grade bone tumour, with an incidence of 4.6 per million persons. (10) Two peaks are seen in the incidence of osteosarcoma: the first in children and early adolescents, the second in patients over 60. (11)which is the most common primary bone tumor, occurs most frequently in adolescents, but there is a second incidence peak among individuals aged > 60 years. Most osteosarcoma epidemiology studies have been embedded in large analyses of all bone tumors or focused on cases occurring in adolescence. Detailed descriptions of osteosarcoma incidence and survival with direct comparisons among patients of all ages and ethnicities are not available. METHODS: Frequency, incidence, and survival rates for 3482 patients with osteosarcoma from the National Cancer Institute's population-based Surveillance, Epidemiology, and End Results (SEER Tumour cells in osteosarcoma produce immature bone cells or osteoid tissue. (12,16) These tumour cells generate a destructive growth pattern in their host

bone and the surrounding soft tissues. Predominant sites of involvement are related to the age of presentation. In children and early adolescents, osteosarcoma is mostly reported in long bones with the distal femur as most affected site. In older adults the axial skeleton is most affected. (11)which is the most common primary bone tumor, occurs most frequently in adolescents, but there is a second incidence peak among individuals aged > 60 years. Most osteosarcoma epidemiology studies have been embedded in large analyses of all bone tumors or focused on cases occurring in adolescence. Detailed descriptions of osteosarcoma incidence and survival with direct comparisons among patients of all ages and ethnicities are not available. METHODS: Frequency, incidence, and survival rates for 3482 patients with osteosarcoma from the National Cancer Institute's population-based Surveillance, Epidemiology, and End Results (SEER Different subtypes of osteosarcoma are described in literature. Conventional osteosarcoma accounts for over 90% of all osteosarcomas and can be divided into fibroblastic, chondroblastic and osteoblastic variants. The remaining percentage is covered by rare variants such as small cell, multifocal, telangiectatic and surface osteosarcomas. (12) Neoadjuvant and adjuvant chemotherapy along with surgical resection is a well-accepted treatment strategy for osteosarcoma. Radiotherapy is sometimes indicated for inoperable lesions or after resections with positive tumour margins.

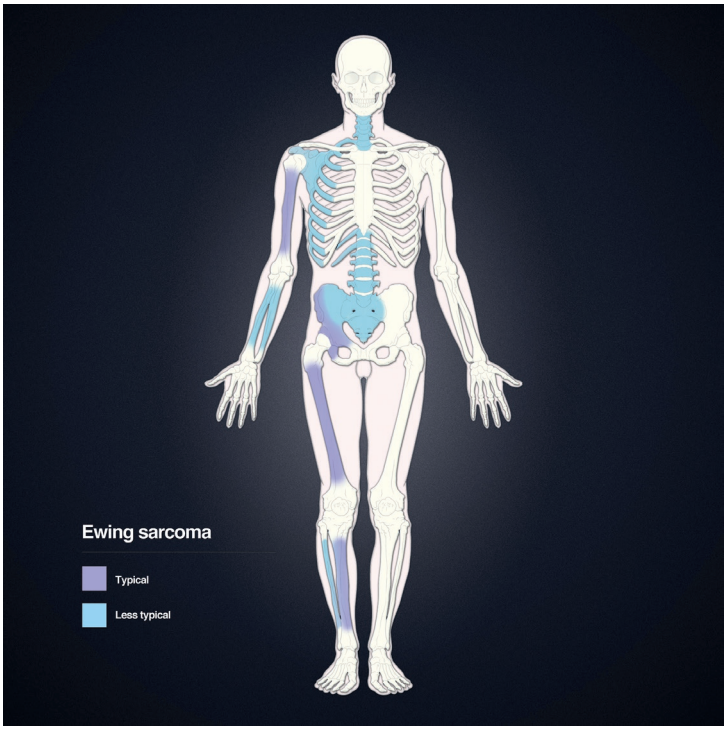
Figure 4. Localisations for osteosarcoma



Case courtesy of Assoc Prof Frank Gaillard, Radiopaedia.org, rID: 6175

Ewing sarcoma is the most lethal high-grade bone malignancy. It is a small round blue cell tumour originating from bone medulla, and grows destructively into soft tissue. (10) Ewing sarcoma has a slight predilection in males, with a peak between ages 15 and 19. The axial skeleton and pelvic region are predominant sites, followed by the femur and tibia. Microscopically, Ewing sarcoma shows a strong resemblance to primitive neuroectodermal tumours. (13) Metastases in Ewing sarcoma most often occur prior to presentation or within weeks to months after the onset of symptoms. Ewing sarcoma is mostly sensitive to chemotherapy and radiotherapy, which are administered along with surgical resection of the tumour.

Figure 5. Localisations for Ewing sarcoma



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Basis for this thesis and key concepts

Given the low incidences of these primary malignant bone tumours, inappropriate histological diagnosis, treatment delays and inappropriate care (so-called whoops

surgeries) have historically influenced survival for bone sarcoma negatively. General practitioners, for example, generally encounter one patient with a primary bone tumour during their working career. Definitive diagnosis of a bone sarcoma is difficult and is based on clinical symptoms, radiological imaging and histological sampling. Appropriate histological diagnosis is challenging and requires an experienced and specialised pathologist. To this end, the Dutch bone tumour committee was founded in 1953, with the mission to study tumours and tumour-like abnormalities of the skeleton. It is a multidisciplinary group consisting of pathologists, radiologists, oncologists, paediatric oncologists, radiotherapists, and orthopaedic, oncological, maxillofacial and neurosurgeons. These days the bone tumour committee reassesses edge cases with their experienced multidisciplinary team on a monthly basis. The combined experience of this group results in alteration of a diagnosis and subsequent treatment strategy in approximately 20% of the discussed cases. (14) This emphasises the complexity of a radiological and histological diagnosis and the need for reassessment by an experienced team to facilitate optimal treatment and maximise survival for bone sarcoma patients. There are three key concepts to present, as they are of importance throughout this thesis:

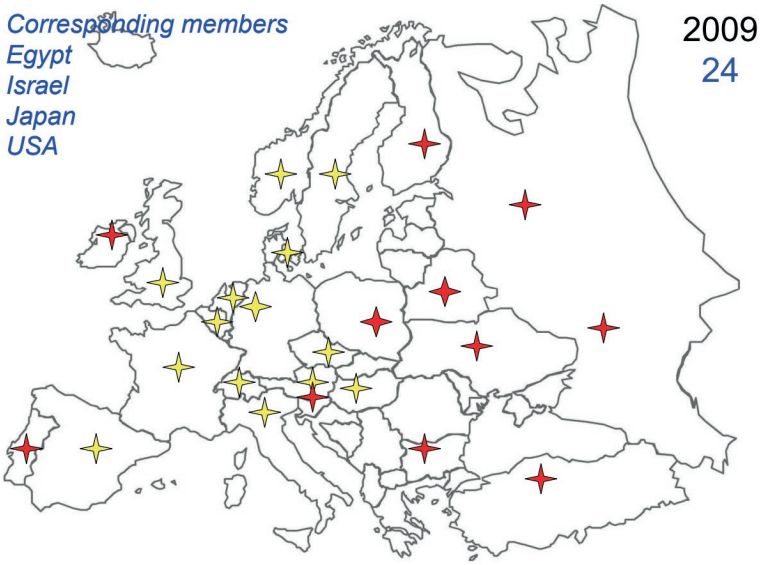
Centralisation of care

Treatment of bone sarcomas in the Netherlands is accredited and centralised to the academic hospitals of Amsterdam, Leiden, Groningen and Nijmegen, all bone sarcoma centres facilitating assessment and treatment by experienced teams. Centralisation increases the caseload for the individual centres, which is critical for the multidisciplinary team to build and maintain sufficient experience and knowledge. In 2018 the Prinses Maxima Center for paediatric oncology was opened. Since then, paediatric patients with a bone sarcoma are primarily treated here in close collaboration with the other bone sarcoma centres.

International collaboration

For Europe, cross-border initiatives to improve international collaboration and disseminate knowledge have resulted in the European Musculoskeletal Oncology Society (EMSOS), founded in 1987. EMSOS aims to facilitate a network for different specialists and institutes in order to improve treatment of musculoskeletal tumours. Virtually all European bone sarcoma centres are affiliated with EMSOS, which offers great opportunities for the exchange of knowledge and best practices. The expert affiliated bone sarcoma centres are scattered throughout Europe. However, when it comes to country-specific organisation of care, the approach towards diagnosis and treatment differs between these hospitals. To identify potential benefits or improvements in centralisation of care, an international collaboration was established which allowed us to conduct two cross-sectional studies among bone sarcoma centres in Europe.

Figure 6. Members of EMSOS in 2009



Yellow signs: original members of EMSOS in 1987
Red signs: additional members of EMSOS in 2009
Case courtesy of EMSOS, emsos.org.

Data storage for quality and improvement of care

Historically, data on bone sarcoma patients has been stored by the Dutch bone tumour committee in Leiden since its establishment. At present the archive contains clinical, radiological and histological data of approximately 38,000 cases, making it the largest documented archive globally. Since 1989, the Netherlands Cancer Registry (NCR) started a population-based registry that included all cancer patients in the Netherlands. The NCR receives histologically confirmed cases from primary notification by the Dutch Pathology Network (PALGA). Additional clinical information is collected by data managers. About 96% of the registry contains histologically confirmed cases; the majority of the remaining 4% of cases represents a clinical diagnosis.

Aims of this thesis

The overall aim of this thesis is assessment of bone sarcoma care. First, bone sarcoma care is assessed in terms of incidence. Second, the impact of centralisation is assessed regarding time to diagnosis and organisation of care. Third, follow-up of bone sarcoma is assessed to ultimately improve the clinical approach towards bone sarcoma care.

Contents of this thesis

Part 1 Bone sarcoma incidence

The establishment of the Dutch bone tumour committee archive and the NCR registry has resulted in extensive data storage of bone sarcoma cases for purposes of quality control, research, and improvement of care. These central registries allowed us to perform two nationwide studies on bone sarcoma incidence. In **Chapter 2** we conducted a nationwide NCR registry study that produced comprehensive incidence estimates for all main primary bone sarcomas over a 15-year period in the Netherlands. We assessed the effect of centralisation of care on tumour biopsy and treatment. **Chapter 3** is another example of how a central tumour registry like the Dutch bone tumour committee archive can facilitate close study of an extremely rare tumour. The presentation, treatment and outcome of periosteal chondrosarcoma in the Netherlands is described over a 59-year period.

Part 2 The impact of centralisation

In the second part of this thesis we assessed centralisation of care in terms of time to diagnosis, organisation of bone sarcoma care and follow-up in Europe in a nationwide study on bone sarcoma follow-up. Patients with a bone sarcoma may benefit from diagnosis and treatment by an experienced multidisciplinary team. This emphasises the importance of centralisation of care. Still, centralisation of bone sarcoma care could induce time-to-diagnosis and treatment delays. In **Chapter 4** we assessed time to diagnosis and its effect on clinical outcome in high-grade sarcoma of bone in a retrospective single bone sarcoma centre study. Patient-related delay as well as the different types of doctor-related delay were singled out and analysed. In **Chapter 5**, organisation of care was assessed in several bone sarcoma centres in Europe affiliated with a cross-sectional study with the input of an EMSOS study group.

Part 3 Follow-up of bone sarcoma

The third and last part of the thesis assessed follow-up in terms of its organisation and sequel of oncological events after bone sarcoma treatment in a nationwide study. In **Chapter 6**, a cross-sectional study was conducted to assess follow-up of bone sarcoma care in Europe. In **Chapter 7** a nationwide NCR registry study was conducted, focusing on follow-up. The aim of the study was to assess the oncological events occurring after index treatment with curative intent during follow-up, including time to local recurrence and distant metastasis, in order to obtain additional evidence to assess current follow-up strategies for high-grade bone sarcomas in the Netherlands. Clinical implications, considerations and future perspectives are discussed in **Chapter 8**. English and Dutch summaries of this thesis are outlined in **Chapter 9** and **Chapter 10**.

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PART I

Bone sarcoma incidence

CHAPTER 2

Bone sarcoma incidence in the Netherlands

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Abstract

Aim

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).

Conclusion

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.

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) Epidemiology, and End Results (SEER These series are based on cohorts from several 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).

Patients and Methods

In the Netherlands, biopsy and treatment of bone sarcomas is centralised in four hospitals: University Medical Center Groningen, Leiden University Medical Center, Amsterdam University Medical Centers and Radboud University Medical Center. 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 clinico-pathological 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.

Results

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 Figure 1.

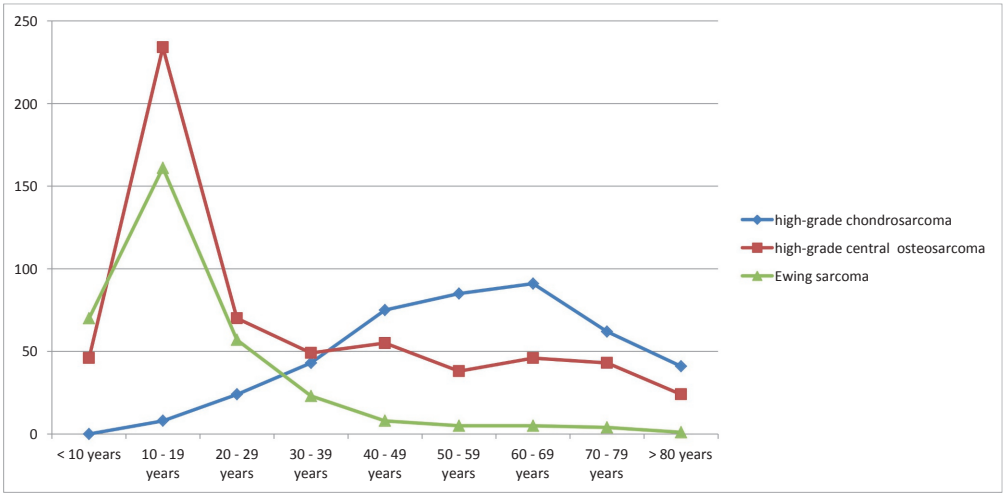
Incidence estimates and incidence changes over time for bone sarcomas between 2000 and 2014 are displayed in Table 2.

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

Figure 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

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.

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

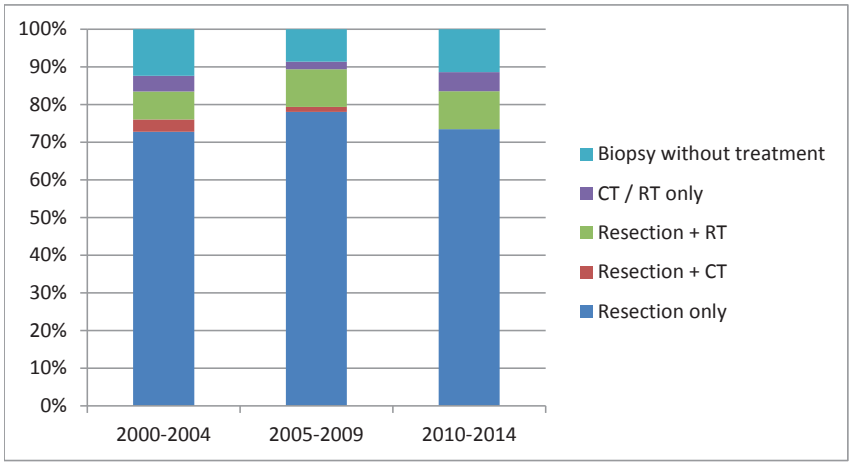
	Total (%)	2000-2004 (%)	2005-2009 (%)	2010-2014 (%)
Tumour Biopsy				
General hospital	476 (30.8)	171 (38.3)	158 (30.2)	147 (24.5)
University hospital	142 (9.2)	43 (9.6)	57 (10.9)	42 (7.3)
Bone tumour centre	927 (60.0)	233 (52.1)	309 (59.0)	385 (66.6)
Treatment				
General hospital	104 (9.3)	38 (11.3)	34 (8.0)	32 (7.2)
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)

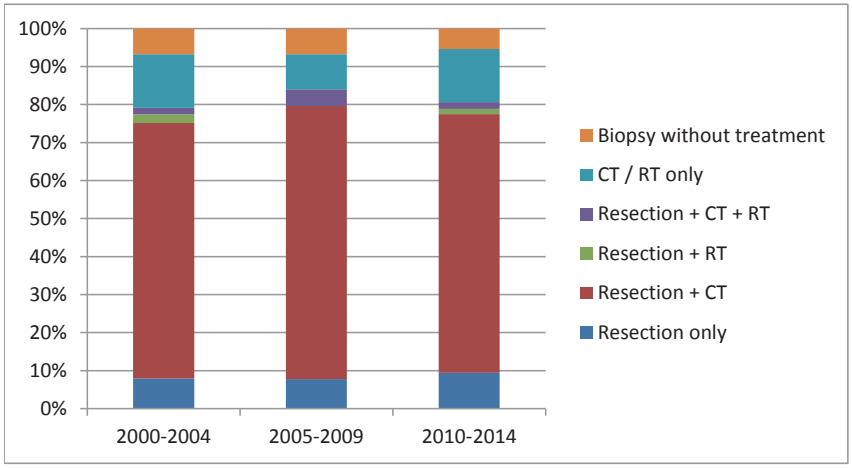
3. Treatment

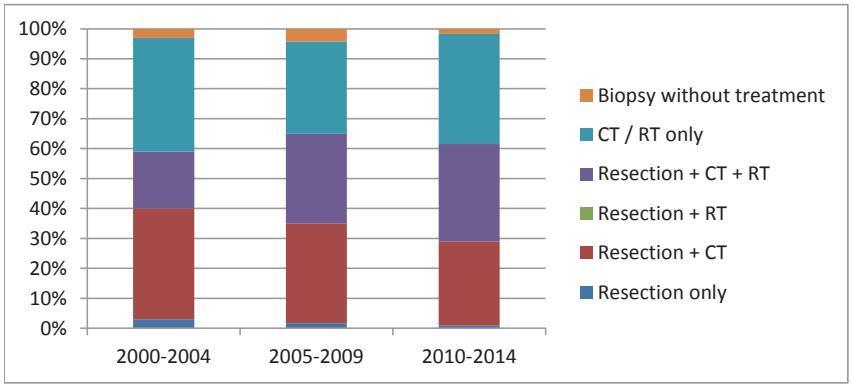
Treatment regimens between the years 2000 and 2014 for high-grade chondrosarcoma, high-grade central osteosarcoma and Ewing sarcoma are displayed in figure 2.

From 2000-2004, 4.9% of 121 patients with high-grade chondrosarcoma were administered chemotherapy (grade 2 (n=1); grade 3 (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 2000-2014.

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







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).

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

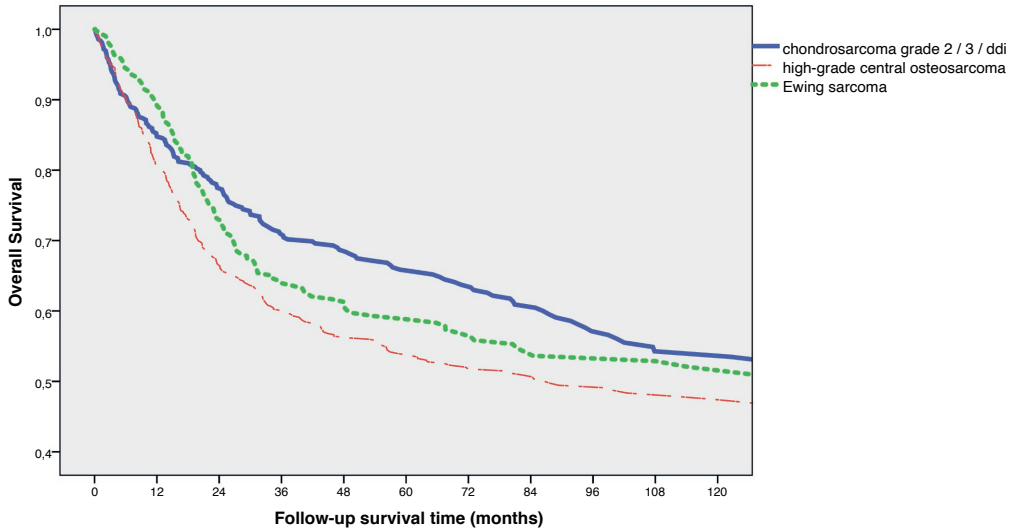
WHO=World Health Organization

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

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 Figure 3.

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



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=2,336) 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)Epidemiology, and End Results (SEER

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 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.

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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

CHAPTER 3

The presentation, treatment and outcome of periosteal chondrosarcoma in the Netherlands

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Abstract

Aim

In this case study, we describe the clinical presentation and treatment of 36 patients with periosteal chondrosarcoma collected over a 59-year period by the archive of the Netherlands Committee on Bone Tumours.

Patients and Methods

The demographics, clinical presentation, radiological features, treatment and follow-up are presented with the size, location, the histological grading of the tumour and the survival.

Results

We found a slight predominance of men (61%), and a predilection for the distal femur (33%) and proximal humerus (33%). The metaphysis was the most common site (47%) and the most common presentation was with pain (44%). Half the tumours were classified histologically as grade 1. Pulmonary metastases were reported in one patient after an intralesional resection. A second patient died from local recurrence and possible pulmonary and skin metastases after an incomplete resection.

Conclusion

It is clearly important to make the diagnosis appropriately because an incomplete resection may result in local recurrence and metastatic spread. Staging for metastatic disease is recommended in grade II or III lesions. These patients should be managed with a contrast-enhanced MRI of the tumour and histological confirmation by biopsy, followed by *en-bloc* excision.

Introduction

A periosteal chondrosarcoma is a cartilageforming, locally aggressive, low grade malignant tumour usually seen on the surface of a long bone. (1) It is rare and forms only 0.5% of all chondrosarcomas. (2) It is therefore important that it is properly treated. (3)

Periosteal chondrosarcomas occur most frequently in young adult males on the distal femur or proximal tibia. (1) Their clinical presentation is non-specific but there may be pain, swelling and loss of function. (4) Most can be identified on plain radiographs by their typical appearance and their location in the bone. The cortex is usually thickened and sclerotic with a solid periosteal reaction. There may be some intra-lesional mineralisation. (1,5)

Information about periosteal chondrosarcoma is scarce: the largest published series consists of 24 cases. (6,7) Although it is usually defined as a lowgrade tumour, two cases of grade III periosteal chondrosarcoma have been described. (1,3,8) In this case study, we describe the presentation and treatment of 36 patients with a periosteal chondrosarcoma.

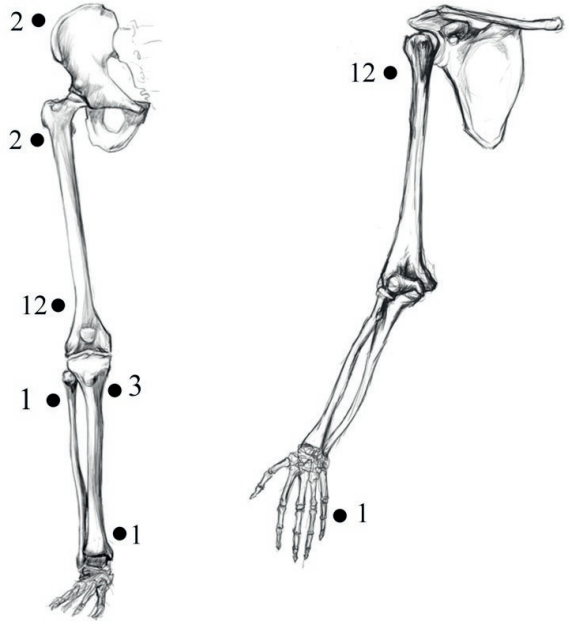
Material and Methods

Between 1953 and 2012 a total of 15 722 cases were reviewed by the Netherlands Committee on Bone Tumours. Chondrosarcoma was diagnosed in 1791, of which 36 (2%) were periosteal chondrosarcomas. There were 22 men and 14 women. Their demographics are shown in Fig. 1. The mean age at presentation was 33.6 years (10 to 76) with a peak in the third decade (39% of cases; Fig. 2). The diagnosis and grade of tumour were reviewed and confirmed by a group of radiologists and pathologists from this committee.

The clinical characteristics including pain, swelling, loss of function and neurological or vascular symptoms are shown in Table I. Radiological features including the diameter and localisation of the tumour (diaphysis, metaphysis or epiphysis) were described using conventional radiographs, MRI or CT. Histological grading used the World Health Organisation (WHO) classification which is similar to that of conventional chondrosarcoma. (8,9) Recurrence was defined as local recurrence, metastasis or death due to metastasis. Differences in age, size, site, pathological grading and completeness of excision were related to outcome.

Follow-up information was available for 28 patients. The oncological result at final follow-up was considered successful if no local recurrence or metastases had occurred. In most cases this was on the basis of plain radiographs.

Figure 1. Distribution: site and gender



Site	N= 36
Distal Femur	12
Proximal Humerus	12
Ilium	2
Proximal Femur	2
Proximal Tibia	3
Proximal Fibula	1
Intermediate Phalanx	1
Distal Tibia	1
Fourth Rib	1
Vertebral body Th4	1

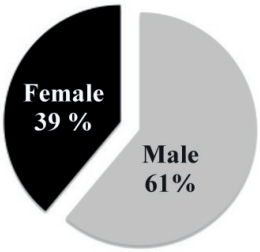


Figure 2. Age distribution

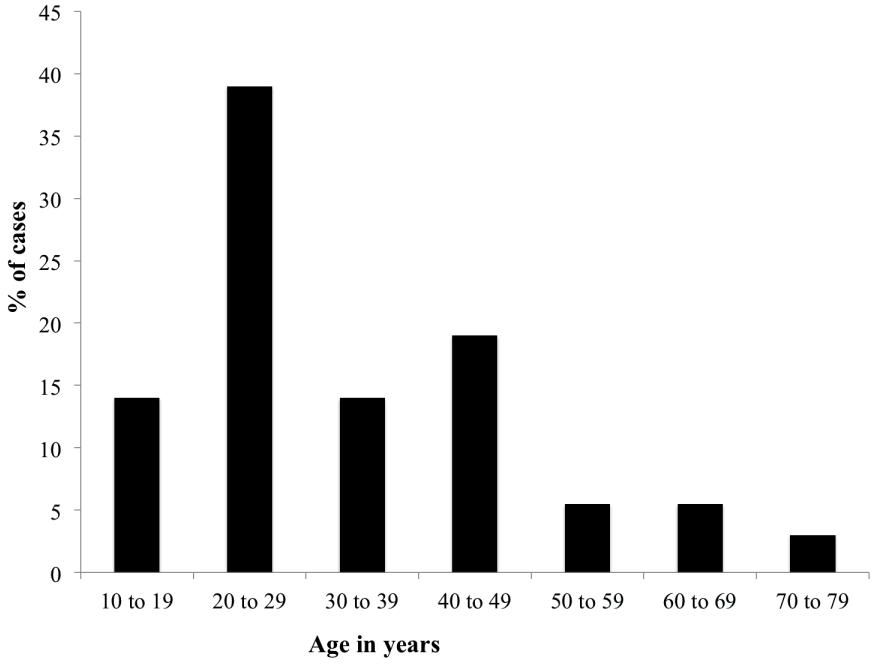


Table 1. 36 cases of periosteal chondrosarcoma

Case	Sex	Age	Symptoms	Site	Size (cm)	Imaging	Histological Grade	Treatment	Follow-up
1	M	47	swelling	Costa IV costosternal	2.7x2.1x3.2	MRI	Grade II Needle biopsy	2012, en-bloc excision	1 year, no recurrences
2	M	22	random finding	Distal femur metaphysis: posteromedial compartment	2.0x2.0x2.2	MRI	Grade II Excision biopsy	2011, en-bloc excision	2 months, no recurrences
3	M	29	painful swelling	Distal femur metaphysis: medial compartment	1.7x1.2x1.6	MRI	Grade I Excision biopsy	2011, en-bloc excision	4 months, no recurrences
4	M	45	random finding	Os ilium	3.6x3.6x3.6	MRI	Grade I Excision biopsy	2012, en-bloc excision	1 year no recurrences
5	F	54	swelling	Proximal humerus diaphysis/ metaphysis: medial compartment	4.7x5.7x5.8	MRI	Grade I Excision biopsy	2010, en-bloc excision	N/A
6	M	23	random finding	Proximal femur diaphysis/ metaphysis: trochanter minor	5.0x4.0x4.0	MRI	Grade I Excision biopsy	2010, en-bloc excision + allograft reconstruction	2 years, no recurrences
7	F	24	random finding	Distal femur diaphysis/ metaphysis: posterior	2.8x4.3x3.4	MRI	Grade II Excision biopsy	2010, Contaminated resection	2 years, no recurrences
8	F	10	painful swelling	Distal femur diaphysis/ metaphysis: medial at vastus medialis	1.4x2.3x5.2	MRI	Grade I CT-guided biopsy	2010, en-bloc excision	2 years, no recurrences
9	M	30	swelling w. loss of function & radiating numbness	Proximal humerus diaphysis/ metaphysis: anterior head	4.5x3.8x2.5	MRI	Grade I Excision biopsy	2009, en-bloc excision	3.5 years, no recurrences
10	M	18	swelling	Proximal fibula diaphysis: medial segment	4.7x6.5x12.5	MRI	Grade I Needle biopsy	2009, en-bloc excision	N/A
11	F	19	swelling + radiating numbness	Proximal humerus diaphysis: anterior m. deltoideus	1.8x1.3x3.8	MRI	Grade II CT-guided biopsy	2009, en-bloc excision	3.5 years, no recurrences
12	M	28	random finding	Distal femur metaphysis: posterior segment	3.1x3.5x4.3	CT	Grade II Excision biopsy	2008, en-bloc excision	4.5 years, no recurrences
13	F	38	painful swelling	Distal femur diaphysis/ metaphysis: medial segment	3.5x2.5x4	MRI	Grade II Excision biopsy	2008	N/A
14	F	40	swelling	Proximal tibia diaphysis/ metaphysis: ventromedial compartment	3.0x3.0	MRI	Grade II Needle biopsy +Excision biopsy	2003, en-bloc excision + allograft reconstruction	8.5 years no recurrences

Case	Sex	Age	Symptoms	Site	Size (cm)	Imaging	Histological Grade	Treatment	Follow-up
15	M	21	painful swelling w. loss of function	Distal femur metaphysis: posterior segment	8.0x4.0x4.0	MRI	Grade II Needle biopsy	1998, en-bloc excision	2 years, no recurrences
16	F	67	swelling	Proximal humerus metaphysis: anterolateral compartment	3.0x3.0x5.0	X-ray	Grade I Incision biopsy	1997, en-bloc excision	N/A
17	F	16	painful swelling w. diffuse muscular atrophy	Proximal humerus diaphysis: anterolateral compartment	4.0x4.0x7.0	X-ray	Grade I biopsy	1995, en-bloc excision + allograft reconstruction	4 years, no recurrences
18	M	76	painful swelling	Distal femur metaphysis: posterior compartment	7.0x11.0	X-ray	Grade I Incision biopsy	1989, en-bloc excision	17 years, no recurrences
19	F	40	painful swelling	Proximal tibia diaphysis/ metaphysis:	5.0x3.5	X-ray	Grade II Needle biopsy	1988, en-bloc excision	5 years, no recurrences
20	M	22	painful swelling	Proximal humerus diaphysis: lateral compartment	1.5 x2.5	X-ray	Grade I Excision biopsy	1988, en-bloc excision	23 years, no recurrences
21	M	47	swelling	Distal tibia metaphysis: superior of medial malleolus	2.0x1.0x1.5	X-ray	Grade II Excision biopsy	1987, resection w. positive margins followed by below-knee amputation three months later	10 years, no recurrences
22	M	31	painful swelling	Proximal tibia metaphysis: medial tuberosity	5.0x3.0	X-ray	Grade I Excision biopsy	1983, resection w. spilling of intralesional fluid	N/A
23	F	21	swelling w. loss of function	Proximal humerus metaphysis: mediodorsal compartment	1.5x3.0	X-ray	Grade I Incision biopsy	1983, en-bloc excision	N/A
24	M	21	swelling w. loss of function	Distal femur diaphysis/ metaphysic: dorsolateral compartment	3.5x5.0x3.0	X-ray	Grade I Excision biopsy	1983, en-bloc excision	6 months, no recurrences
25	F	26	painful swelling	Os ilium	5.0x10.0	X-ray	Grade II Excision biopsy	1981, en-bloc excision + pelvis reconstruction	12 years, no recurrences
26	M	47	painful swelling	Proximal femur metaphysis: cranial to major trochanter	9.6x10.0	X-ray & CT	Grade II Excision biopsy	1980, en-bloc excision + THA	N/A
27	M	22	pain w. loss of function	Proximal humerus metaphysis: head	N/A	None taken	Grade I Excision biopsy	1968, en-bloc excision + vitallium prosthesis	1 year, no recurrences

Case	Sex	Age	Symptoms	Site	Size (cm)	Imaging	Histological Grade	Treatment	Follow-up
28	M	23	swelling	Proximal humerus diaphysis: caudal to major tuberculum	N/A	None taken	Grade II Excision biopsy	1966, intralesional resection followed by en-bloc excision + reconstruction four months later	N/A
29	M	27	painful swelling	Distal femur metaphysis: dorsolateral compartment	N/A	None taken	Grade I Excision biopsy	1964, en-bloc excision	2.5 years, no recurrences
30	F	61	swelling	Proximal humerus metaphysis	N/A	None taken	Grade II Excision biopsy	1963, intralesional excision followed by wide resection two months later	After 17 years suspect bone lesion Th8, + osteoporotic fractures Th6 & Th4
31	M	47	n/a	Proximal humerus metaphysis	N/A	None taken	Grade II Incision biopsy	1963, Amputation proximal humerus & scapula neck	16 years, no recurrences
32	M	32	painful swelling	Dig 5 intermediate phalanx diaphysis: radial side	N/A	None taken	Low-grade (no futher gradation) excision biopsy	1963, Exocochleation	3.5 years, no recurrences
33	M	18	swelling w. loss of function	Distal femur metaphysis	N/A	None taken	Chondrosarcoma (no further gradation) Excision biopsy	1944, local resection + radiation, later above-knee amputation in 1951 after local recurrence	Local recurrence after 6 years. Died after 7 years from skin and pulmonary metastasis
34	M	26	pain w. loss of function	Proximal humerus metaphysis: medial compartment	2.4x3.3x4.0	MRI	Grade I Excision biopsy	2005, en-bloc excision	5 years, no recurrences
35	F	33	swelling w. loss of function	Distal femur metaphysis: lateral femur condyle	3.6x4.9x5.4	MRI	Grade I Excision biopsy	2003, en-bloc excision + allograft reconstruction	7 years, no recurrences
36	F	58	Pain	Fourth thoracal vertebral body	3.5x4.0x4.2	MRI	Grade II Excision biopsy	2010, intralesional resection + radiation	3.5 years, after 2 years local recurrence with pulmonary metastases.

Results

Clinically, the tumour presented as a painless swelling in 14 patients (39%) and with pain in 16 (44%). In eight (22%) there was some limitation of movement due to swelling. Two patients (6%) had radiating numbness due to compression of a nerve by tumour. In five patients (14%) it was an incidental radiological finding.

The distal femur and proximal humerus were each affected in one-third (33%) of cases. Plain radiographs were carried out in 29 patients (80.5%); 17 tumours (47%) were also assessed by MRI and two by CT. Seven patients (19.5%) did not undergo radiological assessment prior to biopsy or excision. Excision biopsy was performed for 24 patients (66.6%), incision biopsy in four (11%) and needle biopsy in seven (19.4%) (in two cases CT-guided). In one patient (3%), the method of biopsy was unknown. The method of treatment and follow-up is shown in Table I. *En-bloc* excision or amputation was the primary treatment for 27 patients (75%), an incomplete excision

with further resection and reconstructive or prosthetic surgery was undertaken in eight (22%). The type of resection in case 13 was unknown and there were no follow-up data.

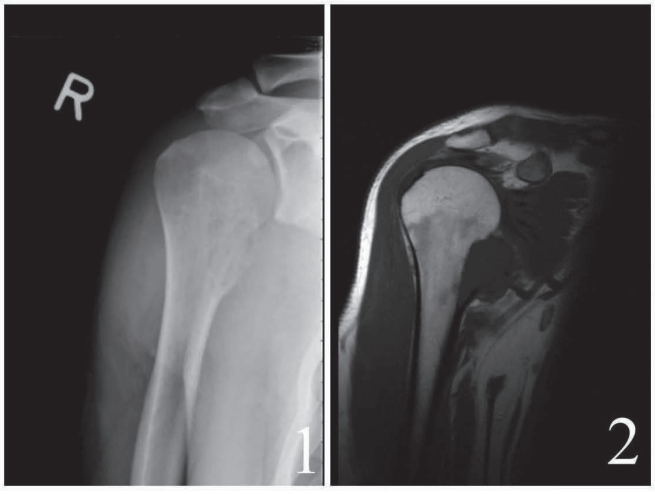
Radiologically, periosteal chondrosarcoma occurred most often in the metaphysis (17, 47%), followed by the metaphyseal-diaphyseal transition zone (9, 25%) and least in the diaphysis (6, 17%). Other sites included vertebrae, rib and pelvis. No periosteal chondrosarcoma originated in the epiphysis. The mean diameter of the tumours was 3.8 cm (1.4 to 9.6) at initial diagnosis. An example of periosteal chondrosarcoma is shown in Fig. 3.

Histological evaluation showed that there were 18 patients with a grade I chondrosarcoma (50%), 16 with a grade II (44%) and none with a grade III tumour. In two (6%) no material was available for histological re-evaluation. Case 36 was a 58-year-old woman who underwent an intralesional resection of a grade II tumour of the body of the fourth thoracic vertebra followed by radiotherapy (Table I). Histologically proven local recurrence and pulmonary metastases were found at follow-up. She subsequently underwent a radical excision with *en-bloc* partial resection of the adjacent ribs and vertebral bodies and palliative radiotherapy. After 3.5 years of treatment she is still alive with a moderate response to her radiotherapy.

Case 33 was an 18-year-old man with a tumour in the metaphysis of the distal femur. A diagnostic excision biopsy was performed followed by radiotherapy. Histological grading was not done at that time. A chest radiograph revealed hilar lymphadenopathy; no further surgery was performed due to the assumption of metastatic disease. In the following three years a pathological femoral fracture occurred twice without progression of the tumour. After six years local recurrence was found in the distal femur and he

Figure 3. Case 34 shows periosteal chondrosarcoma histological grade I located at the metaphysis of the proximal humerus

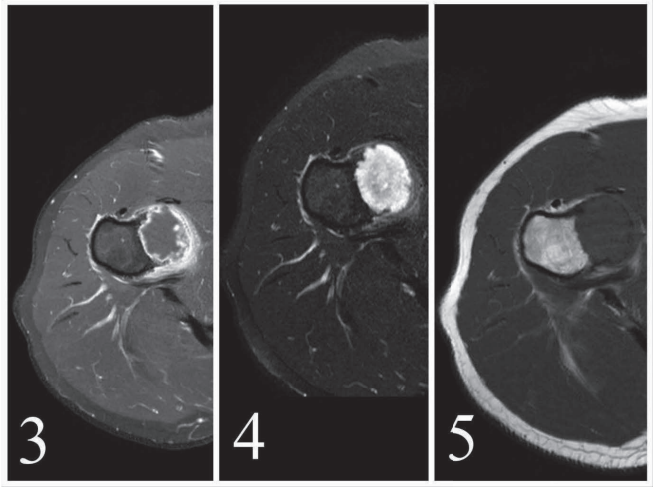
Figure 3a.



1: Antero-posterior radiograph of the right upper arm. Eccentric lobulated osteolytic lesion arising from the metaphysis of the humerus,

2: Coronal T1-weighted MR image. Juxtacortical / periosteal lesion with an intermediate signal intensity arising from the proximal humerus.

Figure 3b.



3: Axial T1-weighted fat-suppressed MR image after intravenous contrast administration. Septonodular enhancement of the tumour indicative of a cartilaginous tumour.

4: Axial T2-weighted fat-suppressed MR mage. Lobulation of the tumour. Very high signal intensity indicating the mucoid nature of the tumour.

5: Axial T1-weighted MR image. The juxtacortical / periosteal origin of the lesion is confirmed. The signal intensity is similar to that in the coronal view.

underwent amputation in May 1951. Histological examination confirmed a chondrosarcoma, although, once more, no grading was reported. A year later he died of skin and lung metastases, most likely due to de-differentiation.

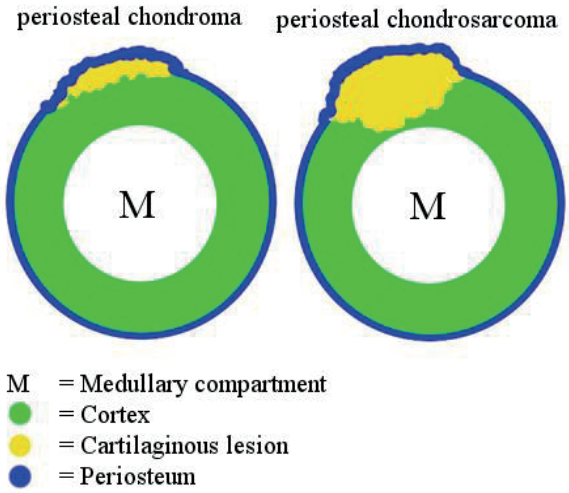
Discussion

The purpose of this case study was to present the demographics, clinical characteristics, treatment and results of a series of periosteal chondrosarcomas. After 59 years our national database contained only 36 cases, which represented 2% of all chondrosarcomas. This is a higher percentage than the 0.5% described in the literature. (2) The study is heterogeneous because patients were referred from a variety of hospitals, which used different methods of radiological and histological diagnosis and of treatment. Follow-up data on eight patients was not available. These factors potentially limit the usefulness of this study.

Despite this, it is, to the best of our knowledge, the largest case study of periosteal chondrosarcoma reported to date so we feel that we are justified in describing the demographics of this condition and offering advice on treatment and follow-up since other information is scarce. (1,3,6,7,10)

When a benign periosteal chondroma is larger than 3 cm in diameter, differentiating it radiologically from a periosteal chondrosarcoma can be difficult11 and histological evaluation becomes essential. (11) Plain radiographs, CT and MRI scans can be helpful; CT

Figure 4. Radiographic differentiation between periosteal lesions



Periosteal chondrosarcoma causes more cortical destruction than periosteal chondroma.

to reveal intralesional mineralisation and MRI for the detection of soft-tissue extension and intramedullary anomalies. (12–14) The addition of intravenous contrast can show septonodular enhancement indicating the cartilaginous nature of the tumour. (15) Periosteal chondrosarcomas are generally larger than benign periosteal chondromas and tend to cause more cortical destruction (Fig. 4). (15,16)

Diagnostic investigations should include conventional radiographs and an MRI scan of the site of the tumour. A CT-guided needle biopsy has proved to be adequate and should be performed to confirm the diagnosis before the start of treatment. (17,18) Metastases from periosteal chondrosarcoma have only been reported in grade II and III lesions. (5,6) Consequently, we only recommend staging for metastatic disease for these grades of tumour when a chest CT and a whole-body isotope bone scan should be carried out to detect pulmonary or bony metastases. (19)

Recent studies have shown that in selected patients a conventional low-grade intramedullary chondrosarcoma can be treated by intra-lesional curettage with or without adjuvant cryotherapy with the same oncological result as an *en-bloc* excision. (20,21) However, this did not apply to tumours which caused cortical destruction or to those with soft-tissue extension. Periosteal chondrosarcoma, unlike conventional chondrosarcoma, is located at the outer layer of the cortex, scalloping its surface and extending towards the surrounding soft tissues. The criteria for intra-lesional curettage are not therefore applicable to periosteal chondrosarcoma. It is known that periosteal chondrosarcoma can recur at a higher grade of malignancy. (22) As shown by cases 33 and 36, local recurrence and metastases can occur after incomplete resection. Although this is not significant when compared with 27 *en-bloc* excisions (or amputations) without recurrence, we feel that this also stresses the importance of *en-bloc* excision for all grades of periosteal chondrosarcoma.

We advise follow-up with plain radiographs for a period of five years. A baseline MRI can be performed after six months and again at two years. No local recurrences

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PART II

The impact of centralisation

CHAPTER 4

Delay in diagnosis and its effect on clinical outcome in high-grade sarcoma of bone: a referral oncological center study

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Abstract

Aim

To investigate delay in diagnosis by both patients and doctors, and to evaluate its effect on outcomes of high-grade sarcoma of bone in a single-referral oncological center.

Patients and Methods

Fifty-four patients with osteosarcoma, 29 with Ewing sarcoma and 19 with chondrosarcoma were enrolled in this retrospective study. Delay in diagnosis was defined as the period between initial clinical symptoms and histopathological diagnosis at our center. The delays were categorized as patient- or doctor-related. Short total delays were defined as <4 months; prolonged delays >4 months were assumed to have prognostic relevance.

Results

Total delay in diagnosis was 688.0 days in patients with chondrosarcoma, which is significantly longer than the 163.3 days for osteosarcoma ($P < 0.01$) and 160.2 days for Ewing sarcoma ($P < 0.01$). Most doctor-related delays were at the pre-hospital stage, occurring at the general practitioner (GP)'s office. However, prolonged total delays (≥4 months) did not result in lower survival rates. Five-year-overall survival rates were 67.0% for osteosarcoma, 49.0% for Ewing sarcoma and 60.9% for chondrosarcoma. Survival was significantly lower for patients with metastatic disease for all three types of sarcoma.

Conclusion

Prolonged delay in diagnosis does not result in lower survival. Metastatic disease has a pronounced effect on survival. Aggressive tumour behavior results in shorter delays. Minimizing GP-related delays could be achieved by adopting a lower threshold for obtaining plain radiographs at the pre-hospital stage.

Introduction

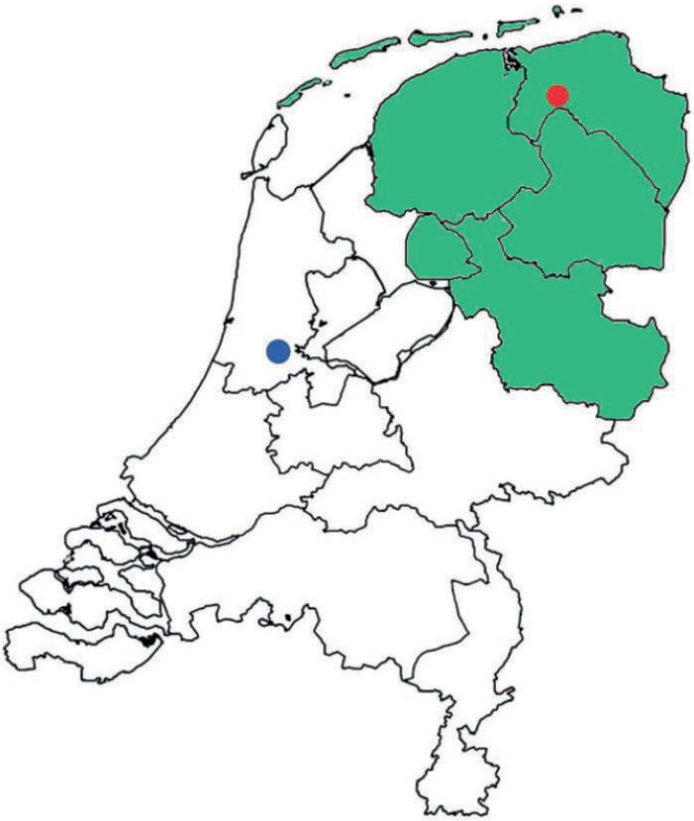
High-grade primary bone sarcomas are rare and aggressively invade soft tissue from bone. The most common high-grade bone sarcomas are osteosarcoma, Ewing sarcoma and chondrosarcoma. Because of their malignant nature and ability to metastasize, aggressive treatment is required. (1) The introduction of chemotherapy has dramatically improved survival of individuals with osteosarcoma and Ewing sarcoma. (2–6) While surgical and medical treatment options have also evolved since then, there has been no further remarkable improvement in survival rates. (7–9) Early diagnosis and treatment are still vital because local control is easier and may help prevent metastasis. Metastasis of high-grade sarcomas of bone greatly impacts survival. (10,11)

A cooperative group of oncologists in the Netherlands, Stichting Oncologische Samenwerking (SONCOS), has issued a general guideline on timely diagnosis of cancer. Diagnosing bone tumours is notoriously difficult and sometimes time-consuming, as in most cases multidisciplinary diagnosis by local or nationwide musculoskeletal tumour committees like the Dutch Committee on Bone Tumours is necessary. Hence, in some cases it is impossible to meet these guidelines.

Only a few series regarding delay in diagnosis have been published. (12–16) Prolonged duration of symptoms is associated with larger tumour size and increased rate of metastasis, but not with inferior outcomes. (12,17) Reducing patients' associated delay seems difficult because of the low incidence of these diseases. Most general practitioner s (GPs) will only encounter a primary bone sarcoma a few times during their entire career, even though they deal with musculoskeletal complaints daily. Kim et al. demonstrated that doctor-related delays followed by inappropriate primary procedures significantly influence survival. (18) A detailed analysis of diagnostic delays may reveal new insights on how to improve awareness among patients and physicians.

The University Medical Center Groningen (UMCG), one of four accredited bone tumour centers in the Netherlands, provides regional coverage for the treatment of bone sarcomas, as shown in Figure 1. In this study, we quantified and analysed patient- and doctor-related delays and their effects on clinical outcomes in a large series of high-grade bone sarcomas with the aim of identifying new strategies for shortening delays.

Figure 1. Regional coverage for the treatment of bone sarcomas in the Netherlands.



The capital of the Netherlands, Amsterdam, is marked in blue and the city of Groningen in red. The University Medical Centre Groningen is located in Groningen and provides regional coverage, being the oncology center for the treatment of bone sarcomas in the northern provinces of the Netherlands. These northern provinces are marked in green.

Patients and Methods

All cases were selected from a prospectively maintained bone tumour registry at UMCG. A minimum follow-up of 12 months was an inclusion criterion. All 102 consecutive patients with high-grade bone sarcoma diagnosed between October 2000 and October 2012 were included. They comprised 54 patients with osteosarcoma, 29 with Ewing sarcoma and 19 with intermediate or high-grade chondrosarcoma.

Delays in diagnosis were calculated in days and categorized as patient-related or doctor-related. Patient-related delays were defined as the period between the initial symptom and first consultation with a GP, which is required for all Dutch patients prior to referral to a specialized service. GPs were asked to provide the date of the first entry

in their medical records concerning tumour-related symptoms (swelling, daytime/night-time pain, loss of function, etc.). Doctor related

delays were further subdivided as follows: (i) between presentation to the GP's office and presentation to a primary hospital, defined as pre-hospital doctor-related delay; (ii) between presentation at a primary hospital and an oncology center, defined as primary clinic doctor-related delay; and (iii) between presentation to an oncology center and definitive histopathological diagnosis, defined as referral clinic doctor-related delay. The third group was further subdivided into two subgroups, ≤42 days and >42 days, according to the SONCOS guidelines. The date of presentation at each general primary hospital was obtained from the referral letters. When these were not available, the hospital was contacted with a request for the date of first presentation. Not every patient had been referred to a general secondary hospital; some had been referred directly to an oncology (referral) center or had presented to an emergency room. Short total delays were defined as <4 months; total delays longer than 4 months were assumed to have prognostic relevance based on expert opinion. Local presenting symptoms comprised pain, swelling, pathological fracture and/or loss of function. The presence of systemic symptoms (fatigue, loss of appetite, weight loss or fever) was recorded separately.

The primary outcome measure was the effect of delay (patient- or doctor-related) on oncological outcomes. The secondary aims were to assess patients' symptoms in and determine whether outcomes were is affected by transgression of the 6-week rule. Statistical analysis was performed using SPSS statistics 20 for Windows. Normality was tested using the Shapiro–Wilk test. Survival analysis was performed separately for each pathological type of sarcoma using Kaplan–Meier survival curves. The impact of delay in diagnosis on joint salvage rate and local recurrence was also investigated using binary logistic regression analysis.

Results

In all, 102 patients, 57 of whom were male and 45 female, were enrolled in this study. The mean age at presentation was 30.0 years (range, 5–89 years). The subjects were categorized according to pathological diagnosis: 54 had osteosarcomas, 29 Ewing sarcoma and 19 chondrosarcoma. Clinicopathological characteristics according to pathological diagnosis are shown in Table 1.

Table 1. Clinicopathological characteristics according to sarcoma type

Characteristic	Osteosarcoma (n = 54)	Ewing sarcoma (n=29)	Chondrosarcoma (n=19)
Age at primary therapy (years, mean [range])	28.9 (8–86)	17.4 (5–56)	52.4 (21–89)
Sex (cases [%])			
Male	30 (55.6)	19 (65.5)	8 (42.1)
Female	24 (44.4)	10 (34.5)	11 (57.9)
Location (cases [%])			
Long bones	50 (92.6)	10 (34.5)	8 (42.1)
Axial skeleton	4 (7.4)	18 (62.1)	7 (36.8)
Other	-	1 (3.4)	4 (21.1)
Primary therapy (cases [%])			
Surgical excision	50 (92.6)	16 (55.2)	19 (100)
Chemo/radiotherapy	4 (7.4)	13 (44.8)	-
Wide excision (cases [%])	46 (92.0)	9 (56.3)	16 (84.2)
Additional therapy (cases [%])			
(Neo-) adjuvant chemotherapy	44 (81.5)	27 (93.1)	-
Radiotherapy	10 (18.5)	22 (75.9)	3 (15.8)
Status after primary therapy (cases [%])			
Disease-free	37 (68.5)	15 (51.7)	15 (78.9)
Non-radical resection	3 (5.6)	3 (10.3)	2 (10.5)
Unresectable lesion	1 (1.9)	-	-
Metastatic disease	13 (24.1)	11 (37.9)	2 (10.5)
Follow-up (months, mean [SD])	54.9 (42.8)	39.2 (31.2)	54.6 (35.8)
Current status (cases [%])			
Continuously disease-free	24 (44.4)	11 (37.9)	10 (52.6)
Alive with disease	2 (3.7)	1 (3.4)	1 (5.3)
No evidence of disease	8 (14.8)	4 (13.8)	1 (5.3)
Dead of disease	18 (33.3)	13 (44.8)	6 (31.6)
Dead of other disease	2 (3.7)	-	1 (5.3)

SD, Standard Deviation.

Clinical Characteristics

Osteosarcomas were located in the long bones in 50 patients (92.6%), the femur being the predominant site (31 patients, 57.4%). Pain was the most frequent symptom, being present in 44 patients (81.4%). Most Ewing sarcomas were located in the axial skeleton (18 patients, 62.1%) with the spine or ribs as the predominant site in nine patients (31.0%), followed by the pelvis in eight patients (27.6%). Ten patients (34.5%) presented with Ewing sarcoma in their long bones. Pain was the commonest symptom, being present in 20 patients (68.9%). Chondrosarcomas were most in the long bones (eight patients,

42.1%); the most frequent symptom was pain, which was present in 13 patients (68.4%). Six patients (11%) with osteosarcoma and 10 (34.5%) with Ewing sarcoma presented with systemic symptoms, whereas were none of the patients with chondrosarcoma had systemic symptoms.

Delays in Diagnosis

The mean delay in diagnosis is shown in Table 2 and Figure 2. The mean total delay was 163.3 days (standard deviation [SD], 176.5 days) in patients with osteosarcoma, 160.2 days (SD, 193.7 days) in patients with Ewing sarcoma, and 688.0 days (SD, 678.4 days) in patients with chondrosarcoma,

this mean total delay being significantly longer than that for osteosarcoma and Ewing sarcoma ($P < 0.01$). The mean patient-related delay for all types of sarcoma was 83.2 days (SD, 208.1 days), being 244.1 days for chondrosarcoma, which is somewhat longer than that for osteosarcoma (44.8 days, $P = 0.058$) and significantly longer than that for Ewing sarcoma (41.0 days, $P = 0.034$). The mean overall doctor-related delay was 156.2 days (SD, 210.9 days). Mean doctor-related delay for chondrosarcoma

was 332.3 days, which is significantly longer than for osteosarcoma (100.0 days, $P \leq 0.01$) and Ewing sarcoma (130.6 days, $P < 0.01$). Mean overall pre-hospital doctor related delay was 101.5 days (SD, 189.7 days); data on this were unavailable for 14 cases (13.5%). The mean overall primary

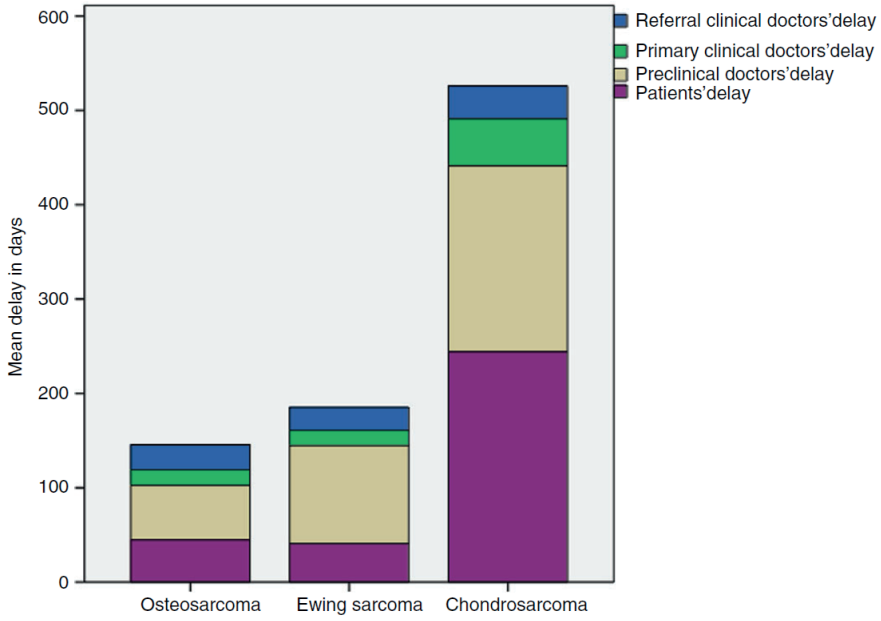
clinic doctor-related delay was 23.5 days (SD, 30.4 days), data being unavailable for 3.9% of cases. This delay was significantly longer for patients with chondrosarcoma (49.7 days) than for those with osteosarcoma (16.5 days; $P < 0.01$) or Ewing sarcoma (16.3 days; $P < 0.01$). The mean overall referral clinic doctor-related delay was 27.6 days (SD, 29.6 days), all data being available.

Table 2. Delay in diagnosis (days, mean [standard deviation]) according to sarcoma type

Mean delay in days	Osteosarcoma (n = 54)	Ewing sarcoma (n=29)	Chondrosarcoma (n=19)
Total delay	163.3 (176.5)	160.2 (193.7)	688.0 (678.4)*
Patient-related delay	44.8 (41.8)	41.0 (40.5)	244.1 (433.5)*
Mean doctor-related delay	100.0 (94.6)	130.6 (217.6)	332.3 (312.7)*
Pre-hospital doctor-related delay	57.8 (56.1)	103.6 (223.8)	197.2 (291.9)
Primary clinic doctor-related delay	16.5 (21.3)	16.3 (21.3)	49.7 (43.6)*
Referral clinic doctor-related delay	26.6 (28.2)	24.5 (28.0)	34.9 (36.0)

*Significant difference ($P < 0.05$).

Figure 2. Mean diagnostic delay in days.



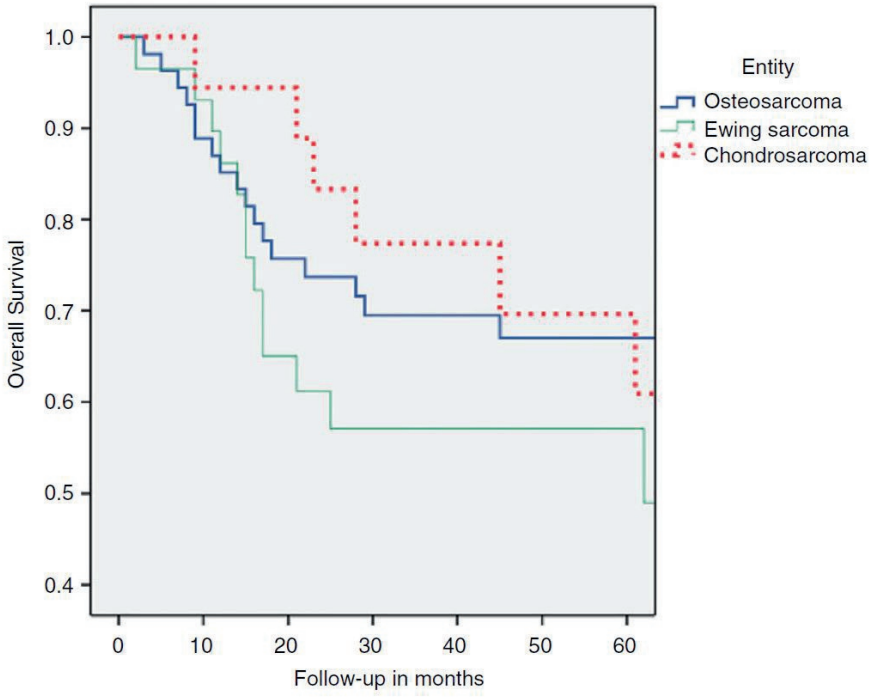
Outcomes

Metastatic disease was present at diagnosis in 24.1% of patients with osteosarcoma, 37.9% with Ewing sarcoma and 10.5% with chondrosarcoma. Surgical resection of the primary tumour was performed in 92.4% of patients with osteosarcoma and 55.2% with Ewing sarcoma; all patients with chondrosarcoma underwent surgical resection. There was no association between length of delay and rate of limb salvage procedures. Overall, 16 patients with tumours in the axial skeleton underwent surgical excision, resulting in intralesional resections in 43.8% of them, compared with 9.4% of 60 patients with tumours in the long bones ($P < 0.01$). Adjuvant chemotherapy was given to 93.7% of patients with Ewing sarcoma. Local recurrence was diagnosed in 16 patients (15.7%), six of whom had osteosarcomas (11.1%), five Ewing sarcomas (17.2%) and five chondrosarcomas (26.3%). There was no association between length of delay and local recurrence rate for any single pathological type or overall. At the end of follow-up, 44.4% of patients with osteosarcoma, 37.9% with Ewing sarcoma and 52.6% with chondrosarcoma were continuously disease-free. After primary treatment, no evidence of disease was seen in 14.8% of subjects with osteosarcoma, 13.8% of those with Ewing sarcoma and 5.3% of those with chondrosarcoma. Patient mortality was highest for Ewing sarcoma; 44.8% of cases dying of disease.

Survival

Thirty-eight patients (37.3%) had a minimum follow-up of 5 years. The mean duration of follow-up in patients with osteosarcoma was 54.9 months (SD, 42.8 months) with a 5-year overall survival rate (60 months) of 67.0% (SD, 6.6 months). The mean duration of follow-up in patients with Ewing sarcoma was 39.2 months (SD, 31.2 months) with a 5-year overall survival rate (62 months) of 49.0% (SD, 11.1 months). The mean duration of follow-up in patients with chondrosarcoma was 54.6 months (SD, 35.8 months) with a 5-year overall survival rate (61 months) of 60.9% (SD, 13.0 months). Five-year overall survival curves are displayed in Figure 3. Overall (all sarcoma types), 5-year-overall survival rates were significantly lower for patients with tumours in the axial skeleton (46.0%) than for those with long bone tumours (72.3%; P = 0.016). In patients with osteosarcoma, the 5-year-overall survival was significantly lower for tumours in the axial skeleton (25.0%) than for those in long bones (71.0%; P = 0.026). For Ewing sarcoma and chondrosarcoma, tumour location did not significantly impact 5-year-overall survival. The 5-year-overall survival of patients with osteosarcoma was significantly lower after intralesional resection (25.0%) than after wide resection (77.3%; P = 0.01). Similarly, for Ewing sarcoma, the 5-year-overall survival was significantly lower after intralesional resection (42.9%) than after wide resection (71.1%; P = 0.048). The excision margin did not significantly impact 5-year-overall survival in subjects with chondrosarcoma. Five-year-overall survival rates were significantly lower in patients with metastatic osteosarcoma (26.9%) than in patients who remained disease-free after resection (79.3%; P < 0.01). Survival of subjects with metastatic Ewing sarcoma was also significantly lower (36.4%) than for disease-free patients (72.7% after 62 months; P < 0.01). The 5-year overall survival rates of patients with chondrosarcoma and metastases was 50% compared 69.5% in patients who remained disease-free (P < 0.01). The mean overall delay from presentation at UMCG to histological diagnosis for each sarcoma type was compared based on the SONCOS guidelines and it was found that the 5-year overall survival rate for osteosarcoma diagnosed in <42 days was 58.2%, as against 76.9% in patients diagnosed ≥42 days (not significant [NS]). The overall survival rate after 62 months for patients with Ewing sarcoma diagnosed in <42 days was 39.4%, compared to 80.0% of patients diagnosed ≥42 days (NS). The overall survival after 61 months for chondrosarcoma was 46.2% in patients diagnosed in <42 days and 83.3% in patients diagnosed ≥42 days (NS). There were no significant differences in 5-year overall survival rates between total delay <4 months and a longer total delay for patients with osteosarcoma and Ewing sarcoma. There was no significant difference in overall survival rates between a total delay <4 months (two patients, 50% overall survival after 40 months) and a delay ≥4 months (17 patients, 63.6% overall survival after 61 months) for patients with chondrosarcoma. No significant differences were identified in metastatic disease rates after a total delay <4 months compared to a longer total delay for any of the three pathological types or for all subjects combined.

Figure 3. Five-year-overall survival for high-grade sarcoma of bone according to sarcoma type.



Discussion

Delay in diagnosis may have an adverse effect on oncologic outcomes. SONCOS guidelines state that diagnosis at an oncology center within 42 days minimizes negative effects on outcome. The purpose of this study was to investigate patient- and doctor-related delays and evaluate their effects on outcomes. High-grade bone sarcomas are rare neoplasms; 102 lesions were seen in our referral oncology center over 12 years. The present study provides a valuable addition to data of other published Dutch series on outcomes of high-grade bone sarcomas. (19–22) Furthermore, this report includes 8.3% of all patients with high-grade bone sarcomas who underwent orthopaedic oncological treatment in the Netherlands during that 12 years. (23) Because our study focused on the effect of delay in diagnosis, one of its limitations is that we did not include tumour size as a prognostic factor. (24) There are few relevant published reports, as shown in Table 3.

Table 3. Relevant published reports on delay in diagnosis of high-grade bone sarcomas.

Authors	Years	Sarcoma type	Conclusion
Sneppen and Hansen (14)	1984	84 osteosarcomas 40 Ewing sarcomas	No association between delay and survival
Wurtz et al. (34)	1999	68 pelvic chondrosarcomas	No association between delay and survival
Widhe and Widhe (15)	2000	102 osteosarcomas 47 Ewing sarcomas	Doctor-related delay significantly longer for Ewing sarcoma
Bacci et al. (26)	2000	965 high-grade osteosarcomas	Aggressive tumour behaviour results in shorter delay
Kim et al. (18)	2009	26 osteosarcomas	Doctor-related delay superimposed on an inappropriate primary procedure has a detrimental effect on survival
Pan et al. (13)	2010	30 knee-region osteosarcomas	Total delay in diagnosis 17 weeks
Goedhart et al. (current study)	2016	54 osteosarcomas 29 Ewing sarcomas 19 chondrosarcomas	Longer delay in patients with chondrosarcoma, no effect on outcome

Bacci et al. reported a shorter delay in patients with metastatic osteosarcomas than in those with localized disease. (12) They concluded that aggressive tumour behaviour results in shorter delays. This conclusion is in accordance with our results, since patients with chondrosarcoma had significantly longer delays in diagnosis than those with osteosarcoma and Ewing sarcoma. However, the long delay in diagnosis of intermediate and high-grade chondrosarcoma did not result in lower survival rates. We believe that this can be explained by less aggressive tumour behaviour, absence of systemic symptoms and the inclusion of intermediate-grade chondrosarcomas. However, it is important to recognize that chondrosarcoma can dedifferentiate and that this is associated with poor survival. Sneppen and Hansen defined treatment delay as the time from the first symptom until presentation at an oncology center. (14) Their mean treatment delay was 6.4 months for osteosarcoma and 9.6 months for Ewing sarcoma, which is longer than our series, in which there was a treatment delay of 3.9 months for osteosarcoma and 5.3 months for Ewing sarcoma. Comparison between the Bacci study and our own is difficult because referral patterns and accuracy have evolved over the past 30 years. Primary orthopaedic hospitals in the Netherlands follow the guidelines on bone tumours, which specify that biopsy and treatment should be performed in an oncology referral center. Although diagnostic delay at an oncology center makes up only a small slice of the total delay, it is the most visible type of delay. According to SONCOS, the acceptable referral clinic doctor-related delay for a Dutch oncological center to diagnose a neoplasm and start treatment is 42 days. (25) In this study, the referral clinic doctor-related delay from presentation to diagnosis was 27.6 days and thus within our national standards. For high-grade chondrosarcoma it was 34.9 days. Because these tumours often present in the pelvis and may therefore be difficult to access for biopsy, multiple

biopsies may be performed before a definitive diagnosis is made. Delay in diagnosis is also associated with other clinical variables; Kim et al. found that misdiagnosis and inappropriate treatment resulted in inferior outcomes in subjects with osteosarcoma. (18) This is in accordance with our study, in which we found significantly lower survival rates in patients with osteosarcoma and Ewing sarcoma after intralesional surgical resection. Furthermore, intralesional surgical resection occurred more often with tumours located in the axial skeleton. Location of a tumour in the axial skeleton is also associated with lower survival rates. According to our data, diagnosis after 42 days of high-grade bone sarcomas does not result in lower survival; neither do total delays exceeding 4 months. And yet, paradoxically, metastatic disease after primary resection is associated with significantly lower survival rates. This discrepancy may be explained by the fact that aggressive tumour behaviour results in early clinical symptoms, thereby facilitating a timely diagnosis. Our findings imply that tumour location and resectability have more influence on survival than delay in diagnosis in patients with osteosarcoma and Ewing sarcoma. Tumour location and resectability, metastatic disease at diagnosis, response to chemotherapy and local recurrence are known prognostic factors for osteosarcoma and Ewing sarcoma according to published reports. (8,26–33) Most of the diagnostic delay occurred in the prehospital setting at the GP's office. We realize that is very difficult for GPs to recognize a bone malignancy because they generally only encounter one or two primary bone sarcomas in their entire careers. Pain was the most common symptom in our study and in other reports. (14,15) Therefore GPs should have a low-threshold for requesting plain radiographs in patients with pain and no history of trauma; such a policy would likely decrease mean doctor-related delay by accelerating referral to an oncology center. Persistent pain for more than 6 weeks is a red flag and an indication for a radiograph.

In conclusion, this study provides valuable insight into diagnostic delay patterns for high-grade bone sarcomas in the Netherlands. Prolonged delay in diagnosis of high-grade sarcomas of the bone does not result in lower survival. The SONCOS guidelines for diagnosing neoplasms are easily met, but do not seem clinically relevant to high-grade bone sarcomas. Persistent pain for more than 6 weeks in the prehospital (GP) setting is an indication for a radiograph.

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CHAPTER 5

Organization of bone sarcoma care: a cross-sectional European study

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Abstract

Aim

To assess organization of care in several bone sarcoma centres in Europe affiliated to the European Musculoskeletal Oncology Society (EMSOS) for comparison and identify potential improvements in organization of care.

Patients and Methods

Data for this observational cross-sectional study was obtained through healthcare professionals affiliated to EMSOS. The authors formulated 10 questions regarding organization of care. The questions were focused on guidance, multidisciplinary decision-making, and data storage. A digital questionnaire was synthesized and included quality control. The digital questionnaire was sent to 54 representative members of EMSOS. We did not receive responses from 29 representative countries (53.7%) after one digital invitation and two digital reminders.

Results

We received data from 25 representatives of bone sarcoma centers from 17 countries across Europe (46.3%). Authorization to perform oncological care in a bone sarcoma center was government issued in 41.2% of cases and based on expertise without governmental influence in 52.9% of cases. In 64.7% of the countries, a national bone tumor guideline regarding for diagnosis and treatment is used in oncological care. A national bone tumor board for extensive case evaluation including classification and advice for treatment is available for 47.1% of the countries. All participating bone sarcoma centers have a mandatory local multidisciplinary meeting before the start of treatment; in 84.0% this meeting takes place once a week. During this multidisciplinary meeting a median of 15 cases (range, 4–40 cases) are discussed. In terms of storage of oncological data, a local registry is used in eight countries (47.1%). A national registry is used in eight countries (47.1%).

Conclusion

A national bone tumor board gives bone sarcoma centers with little adherence the opportunity to gain knowledge from a more experienced team. Centralization of care in a bone sarcoma center is important to lower incidences. The optimal size for a bone sarcoma center in terms of patient adherence is not known at present.

Introduction

High-grade bone sarcomas are aggressive tumors with a high potential of metastasis. Diagnosis and treatment of these neoplasms is challenging due to low incidences. (1–5) Therefore, centralization of sarcoma care is important in order to realize a multidisciplinary approach by an experienced team. (6,7) Nowadays, the majority of patients with a primary bone sarcoma are diagnosed and treated in a bone sarcoma centre. A few dozen bone sarcoma centres with expertise are scattered across Europe. However, as for differences in nationwide organization of care, the approach towards diagnosis and treatment differs between these hospitals. Further differences are seen in size in terms of patient adherence of bone sarcoma centres due to centralization of care. Based on a single study, treatment in a bone sarcoma centre was associated with higher survival for high-grade osteosarcoma patients. (8) However, this association was not seen for high-grade chondrosarcoma and Ewing sarcoma patients. Furthermore, the optimal size for a bone sarcoma centres in terms of patient adherence is not known at this moment. The European Musculoskeletal Oncology Society (EMSOS) aims to promote advance in science, disseminate knowledge and promote mutual collaboration for bone sarcoma care between the different affiliated bone sarcoma centres.

This study aims to assess organization of care in several bone sarcoma centres in Europe affiliated to EMSOS for comparison and improvement of knowledge.

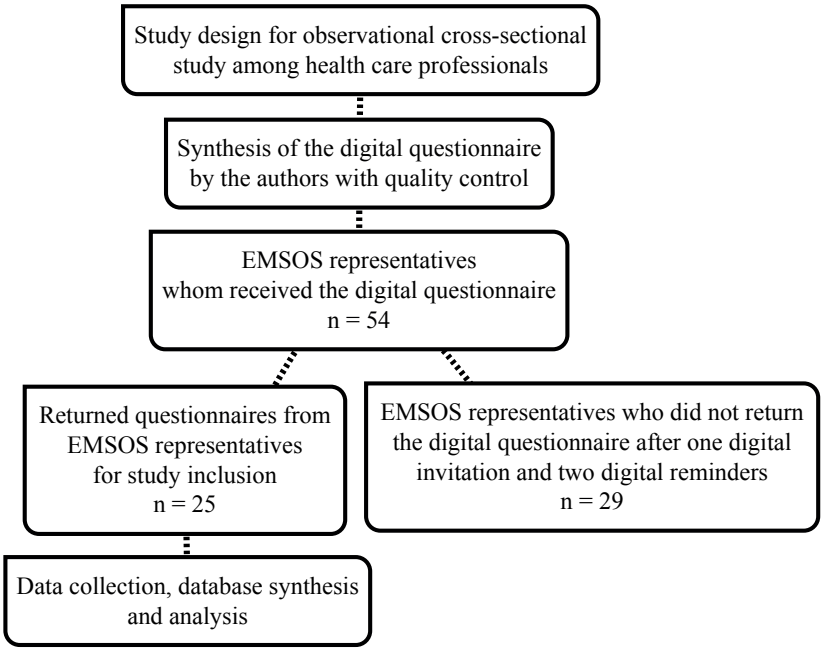
Patients and Methods

The European Musculoskeletal Oncology Society (EMSOS) was founded in 1987. The particular purpose of EMSOS is to facilitate a network for different specialists and institutes in order to improve treatment of musculo-skeletal tumors. This is realised by collaborative research projects and to disseminate knowledge through an annual congress.

Data for this observational cross-sectional study was obtained through health care professionals affiliated to EMSOS. The authors formulated ten questions regarding organization of care and produced a digital questionnaire, which is displayed in the appendix. The questions were focused on guidance, multidisciplinary decision-making and data storage. The digital questionnaire was not validated. EMSOS members were approached as representatives from all over Europa. These representatives were asked to return this digital questionnaire. A flowchart of the study design was displayed in figure 1. Observational research among health care professionals does not fall under the scope of the Dutch Act on Medical Scientific Research involving Human Beings (WMO).

Analyses were performed using IBM SPSS Statistics for Windows (Version 23.0, United States) and Microsoft Excel 2013 (United States).

Figure 1. Flowchart of the study design



Results

A digital questionnaire was sent to 54 representative members of EMSOS, we received a response of 25 representatives (46.3%) from 17 countries after one digital invitation and two digital reminders. These representatives were acknowledged as EMSOS study group. The geographical dispersion across Europe of responding bone sarcoma centres was displayed in figure 2. Questionnaire output data regarding bone sarcoma centres per country were displayed in table 1.

Figure 2. Geographical dispersion across Europe of responding bone sarcoma centres

1. Netherlands: University Medical Center Groningen, Leiden University Medical Center.
2. Belgium: Jules Bordet Institute Brussels.
3. Germany: Medical Center of the University of Munich, Stuttgart Cancer Center Olgahospital.
4. United Kingdom: University College Hospital London, Royal Orthopaedic Hospital Birmingham.
5. France: Limoges Teaching Hospital, University Hospital Hotel-Dieu Nantes, Hospital Cochin Paris.
6. Spain: Hospital Universitario de Bellvitge Barcelona, Hospital Universitario La Paz Madrid.
7. Italy: Centro Traumatologico Ortopedico Florence, Regina Elena National Cancer Institute Rome, Cancer Institute G. Pascal Foundation Naples.
8. Norway: Oslo University Hospital.
9. Sweden: Karolinska Hospital Stockholm.
10. Finland: Helsinki University Central Hospital.
11. Austria: Medical University of Graz.
12. Switzerland: Balgrist University Hospital Zürich.
13. Poland: Pomeranian Medical University of Szczecin.
14. Slovenia: Ljubljana University Medical Centre.
15. Serbia: Institute for Oncology and Radiology Belgrade.
16. Ukraine: National Cancer Institute Kiev.
17. Turkey: Acibadem Maslak Hospital Istanbul.

Table 1. Questionnaire output data regarding bone sarcoma centres per country

	Number of bone sarcoma centres	Million inhabitants in 2018(22)	Million inhabitants per bone sarcoma centre	Authorisation basis	Bone tumour guideline	National bone tumour board	Number of cases discussed per week in local meeting	Referral to a bone sarcoma centre (%)	Treatment in a bone sarcoma centre (%)	Registry for oncological data
Netherlands	4	17.15	4.28	Government	National	Yes	25-30	90	98	National
Belgium	5	11.57	2.31	Expertise	Local	No	12	50	90	Local
Germany	Not clear*	80.46	Not clear*	Not clear*	National	No	5-20	Not clear*	Not clear*	Local **
United Kingdom	5	65.11	13.02	Government	National	Yes	40	90	100	National
France	12	67.36	5.61	Expertise	National	Yes	15-40	90	98	National
Spain	10	49.33	4.93	Expertise	National	No	6-10	70	30	Local
Italy	10	62.25	6.22	Expertise	Local	No	10-15	90	95	Local
Norway	2	5.37	2.69	Government	National	No	10	90	100	Local
Sweden	3	10.04	3.35	Government	National	Yes	20	95	95	National
Finland	4	5.54	1.38	Government	Local	Yes	25	90	99	Local
Austria	4	8.79	2.19	Expertise	Local	No	15	70	90	National
Switzerland	5	8.29	1.66	Expertise	National	No	12	95	N/A	Local
Poland	5	38.42	7.68	Government	National	Yes	4	70	80	National
Slovenia	1	2.10	2.10	Expertise	National	Yes	12	N/A	95	National
Serbia	1	7.08	7.08	Expertise	Local	Yes	10	70	80	Local
Ukraine	4	43.95	10.98	Government	National	No	4	50	30	National
Turkey	5	81.26	16.25	Expertise	Local	No	20	5	20	No registry

N/ A= not available

Not clear* = In Germany bone sarcoma centres are not defined, therefore it is not clear where bone sarcoma patients are treated in this country.

** = COSS: Cooperative German-Austrian-Swiss Osteosarcoma Study Group and CESS: Cooperative German-Austrian-Swiss Ewing sarcoma Study Group are multinational initiatives for registration of oncological data.

Guidance

Authorization to perform oncological care in a bone sarcoma centre was government issued in the Netherlands, the United Kingdom, Norway, Sweden, Finland, Poland and Ukraine (41.2%). Authorization based on expertise without governmental influence was seen in Belgium, France, Spain, Italy, Austria, Switzerland, Slovenia, Serbia and Turkey (52.9%). A lack of consensus towards authorization of bone sarcoma centres was seen in Germany, there are not a defined number of bone sarcoma centres in this country. In 64.7% of the countries a national bone tumor guideline regarding for diagnosis and treatment is used in oncological care. In Belgium, Italy, Finland, Austria, Serbia and Turkey local hospital guidelines are used for diagnosis and treatment (35.3%). Several (national) bone tumor guidelines, obtained through the questionnaire, are displayed in the appendix.

Multidisciplinary decision-making

A national bone tumor board for extensive case evaluation including classification and advice for treatment is available in the Netherlands, the United Kingdom, France, Sweden, Finland, Poland, Slovenia and Serbia (47.1%). All participating bone sarcoma centres have a mandatory local multidisciplinary meeting before the start of treatment; in the vast majority this meeting takes place once a week (84.0%). During this multidisciplinary meeting a median of 15 cases (range, 4-40) are discussed. Regarding referral towards and treatment in a bone sarcoma centre, most countries had percentages in the upper quartiles as shown in table 1. Lower referral percentages were seen in Belgium (50%), Ukraine (50%) and Turkey (5%). With regards to treatment in a bone sarcoma centre, relatively low treatment percentages were seen in Spain (30%), Ukraine (30%) and Turkey (20%).

Data storage

A local registry for oncological data is used in Belgium, Germany, Spain, Italy, Norway, Finland, Switzerland and Serbia (47.1%). A national registry is used in the Netherlands, the United Kingdom, France, Sweden, Austria, Poland, Slovenia and Ukraine (47.1%). Bone tumors are not registered in Turkey (5.8%).

Discussion

Dedicated health care professionals all over Europe perform bone sarcoma care. This is the first study to provide cross-sectional data regarding organization of bone sarcoma care in Europe. A wide range of centralization across Europe was identified. Limitations of this study are clear because of the observational concept. Furthermore, the questionnaire we used was not validated. Finally although the respondents represent a large proportion of Europe, the response rate of 46.3% could have led to response bias.

The basis on which oncological care in a bone sarcoma centre is performed differs. Most bone sarcoma centres are authorized based on expertise, government authorization has been issued in the countries where the government has extensive responsibilities for national health care. In a considerable number of countries bone tumor guidelines are issued for diagnostic work-up, referral and treatment. We believe that these guidelines are a valuable instrument for the clinicians. A recent development is that the European Commission launched an initiative for European Reference Networks (ERN) to create a network of excellence in clinical practice. These networks aim to facilitate discussion on and improve care of complex or rare diseases. (9) Furthermore, essential requirements for quality cancer care for soft-tissue and bone sarcoma in adults were defined by the European CanCer Organization (ECCO). (10) Partially based on these developments, a survey among Italian oncological health care professionals resulted in a set of minimum requirements needed to define a referral centre for rare cancers. (11)

An interesting finding from our study is the lack of consensus towards authorization of bone sarcoma centres in Germany as shown in table 1. Germany is clearly different from the other countries regarding its organization and centralization. Until now, a definition of a bone sarcoma centre has never been developed in Germany resulting in decentralization of bone sarcoma care towards treatment centres.

Decentralization of bone sarcoma care in a country could have adverse effects in terms of delay in diagnosis, misdiagnosis and inappropriate treatment. Delay in diagnosis in high-grade bone sarcomas from symptoms until start of the treatment has been described in the literature. (12) Delay is inevitable, but minimizing delay using clear guidelines and referral patterns seems judicious. As mentioned earlier, assessment of radiology and histology by an experienced team is essential for a good prognosis in chondrosarcoma. (7) Furthermore, misdiagnosis and subsequent inappropriate treatment resulted in inferior outcomes in osteosarcoma. (13) For Ewing sarcoma, inadequate surgical margins are significantly correlated with inferior outcome. (14) A study regarding soft-tissue sarcoma concluded that patients treated in high-volume hospitals less often had macroscopic residual disease. (6) At an earlier stage, comprehensive incidence estimates were published for all the main primary bone sarcomas in the Netherlands. (8) These incidences for high-grade chondrosarcoma (0.15

per 100,000 European Standardised Rate (ESR)), high-grade central osteosarcoma (0.25 per 100,000 ESR) and Ewing sarcoma (0.15 per 100,000 ESR) are relatively low compared to other cancer types.

We believe that centralization of care towards a bone sarcoma centre is sensible given these incidences, regardless of the basis of authorization or government inference.

In our study, we reproduced the availability of a bone sarcoma centre for bone sarcoma patients based on the number of inhabitants of the represented country. A major increase of the adherence per bone sarcoma centre could result in a low referral and treatment percentage with Turkey and Ukraine as an example as shown in table 1. A possible explanation could be the increased geographical dispersion in the less populated areas of these big countries.

The ECCO expert group recommends that at least 50 bone sarcoma patients are treated in a bone sarcoma centre every year. (10) This threshold is based on guidance from the British National Institute for Health and Care Excellence (NICE). (15) Conversely, the authors state that this threshold of bone sarcoma 50 patients every year is dependent on referral patterns and expertise distribution. Bone sarcoma patients are defined by the ECCO as patients with chondrosarcoma, Ewing sarcoma, and osteosarcoma. Furthermore, very rare entities as undifferentiated bone sarcoma, chordoma and giant cell tumor of bone are defined as bone sarcomas by the ECCO. (10) Interestingly, the actual exposure of a bone sarcoma centre could be calculated based on our data. A calculation could be made in which the combined incidence for high-grade chondrosarcoma, high-grade central osteosarcoma and Ewing sarcoma (0.55 per 100,000 ESR) is matched with a minimum exposure of 50 bone sarcoma patients for a single bone sarcoma centre every year. This is roughly 4 patients per month. Based on the ECCO recommendation, a single bone sarcoma centre should minimally have an adherence of around 9 million inhabitants to match the exposure of 50 bone sarcoma patients. Based on our study, this exposure can only be matched by bone sarcoma centres in the United Kingdom, Turkey and Ukraine. However, as mentioned earlier regarding Turkey and Ukraine, more inhabitants per bone sarcoma centre could result in a low referral and treatment percentage of bone sarcoma patients, which seems undesirable. Based on our study, the effects of centralization could not be assessed. Therefore, the optimal size for a bone sarcoma centre is not known at this moment. We believe that the participating bone tumor centres in our study provide excellent bone sarcoma care. The recommendation of 50 bone sarcoma patients per year is based on existing evidence as stated in the ECCO article with a reference to the 2006 NICE guidance document. (10,15) In this guidance document the authors refer to studies from the United Kingdom and Sweden, which conclude that treatment of a bone sarcoma in a specialist centre is preferred, without notice of a minimum threshold for treatment per year. (16,17) This suggests that the treatment threshold for a bone sarcoma centre of 50 bone sarcoma patients per year

is not evidence based. We believe that the treatment threshold for a bone sarcoma centre per year for adequate treatment of their patients is not known at this moment. To evaluate this, a comparative study between differently sized bone sarcoma centres regarding survival in high-grade bone sarcoma patients could be a next step. This should give more clarity about the actual effect of centralization of care on survival. Although the treatment threshold is not known, we think that a minimum treatment threshold of at least one bone sarcoma patient every month in a single bone sarcoma centre is desirable. This preserves the available expertise of the multidisciplinary team. Reasonably, bone sarcoma centres with little adherence could benefit from a national bone tumor board for extensive case evaluation including classification and advice for treatment from a team with more experience.

A national registry is the basis for adequate monitoring and reporting of outcomes. Furthermore, a complete national registry could provide in valuable and comparative big data for collaborative research, which is needed with the given low incidences for high-grade bone sarcomas. This is emphasised by the previously published collaborative EMSOS studies for several rare entities. (18–21) In our study, the effect of evaluation of care using a national registry was not investigated. Still we think that better evaluation of care, as one can do with a registry, provides essential information to improve quality of care and outcome for bone sarcoma patients.

In conclusion, we believe that centralization of care towards a bone sarcoma centre should be mandatory. The optimal size for a bone sarcoma centre in terms of patient adherence is not known at this moment. Furthermore, a national registry is essential for adequate storage and reproduction of oncological data.

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Appendix 1. Digital questionnaire regarding organization of bone sarcoma care containing ten questions.

1. On which grounds is a bone sarcoma centre in your country authorized to perform oncological care?

2. Is there national bone tumor guideline regarding referral for diagnosis and treatment to a bone sarcoma centre?
   If yes, could you please provide the URL links of this national bone tumor guideline.

3. Is there a national bone tumor board for extensive case evaluation including classification and advice for treatment?

4. How many bone sarcoma centres does your country have?

5. Please give an estimate of the percentage of patients that are referred to a bone sarcoma centre before biopsy?

6. Is there a mandatory multidisciplinary meeting in your bone sarcoma centre before start of the treatment?

7. How frequent does the multidisciplinary meeting in your bone sarcoma centre take place? (e.g. once a week)

8. How many patients are discussed on average during this multidisciplinary meeting?

9. Could you give an estimate of the percentage of patients with a bone sarcoma treated in a bone sarcoma centre in your country?

10. How is oncological data regarding tumor type and treatment archived / stored in your country?

Appendix 2. Available bone tumor guidelines

The Netherlands
https://www.soncos.org/kwaliteit/normeringsrapport/
https://www.oncoline.nl/beentumoren

Germany
https://www.awmf.org/uploads/tx_szleitlinien/025006l_S1_Ewing_Sarkome_Kinder_Jugenliche_2014-06.pdf

United Kingdom
https://www.nice.org.uk/guidance/qs78

France
http://www.infosarcomes.org/les-reseaux-netsarc-et-resos
https://resos.sarcomabcb.org/

Spain
http://www.grupogeis.org/en/scientific-activity/guides-and-nomograms/geis-guides

Italy
http://www.italiansarcomagroup.org/

Norway
https://www.helsedirektoratet.no/retningslinjer/sarkomer-handlingsprogram

Switzerland
http://www.sarkomkompetenzzentrum.ch/

Poland
https://journals.viamedica.pl/nowotwory_journal_of_oncology/article/view/51993

Slovenia
https://www.onkoi.si/fileadmin/onko/datoteke/dokumenti/Onkologija_letnik_XV_st1/Onkologija_junij_2011_web_2_9.pdf

Society
Oncolink
https://www.oncolink.org/cancers/sarcomas

European Society for Medical Oncology (ESMO) Guidelines
https://www.esmo.org/Guidelines/Sarcoma-and-GIST/Bone-Sarcomas

PART III

Follow-up of bone sarcoma

CHAPTER 6

Follow-up in bone sarcoma care: a cross-sectional European study

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Abstract

Aim

Follow-up of high-grade bone sarcoma patients with repeated radiological imaging aims at early detection of recurrent disease or distant metastasis. Repeated radiological imaging does expose (mostly young) patients to ionising radiation. At this point it is not known whether frequent follow-up increases overall survival. Additionally, frequent follow-up subjects patients and families to psychological stress. This study aims to asses follow-up procedures in terms of frequency and type of imaging modalities in bone tumour centres across Europe for comparison and improvement of knowledge as a first step towards a more uniform approach towards bone sarcoma follow-up.

Patients and Methods

Data was obtained through analysis of several follow-up protocols and a digital questionnaire returned by EMSOS members of bone tumour centres all across Europe.

Results

All participating bone tumour centres attained a minimum follow-up period of ten years. National guidelines revealed variations in follow-up intervals and use of repeated imaging with ionising radiation. A local and a chest X-ray were obtained at 47.6% of the responding clinics at every follow-up patient visit.

Conclusion

Variations were seen among European bone sarcoma centres with regards to follow-up intervals and use of repeated imaging. The majority of these expert centres follows existing international guidelines and finds them sufficient as basis for a follow-up surveillance programme despite lack of evidence. Future research should aim towards evidence-based follow-up with focus on the effects of follow-up strategies on health outcomes, cost-effectiveness and individualised follow-up algorithms.

Introduction

High-grade bone sarcomas are known as rare and aggressive malignancies with chondrosarcoma, osteosarcoma and Ewing sarcoma as the most common entities. (1) Multimodal treatment including surgery and (neo)-adjuvant therapy by an experienced multidisciplinary team are essential for survival. (2,3) Disease recurrences, local or metastatic, result in significant reduction of survival. (4–9)

Follow-up through outpatient visits with radiological imaging are important to assess postoperative function and to detect local recurrent disease at an early stage. Follow-up is also useful to monitor surgical reconstruction as well as long-term cytotoxic effects of systemic therapy. Osteosarcoma and Ewing sarcoma patients are relatively young though, which results in increased sensitivity to late stochastic effects of ionising radiation due to repeated radiological imaging. (10–12) Repeated follow-up visits raise healthcare expenses and may not lead to improved survival. (13)

The most commonly used international guideline for follow-up is the ESMO-PaedCan-EURACAN Clinical Practice Guideline. (14) Based on a recent Asian single-centre randomised study, a less intensive surveillance protocol in terms of frequency and imaging seems non-inferior to a more intensive surveillance protocol in terms of survival after treatment of a sarcoma of the limb. (15) An American/Canadian study group has described a large retrospective cohort with data on follow-up frequencies and timing of recurrences, and proposed an alternative (less intensive) follow-up schedule. (13) Based on these findings, more insight into follow-up procedures used in daily practice in Europe is valuable for comparisons. Regional or cultural differences may very well influence decision-making on follow-up procedures.

The European Musculoskeletal Oncology Society (EMSOS) aims to promote advance in science, disseminate knowledge and promote mutual collaboration for bone sarcoma care between the different affiliated bone tumour centres. This observational cross-sectional study aims to assess follow-up procedures in terms of frequency and imaging modalities in several bone tumour centres all across Europe to compare and improve knowledge as a first step towards a more uniform approach of bone sarcoma follow-up.

Patients and Methods

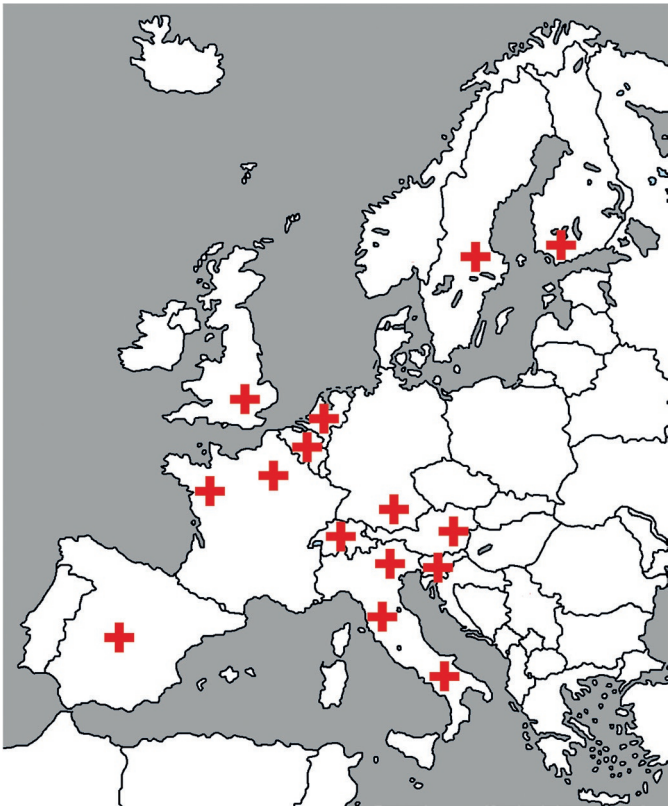
Data for this observational cross-sectional study was obtained from healthcare professionals. The authors formulated nine questions about organisation of care and produced a digital questionnaire using Google Forms (displayed in the Appendix). The questionnaire was not validated. Representatives of EMSOS-affiliated bone tumour centres were approached by the authors based on the EMSOS members archive. We

aimed for a proportional distribution across Europe in order to obtain a wide overview. The approached representatives who did return the questionnaire after one digital invitation and one digital reminder were acknowledged and specified as EMSOS study group. All responses came from orthopaedic surgeons. Observational research among healthcare professionals does not fall under the scope of the Dutch Act on Medical Scientific Research involving Human Beings (WMO). Data processing was performed using Microsoft Excel 2013 (United States) and analyses were performed using IBM SPSS Statistics for Windows (Version 23.0, United States).

Results

A digital questionnaire was sent to 54 EMSOS member representatives; we received a response of 17 representatives (31.5%) from 12 different countries across Europe. The geographical dispersion across Europe of responding bone tumour centres is displayed in Figure 1.

Figure 1. Geographical dispersion across Europe of responding bone tumour centres.



Using the digital questionnaire as basis, all participating bone tumour centres use a protocol for oncological follow-up after treatment of high-grade bone sarcomas. The bases of these protocols are displayed in Table 1. Authorization for the oncological follow-up protocol was government-based in 33.3% and expertise-based in 66.6% of centres. The guideline as basis for the oncological follow-up protocol used differed across respondents. An international guideline (such as ESMO-PaedCan-EURACAN) was used by 66.6% of centres and a local/national guideline by 33.3%. In terms of duration of oncological follow-up, all participating bone tumour centres attained a minimum of ten years. In two centres (12.5%) the duration of oncological follow-up exceeded ten years. Separate sections and recommendations for osteosarcoma, chondrosarcoma and Ewing sarcoma were seen in 62.5% of the respondents' follow-up protocol.

Table 1. Baseline characteristics

	No. bone sarcoma centres	Authorisation basis	Bone tumour guideline	Guideline as basis for oncological follow-up protocol	Minimum follow-up
Netherlands	4	Government	National	International	10 years
Belgium	5	Expertise	Local	International	10 years
Germany	Not clear*	Expertise	National	International	10 years
United Kingdom	5	Government	National	Local/national	10 years
France	12	Expertise	National	Local	10 years
Spain	10	Expertise	National	International	10 years
Italy	10	Expertise	Local	Local/national	10 years
Sweden	3	Government	National	International	10 years
Finland	4	Government	Local	International	10 years
Austria	4	Expertise	Local	International	10 years
Switzerland	5	Expertise	National	International	>10 years
Slovenia	1	Expertise	National	National	>10 years

Regarding radiological imaging, a local X-ray only was performed during an oncological follow-up visit in one bone sarcoma centre (5.9%). A local and chest X-ray was performed every follow-up visit in eight responding centres (47.6%). In six of the responding centres (35.3%) a local X-ray was performed every follow-up visit with a chest X-ray at a different interval.

We received data points on follow-up intervals from 12 different countries for this study; variations in these intervals are displayed in Table 2. Finland has the shortest follow-up intervals with outpatient visits every two months for the first two years, then outpatient visits every four months up to five years postoperatively. The longest follow-up intervals are seen in the Netherlands, with an outpatient visit every four months between the first and second year of follow-up, downgraded to a follow-up interval of one year between two and five years postoperatively.

Table 2. Interval variations in the available follow-up protocols

	Follow-up interval 0-1 years	Follow-up interval 1-2 years	Follow-up interval 2-4 years	Follow-up interval 4-5 years	Follow-up interval 5-10 years
ESMO guideline	2-3 months	2-3 months	3-4 months	6 months	6 months
Netherlands	3 months	4 months	12 months	12 months	12 months
Belgium	3 months	3 months	6 months	6 months	12 months
Germany	3 months	3 months	6 months	12 months	12 months
United Kingdom	3 months	3 months	6 months	6 months	12 months
France	4 months	4 months	6 months	6 months	12 months
Spain	3 months	3 months	6 months	6 months	12 months
Italy	3 months	3 months	4 months	6 months	12 months
Sweden	3 months	3 months	6 months	6 months	12 months
Finland	2 months	2 months	4 months	4 months	12 months
Austria	3 months	3 months	3-6 months	6 months	12 months
Switzerland	3 months	3 months	3 months	6 months	12 months
Slovenia	3 months	3 months	6 months	6 months	6 months

Lastly, respondents were asked for their opinion on several topics. Most respondents believe that early detection of a local recurrence as well as of a distant metastasis is important and of clinical relevance for additional treatment. However, some respondents emphasised that survival could depend more on type and grade of the tumour than on early detection of recurrent disease. Only 25% of respondents believe in added value of an additional, dedicated follow-up guideline for orthopaedic oncology, whereas the vast majority (62.5%) believes the current international ESMO guideline is sufficient. Differentiation between osteosarcoma, Ewing sarcoma and chondrosarcoma in a follow-up guideline was found useful by 68.8% of respondents.

Discussion

The aim of this observational cross-sectional study was to assess follow-up as a first step towards a more uniform approach of bone sarcoma follow-up. This study shows variation in follow-up protocols regarding frequency and use of imaging modalities. With the input from the EMSOS study group we were able to gather valuable additional information and received several guidelines on oncological follow-up from across Europe.

Limitations for this publication are the observational nature of the study and the disproportional distributed participation from countries and centres. Furthermore, the questionnaire we used was not validated. Despite a digital invitation and reminder we received a slightly disappointing response rate of 31.5%. This might introduce response bias in this study. On the other hand, we did get a good general impression from most

countries which may very well be representative for current policy, and the variation was clearly visible in our data. Regarding the displayed data, the follow-up intervals displayed are based on the input of the study group representatives and arranged by country. In Germany, there is a known lack of consensus on authorisation of bone sarcoma centres. We therefore believe that for Germany variability in follow-up intervals and imaging modalities between centres is likely.

As shown in the results, most of the participating bone tumour centres used an international guideline as basis for their national follow-up protocol, the most commonly used being the ESMO-PaedCan-EURACAN Clinical Practice Guideline. (14) The National Institute for Health and Clinical Excellence (NICE) guideline is an extensive and evidence based reference as well. (16)

In general, follow-up surveillance programs are based on the implication that early detection of recurrent disease or distant metastasis is of benefit to bone sarcoma patients. Cool et al. evaluated the efficiency of their local follow-up surveillance programme for extremity bone sarcoma patients in a single-centre retrospective cohort study. (17) Regarding local recurrence, only 38% was detected with follow-up whereas 62% of patients with a local recurrence presented with symptoms in between a follow-up interval. On the other hand, most pulmonary metastases (64%) were detected using follow-up with repeated imaging while 36% of patients with pulmonary metastases were diagnosed outside the surveillance programme.

The non-inferiority trial of Puri et al. outlined that almost 90% of local recurrences are detected by patient themselves, stressing the importance of self-education. (15) Several small retrospective studies have described beneficial results from pulmonary metastasectomy in selected osteosarcoma patients. Beneficial prognostic factors were identified as small pulmonary metastases (<2.0 cm), less than five pulmonary metastases at diagnosis, and a relatively long disease-free interval (DFI) between primary disease and metastatic disease. (18–20) DFI is an interesting parameter for closer analysis, Yamamoto et al. associated a DFI <12 months with significantly lower overall survival compared to a DFI >12 months for patients eligible for primary pulmonary metastasectomy. (19) This means that for osteosarcoma patients, recurrence or metastasis within one year of surgical treatment is a negative prognostic factor. This is acknowledged by Cool et al., their study showed that only 10% of patients with detected pulmonary metastasis survived. (17) In a subsequent study, Cool et al. followed 131 high-grade sarcoma patients. Metastatic disease developed in 15 patients, only 13% was referred for metastectomy. This resulted in a prolonged disease free survival, but curation was not achieved. (21) A retrospective cohort study from Kim et al. focused on post-metastatic survival. They found that the 5-year post metastatic survival rate was 31% with a median length of 22 months. Local recurrence prior to metastasis, extra-pulmonary metastasis and poor histological response to preoperative chemotherapy were identified as

negative prognostic factors. (22) In summary, the efficiency of follow-up surveillance programmes to detect local recurrences seems to be limited. Furthermore, the effects of intensive follow-up on overall survival remains controversial since early pulmonary metastasis results in inferior prognosis.

Regarding follow-up intervals, earlier detection of local recurrence facilitates the possibility for additional therapy which could lead to a longer subsequent survival period – but will the overall survival be affected? The follow-up interval advised by ESMO for high-grade bone sarcomas is every 3 months for first two years after start of treatment. After two years, a follow-up interval of 4 months is advised from years 2 to 4. Between 4 and 10 years a follow-up interval of 6 to12 months is recommended. (14) For this study we received follow-up intervals from eleven countries that showed variation. The differences in follow-up intervals and use of repeated imaging as described in the results imply a lack of consensus, which reflects the lack of evidence. None of the responding bone sarcoma centres abides to the follow-up intervals after 2 years as advised in the ESMO guideline. This lack of consensus regarding follow-up intervals among experts for high-grade bone sarcomas is explicated in the 2018 ESMO guideline. (14) Furthermore, the authors of the NICE guideline state that, at the time of publication of their guideline, no comparative studies regarding follow-up strategies and the effects on health outcomes were found. (16) Gerrand et al. acknowledged that evidence is lacking for determination of optimal follow-up intervals. (23) However, Puri et al. found that a less intensive 6-month follow-up interval was non-inferior to a 3-month interval in terms of recurrence free survival and overall survival. (15) Furthermore, a recent retrospective cohort study by Cipriano et al. (including chondrosarcoma, osteosarcoma and Ewing sarcoma) concluded that most cases of local recurrence occur within the first two years. (13) Late local recurrences (after four years) were uncommon. The highest rates of metastasis was also seen in the first two years for high-grade bone sarcomas with a ratio of 0.66 lung metastases per patient per year. After two years metastases were seen at lower rates up to ten years. A ratio of 0.018 lung metastases per patient per year was seen 5-10 years post-treatment. Based on their study, Cipriano et al. proposed a follow-up protocol for high-grade bone sarcomas. Follow-up should consist of a 3-month interval from 0-2 years, a 6-month interval between 3-4 years and a 12-month interval from 5-10 years.

Regarding duration of follow-up, ten years was defined as final follow-up moment in 87.5% of the responding centres in this study. In an observational study by Marina et al., adult Ewing sarcoma survivors were compared with their siblings in terms of survival, cause-specific mortality and chronic conditions. (24) This study with extended follow-up, up to 35 years after treatment, showed that the incidence of late mortality

and subsequent neoplasms kept increasing over the years. Chronic cardiac and musculoskeletal conditions related to treatment (chemotherapy, radiation and surgery) were also seen to increase after 10 years of follow-up. These findings support the need for a lifelong follow-up to assess the late effects of treatment.

In our study, variations were also seen in the use of imaging modalities as well as repeated imaging frequency based on the available guidelines. The ESMO guideline states that imaging of local recurrence or screening for distant metastases could be achieved with local imaging and chest X-ray / CT scanning. Based on the data we obtained, some bone sarcoma patients had up to 10 low-dose chest CT scans in five years while others did not have a single scan. Puri et al. found that even though a CT scan facilitates an earlier diagnosis of pulmonary metastasis, the effects on recurrence free survival and overall survival are not significantly different compared to a chest X-ray. (15) As mentioned earlier, repeated imaging during follow-up with ionising radiation has proven late stochastic effects in young bone sarcoma patients. (10–12)

Several prognostic factors are known for chondrosarcoma, Ewing sarcoma and high-grade central osteosarcoma. Metastasis at presentation, large primary tumour size and tumours in the axial skeleton are associated with lower survival for Ewing sarcoma and high-grade central osteosarcoma. (4,5) For chondrosarcoma, a high-tumour grade and axial localisation of the tumour are poor prognostic factors. (6) Based on these findings we believe that such prognostic factors could be used to identify high-risk patients after primary treatment. Intensification of imaging during follow-up could be considered for these high-risk patients, despite the lack of evidence whether this will improve overall survival.

We believe that future research should elaborate on the effect of follow-up strategies on survival for comparison with the data presented by Puri et al. and Cipriano et al. (13,15) Furthermore, cost-effectiveness of bone sarcoma follow-up is an interesting research perspective. Additionally, big data analysis could contribute to the development of an algorithm for individualised follow-up using known prognostic factors. For soft-tissue sarcomas, the PERSARC prediction model is an example to facilitate individualised follow-up. (25)

In conclusion, variations were seen among European bone sarcoma centres with regards to follow-up intervals and use of repeated imaging. The majority of these expert centres follows existing international guidelines and finds them sufficient as basis for a follow-up surveillance programme despite lack of evidence. Therefore, we believe that future research should aim towards evidence-based follow-up with focus on the effects of follow-up strategies on health outcomes, cost-effectiveness and individualised follow-up algorithms.

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Appendix 1. Nine-question digital questionnaire on organisation of bone sarcoma care.

1. Do you use a protocol for oncological follow-up after treatment of high-grade bone sarcomas? (yes, no)
2. If yes, what is this oncological follow-up protocol based on?
   - Expert opinion/local guideline
   - National tumour guideline
   - International tumour guideline (e.g. ESMO guideline)
3. According to your protocol, for how many years are bone sarcoma patients (OS, CS, ES) monitored in terms of oncological follow-up? (5, 10, >10 years)
4. Does your protocol contain separate sections/recommendations for OS, CS or ES? (yes, no)
5. Which radiological imaging tests are performed during an oncological follow-up visit?
   - Only local X-ray
   - Local X-ray & chest X-ray
   - Local X-ray at every visit, chest X-ray at different interval
6. In your opinion, how relevant is early detection of a local recurrence of high-grade bone sarcomas?
7. In your opinion, how relevant is early detection of distant metastases (e.g. lung) from high-grade bone sarcomas?
8. In your opinion, does a dedicated follow-up guideline for orthopaedic oncology have any added value?
   - No, a local guideline is sufficient.
   - No, a national guideline is sufficient.
   - No, an international guideline (e.g. ESMO) is sufficient.
   - Yes.
9. In your opinion, would a specific follow-up guideline for orthopaedic oncology have to differentiate between OS, CS or ES? (yes, no)

CHAPTER 7

Bone sarcoma follow-up; a nationwide analysis of oncological events after initial treatment

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Abstract

Aim

Follow-up strategies for high-grade bone sarcomas have been optimized to facilitate early detection of local recurrence and distant metastasis. The ideology is that early detection enables early treatment presuming better survival. However, the clinical value for each individual patient remains questionable. This study aims to evaluate oncological events after initial treatment in order to asses current follow-up strategies for high-grade bone sarcomas in the Netherlands.

Patients and Methods

A retrospective cohort study was conducted based on a national registry. All cases were retrieved from the Netherlands Cancer Registry. Our study consisted of 393 patients treated between 2007 and 2011 with complete follow-up data. Baseline characteristics were analysed for all entities. Local recurrence and distant metastasis was analysed along with overall survival for high-grade chondrosarcoma, high-grade osteosarcoma, Ewing sarcoma and chordoma.

Results

Median follow-up was 8,3 years for high-grade chondrosarcoma, 4,9 for high-grade osteosarcoma, 3,8 for Ewing sarcoma and 7,5 for chordoma. Median time to local recurrence and distant metastasis was 1,2 years for high-grade osteosarcoma and 1,5 years for Ewing sarcoma. For high-grade osteosarcoma with localized disease at presentation, 0.09 new distant metastatic events per patient per year were seen after five years of follow-up with 11,1 patients needed to follow-up for any event. Five-year overall survival was 60,0% for high-grade chondrosarcoma, 50,0% for high-grade osteosarcoma, 45,3% for Ewing sarcoma and 71,4% for chordoma.

Conclusion

This nationwide study shows a plateau in local recurrences and distant metastatic events after four years of treatment for patients with high-grade osteosarcoma and Ewing sarcoma. Due to a lack of reliable evidence however, we were not able to provide additional guidance on follow-up intervals and duration. Collaborative research with larger groups is needed in order to provide a solid scientific recommendation for follow-up in the heterogenous patient population with bone sarcoma.

Introduction

For more than three decades, survival of high-grade bone sarcoma patients has not significantly improved despite multimodal treatment by experienced teams. (1–3) Recurrent disease (local or metastatic) is a strong negative prognostic factor for chondrosarcoma, osteosarcoma and Ewing sarcoma. (4–8) Follow-up surveillance programmes are aimed at early detection of local recurrence or metastatic disease presuming better survival with early detection. The follow-up concept is based on the hypothesis that early detection of recurrences would lead to smaller lesions that are more likely to be treated with success and less morbidity. Nevertheless, the efficiency and yield of radiologic detection of local recurrences using protocolised follow-up may be limited. (9) Pulmonary metastases are most frequently detected within the first two years of follow-up. (10) Furthermore, only a small subgroup of patients with metastatic disease is found eligible for additional treatment. (11) Promising results from pulmonary metastectomy have been published for osteosarcoma and Ewing sarcoma. A relatively long disease-free interval (DFI) between primary disease and metastatic disease was identified as an important beneficial prognostic factor. (12–14) The relatively low yield of protocolled radiographic follow-up along with low survival rates after treatment of metastasized bone tumours, questions the added value of follow-up for bone sarcoma patients treated with curative intend. Additionally, follow-up is time consuming, strains health care expenses and repeated CT imaging has late stochastic effects. (15,16) Lastly, psychological distress during follow-up has been reported in up to 25% of sarcoma patients. (17)

Few studies regarding follow-up strategies and the effects on survival are known. Puri et al. found that a less intensive follow-up scheme was non-inferior in terms of recurrence free survival and overall survival. (18) Furthermore, a recent American/Canadian study based on a retrospective cohort proposed a follow-up protocol for high-grade bone sarcomas with prolonged intervals two years after treatment. (10) Consensus regarding follow-up in the existing guidelines is brief and only reinforced by low-level evidence, which questions the effectiveness of follow-up on survival for the individual patient. (19)

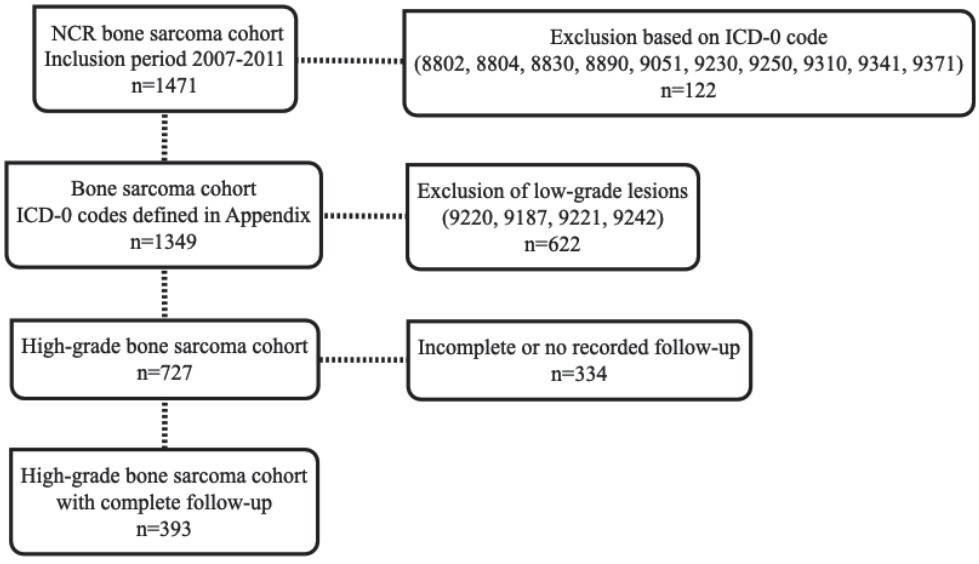
Therefore, this nationwide study aims to evaluate the oncological events occurring after index treatment with curative intent during follow-up, including time to local recurrence and distant metastasis, in order to obtain additional evidence to assess current follow-up strategies for high-grade bone sarcomas in the Netherlands.

Patients and methods

A retrospective cohort study was conducted based on a national registry. All cases were retrieved from the Netherlands Cancer Registry (NCR), which receives primary notification from the Dutch Pathology Network (PALGA). This notification resulted in a complete and pathology based cohort. Patients who were treated between 2007 and 2011 were included in order to achieve a substantial follow-up period. Additional clinical information (on patient and tumour characteristics and treatment regimens) was collected by data managers of the NCR from hospitals' patient records. 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. The Institutional Review Board of University Medical Center Groningen approved this study (M19.224412) and waived patient informed consent.

For inclusion, 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 as shown in Appendix A. We excluded several entities from the original cohort, as shown in Appendix A as well. Additionally, we excluded patients with low-grade tumours as well as patients with incomplete follow-up in order to obtain a high-grade bone sarcoma cohort with complete follow-up. The flowchart for inclusion is shown in figure 1.

Figure 1. Flowchart for inclusion



For analysis, descriptive statistics were used for the clinicopathological characteristics. Time to local recurrence and distant metastasis along with metastatic events were calculated for high-grade chondrosarcoma, high-grade osteosarcoma, Ewing sarcoma and Chordoma. For the visualisation of the timing of local recurrence and distant metastasis, we used Kaplan Meier curves. For analysis of local recurrence and distant metastasis free survival, we performed a competing risk analysis Stata (Version 17.0; StataCorp, College Station, TX, USA). New distant metastatic events for patients with localized disease during follow-up were calculated using Poisson regression analysis in order to estimate incidence over time. Univariable overall survival analysis was performed for high-grade chondrosarcoma, high-grade osteosarcoma, Ewing sarcoma and chordoma using normal Kaplan-Meier curves. For survival analyses, information on patients' vital status was obtained through linkage with the Municipal Personal Records Database. Statistical analysis was performed using SPSS software (Version 23.0; SPSS Inc, Chicago, IL,USA).

Results

1. Clinicopathological characteristics

A total of 393 bone sarcoma patients with complete follow-up, median age of 39 years, were included. High-grade chondrosarcoma was diagnosed in 104 patients, 144 patients with high-grade osteosarcoma were seen along with 55 Ewing sarcoma patients. Chordoma (n=44), Surface osteosarcoma (n=12), classic adamantinoma (n=15), angiosarcoma of bone (n=4) and sarcoma of bone Not Otherwise Specified (NOS) (n=15) were also included.

Clinicopathological characteristics for high-grade chondrosarcoma, high-grade osteosarcoma, Ewing sarcoma and chordoma are displayed in table 1. For the other sarcoma subtypes with lower incidences, these characteristics are shown in table 2.

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

	High-grade chondrosarcoma (grade 2 / 3 / ddif) n=104	**High-grade osteosarcoma n=144**	**Ewing sarcoma n=55**	**Chordoma n=44**
Gender (%)	M 62 (59,6) F 42 (40,4)	M 81 (56,3) F 63 (43,8)	M 40 (72,7) F 15 (27,3)	M 30 (68,2) F 14(31,8)
Median age at diagnosis in years (range)	55 (19-88)	22,5 (5-83)	19 (6-62)	63,5 (29-85)
Localisation (%)	Long bones 60 (57,7) Axial skeleton 44 (42,3)	Long bones 124 (86,1) Axial skeleton 20 (13,9)	Long bones 25 (45,5) Axial skeleton 30 (54,5)	Long bones - Axial skeleton 44 (100)
Extent of disease at time of diagnosis (%)	Localized 85 (81,7) Metastasized 19 (18,3)	Localized 107 (74,3) Metastasized 37 (25,7)	Localized 29 (52,7) Metastasized 26 (47,3)	Localized 27 (61,4) Metastasized 3 (6,8) Missing 14 (31,8)
Median follow-up in years (range)	8,3 (0-14)	4,9 (0,3-14)	3,8 (0,5-13,8)	7,5 (0,9-13,5)
Median time to Local Recurrence in years (range)	1,9 (0-10,7)	1,2 (0,2-13,25)	1,5 (0,5-12,7)	2,7 (0,7-6,9)
Median time to Distant Metastasis in years (range)	2,1 (0-10,7)	1,2 (0,2-13,25)	1,5 (0,5-12,7)	2,9 (0,7-7,3)

M=male; F=female; ddif=dedifferentiated; n=number

Table 2. Clinicopathological characteristics for other bone sarcomas

	Surface osteosarcoma n=12	**Adamantinoma n=15**	**Angiosarcoma of bone n=4**	**Sarcoma of bone NOS n=15**
Gender (%)	M 5 (41,7) F 7 (58,3)	M 8 (53,3) F 7 (46,7)	M 3 (75,0) F 1 (25,0)	M 6 (40,0) F 9 (60,0)
Median age at diagnosis (range)	29 (13-58)	14 (1-63)	63 (39-74)	52 (9-83)
Localisation (%)	Long bones 12 (100) Axial skeleton -	Long bones 15 (100) Axial skeleton -	Long bones 4 (100) Axial skeleton -	Long bones 8 (53,3) Axial skeleton 7 (46,7)
Disease extent at presentation (%)	Localized 4 (33,3) Metastasized 1 (8,3) Missing 7 (58,3)	Localized 15 (86,7) Metastasized 2 (13,3)	Localized 1 (25,0) Metastasized 3 (75,0)	Localized 10 (66,7) Metastasized 5 (33,3)
Median follow-up in years (range)	10,8 (5,2-13,7)	11,8 (7,3-13,9)	1,3 (0,3-13,3)	2,3 (0,1-13,3)

M=male; F=female;

2. Follow-up

Follow-up time, time to local recurrence and distant metastasis and overall survival was only analyzed for high-grade chondrosarcoma, high-grade osteosarcoma, Ewing sarcoma and Chordoma.

Median follow-up was 8,3 years for high-grade chondrosarcoma, 4,9 for high-grade osteosarcoma, 3,8 for Ewing sarcoma and 7,5 for chordoma. For these entities, time to local recurrence and distant metastasis in years for patients with localized disease are displayed in table 1.

3. Local recurrence and distant metastasis

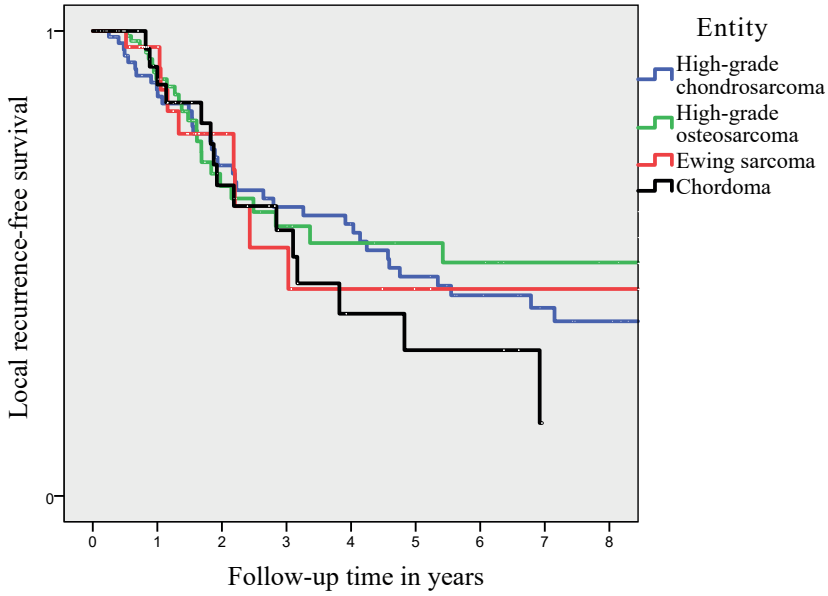
Five-year local recurrence rates for patients with localized disease was 37.6% for high-grade chondrosarcoma, 21.5% for osteosarcoma, 31.0% for Ewing sarcoma and 51.9% for Chordoma patients respectively. Five-year distant metastasis rates were 22.3% for high-grade chondrosarcoma, 48.6% for osteosarcoma, 55.1% for Ewing sarcoma and 18.5% for Chordoma. The incidence of distant metastasis during follow-up is defined as new distant metastatic events per patient per year for patients with localized disease at diagnosis. This is displayed in table 3. Median time to local recurrence and distant metastasis is displayed in table 1. The trends in timing of local recurrence and distant metastasis are visualised in figures 2a and 2b. For high-grade chondrosarcoma, a decrease in local recurrences and distant metastatic events occurred after approximately seven years. For patients with high-grade osteosarcoma and Ewing sarcoma, a plateau in local recurrences and distant metastatic events was reached after approximately four years. A different pattern was seen for patients with chordoma with ongoing events of local recurrence and metastasis during ten-year follow-up. . Competing risk analysis of local recurrence and distant metastasis free survival was displayed in figure 3a and 3b. For local recurrence free survival, correction for competing risks resulted in higher local recurrence free survival for all entities. For distant metastasis, no significant differences were seen.

Table 3. New Distant Metastatic events for patients with localized disease at diagnosis

Entity	Follow-up in years	New Distant Metastasis per patient per year	Number of patients needed to follow-up* (CI)
High-grade chondrosarcoma n=85 (95% CI)	0-2	0.13 (0.08 – 0.21)	7,7 (4,8 - 12,5)
	2-5	0.03 (0.01 – 0.09)	33,3 (11.1 - 100)
	5-10	0.09 (0.04 – 0.20)	11,1 (5 - 25)
	>10	0	
High-grade osteosarcoma n=107 (95% CI)	0-2	0.30 (0.22 – 0.41)	3,3 (2,4 – 4,5)
	2-5	0.22 (0.12 – 0.38)	4,6 (2,6 – 8,3)
	5-10	0.09 (0.03 – 0.24)	11,1 (4,2 – 33,3)
	>10	0	-
Ewing sarcoma n=29 (95% CI)	0-2	0.24 (0.13 – 0.44)	4,2 (2,3 – 7,7)
	2-5	0.38 (0.17 – 0.83)	2,6 (1,2 - 5,9)
	5-10	0	
	>10	0	
Chordoma n=27 (95% CI)	0-2	0.02 (0.003 – 0.15)	50 (6,7 – 333,3)
	2-5	0.11 (0.04 – 0.30)	9,1 (3,3 – 25)
	5-10	0.37 (0.14 – 0.99)	2,6 (1,0 – 7,1)
	>10	No follow-up	-

* Number of patients needed to screen to detect 1 new metastatic event per year
CI Confidence interval

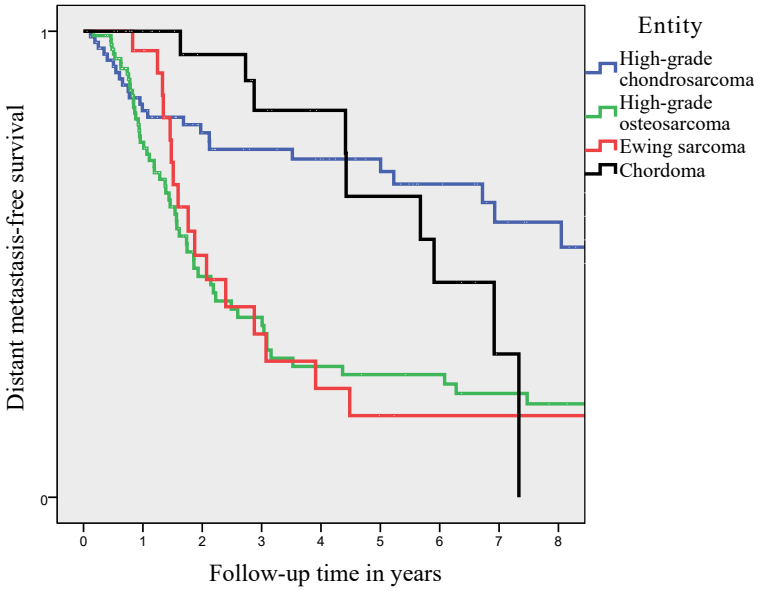
Figure 2a. Visualisation of the trends in timing of Local Recurrence in localized disease for high-grade chondrosarcoma, high-grade osteosarcoma, Ewing sarcoma and chordoma



Entity	Median local recurrence free survival % (CI)	N in follow-up 1 years after treatment [1]	N in follow-up 2 years after treatment	N in follow-up 5 years after treatment
High-grade chondrosarcoma N=85	4,6 (3,1 -6,0)	58	40	25
High-grade osteosarcoma N=107	-	61	25	13
Ewing sarcoma N=29	3,0 (1,8 – 4,3)	22	11	2
Chordoma N=27	3,2 (1,9 – 4,3)	23	15	4

N Number of patients
[1] Number of patients still in follow-up without an event of local recurrence

Figure 2b. Visualisation of the trends in timing of Distant Metastasis in localized disease for high-grade chondrosarcoma, high-grade osteosarcoma, Ewing sarcoma and chordoma



Entity	Median metastasis free survival in years % (CI)	N in follow-up 1 years after treatment [1]	N in follow-up 2 years after treatment	N in follow-up 5 years after treatment
High-grade chondrosarcoma N=85	9,2 (-)	60	44	27
High-grade osteosarcoma N=107	1,9 (1,3 - 2,4)	60	27	14
Ewing sarcoma N=29	2,1 (1,2 - 2,9)	22	10	2
Chordoma N=27	5,9 (2,7 – 5,9)	24	17	7

N Number of patients
[1] Number of patients still in follow-up without an event of distant metastasis

Figure 3a. Competing risk analysis for local recurrence free survival for high-grade chondrosarcoma, high-grade osteosarcoma, Ewing sarcoma and chordoma

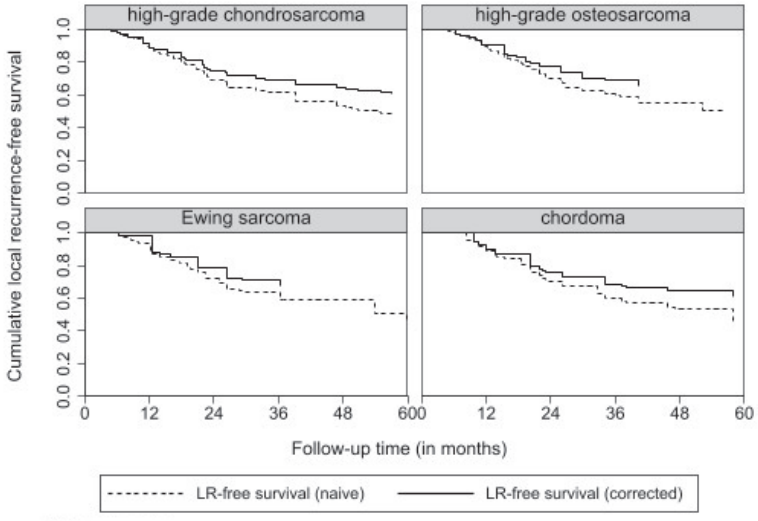
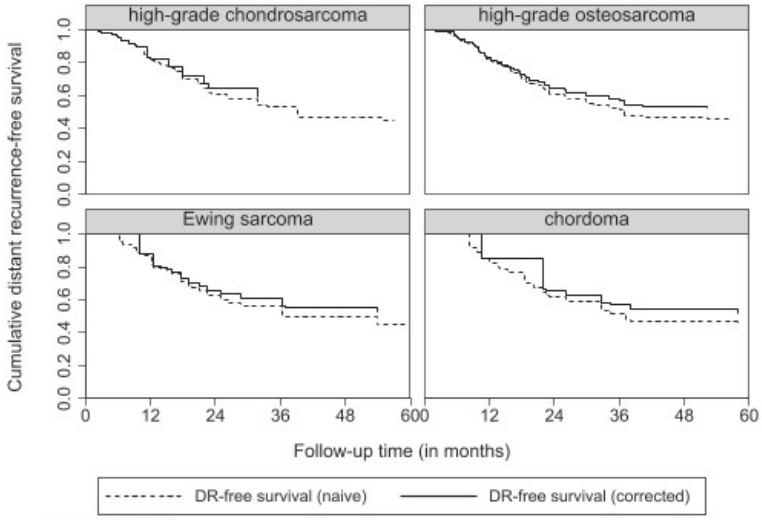


Figure 3b. Competing risk analysis for distant metastasis free survival for high-grade chondrosarcoma, high-grade osteosarcoma, Ewing sarcoma and chordoma



4. Survival

Median survival time in years, 2- and 5-year survival rates are displayed in table 4 for patients with localized disease and the overall population. Five-year overall survival was 60,0% for high-grade chondrosarcoma, 50,0% for high-grade osteosarcoma, 45,3% for Ewing sarcoma and 71,4% for chordoma.

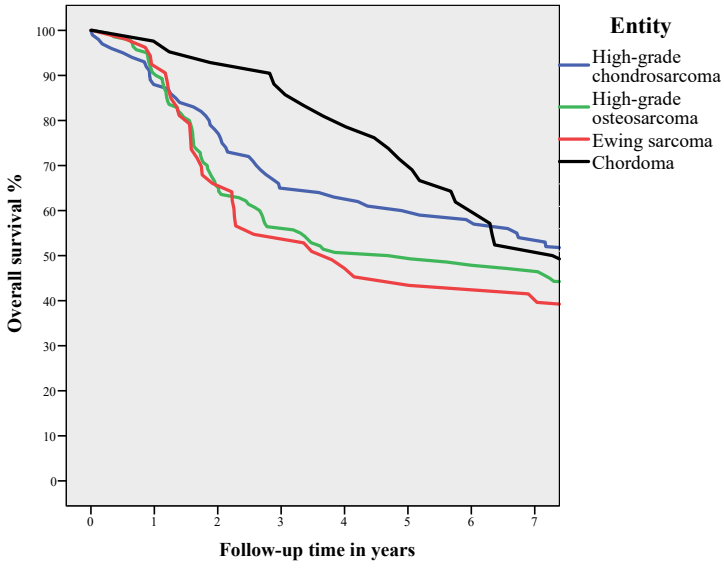
Table 4. Median, 2- and 5-year survival for high-grade chondrosarcoma, high-grade osteosarcoma, Ewing sarcoma and chordoma.

	N	median survival time in years (CI)	2-year survival (%)	5-year survival (%)
Chondrosarcoma (high-grade, grade 2/3/ddif)	100	8,3 (-)	78,0	60,0
High-grade osteosarcoma	140	4,7 (1,4-7,9)	65,7	50,0
Ewing sarcoma	53	3,8 (1,0-6,6)	66,0	45,3
Chordoma	42	7,3 (5,4-9,2)	92,9	71,4

CI Confidence Interval

Five-year overall survival for these entities is illustrated in figure 4. Survival more or less reaches a plateau after approximately six years of follow-up as a result of the timing of appearance of local recurrence and metastasis for patients with high-grade osteosarcoma and Ewing sarcoma. This plateau in survival is reached after approximately eight years for high-grade chondrosarcoma patients. Interestingly, the survival curve for chordoma is clearly different with a steady decline in survival during ten-year follow-up.

Figure 4. Overall survival for high-grade chondrosarcoma, high-grade osteosarcoma, Ewing sarcoma and chordoma



Discussion

With comprehensive evaluation of oncological events after treatment, we aimed to assess current follow-up strategies for high-grade bone sarcomas in the Netherlands. The NCR is a population-based registry that covers the total population of the Netherlands since 1989 (approximately 17,5 million inhabitants in 2022). (20) At present, about 96% of records concerns histologically verified cases, with the majority of remaining cases representing clinical diagnoses. (21) Only high-grade bone sarcomas were included in this study. As a result of extensive centralisation in the Netherlands it can be hypothesized that virtually all high-grade lesions are histologically verified with tumour biopsy. (22) Therefore, the rate of missing data in our study can be considered negligible. The results of our nationwide retrospective cohort study showed clear patterns for the occurence of local recurrence and metastasis during follow-up for high-grade bone sarcomas.

High-grade chondrosarcoma, high-grade osteosarcoma, Ewing sarcoma and chordoma were deemed eligible for the analysis of local recurrence, distant metastasis based on the sample size.

In figure 2, we used Kaplan Meier curves for visualisation of the trends in timing of oncological events after initial treatment. Due to competing risks and censoring, the Kaplan Meier curves in figure 2 do not resemble actual survival. The primary goal of these figures was to observe the trends in timing of local recurrence and distant metastasis, not to determine specific survival. For high-grade chondrosarcoma patients, on-going local recurrences and distant metastasis after seven years of follow-up were seen without a decrease in survival between seven and ten years of follow-up. However, it is uncertain if causality can be assumed with a median follow-up of 8,3 years. By performing a competing risk analysis as shown in figure 3 for local recurrence free survival, more accurate and slightly higher survival was seen compared to survival analysis with Kaplan Meier curves.

For high-grade osteosarcoma patients, survival plateaus after approximately six years of follow-up as a result of a stabilisation in the occurrence of local recurrence and distant metastasis after approximately four years. Extended follow-up beyond five years seems of limited added value. However, with only a few patients left in follow-up after five years, a recommendation for extended follow-up is not justified.

A small increase in incidence of new distant metastatic events for patients with localized Ewing sarcoma was seen between two and five years of follow-up. However, a plateau in the timing of local recurrence and distant metastasis was reached after approximately four years. A plateau in survival is reached after approximately six years of follow-up, but this finding is doubtful as well with only a few patients left in follow-up.

Comparison of new distant metastatic events for patients with localized disease with existing literature proved to be difficult. Cipriano et al. defined their groups on gradation

rather than entity and did not define extent of disease. (10) This gives a different, but still a valuable picture compared to the calculations in our study which was focused on patients with high-grade bone sarcomas with localized disease. In a comparable series from a single centre, most local recurrences and metastatic events for high-grade extremity osteosarcoma were seen within the first two years of follow-up. (23) The median follow-up time in this study was limited though with 2,6 years, compared to 4,9 years in our study, resulting in limited follow-up and only five-year survival rates. More importantly the results of our study, with a smaller population and shorter follow-up, were in concordance with another large series of 402 osteosarcoma patients and 11,3 years of median follow-up. In this study, a plateau in events (local recurrence, new or progressive distant metastasis or death) was seen five years after treatment. (24)

Interestingly, the survival curve for chordoma appeared to be clearly different with elongated median time to local recurrence and distant metastasis along with a steady decline in survival during five-year follow-up. This was resembled by the incidence of local recurrence and metastasis. According to literature, stabilisation in disease specific survival is seen after 15 years. Furthermore, older age above 59 years (accompanied by comorbidities) was identified as a prognostic factor for worse survival. (25) Therefore, although chordoma is also defined a high-grade bone sarcoma, a different follow-up strategy seems indicated. Extended follow-up after five years without prolonged intervals is deemed to be justified for this entity.

Overall survival rates for all entities in our study were lower in comparison with available literature. (4,6–8,24,26,27) This could be explained by inclusion of patients with primary metastatic disease and the exclusion of patients with missing follow-up data which likely resulted in selection bias. Furthermore, based on our database, the cause of death could not be linked to the disease itself or other causes (e.g. after adjuvant treatment, other disease, unknown). This likely affected overall survival negatively as well.

Follow-up intervals were not recorded in our database and therefore not available for analysis. Treatment and follow-up of bone sarcoma patients is centralised in four hospitals, generic follow-up intervals in the Netherlands have been described earlier. (28) At present, follow-up intervals for adults with high-grade chondrosarcoma, high-grade osteosarcoma and Ewing sarcoma are every 3 months in the first year after treatment, every 4 months in the second year and then prolonged towards a 6-month-interval until 5 years of follow-up. A 1-year-interval is used until 10 years of follow-up. This surveillance scheme is consistent with well-established international guidelines. (29–31) Puri et al. found that a less-intensive follow-up protocol did not result in a decreased overall survival. Comparison is difficult however due to the heterogeneous study population with both soft-tissue and bone sarcoma of the limb included. (18)

Based on the findings and sample size of our study, a new recommendation with specified follow-up intervals for high-grade bone sarcomas would not be justified. However, our findings regarding time to local recurrence and distant metastasis questions the necessity for extended surveillance after five years of follow-up for high-grade osteosarcoma and Ewing sarcoma, consistent with the existing literature. (10,23)

Limitations of our study are the retrospective study design. However, the registration of the pathological data from PALGA is a continuous prospective process which amplifies our results. Although complete follow-up was essential for our analysis, this resulted in a relatively small sample size and short follow-up time for high-grade chondrosarcoma, high-grade osteosarcoma and Ewing sarcoma which could have resulted in selection bias. Moreover, detection of local recurrences and distant metastasis in our study is based on the PALGA database for which pathological samples from biopsy or resection are mandatory. Since our inclusion is based on pathological data, we may have missed cases where no histological sampling was performed.

For future research, larger cohorts could be valuable to validate the findings in our study. In addition, we believe that cost-effectiveness analyses of follow-up surveillance programmes are important. Future research must address the psychological distress of follow-up as well and try to find a healthy balance between usefulness and distress. Finally, a prediction model for clinical guidance to facilitate individualized follow-up would be the next step for high-grade bone sarcoma patients similar to the PERSARC model for soft-tissue sarcoma. (32)

In conclusion, our study shows a plateau in new local recurrences and distant metastatic events four years after initial treatment for patients with high-grade osteosarcoma and Ewing sarcoma. Even though our study is based on a nationwide population, collaborative research with larger groups is needed in order to do provide a solid scientific basis for future recommendations for follow-up interval and duration in the heterogenous patient population with bone sarcoma. Importantly, with the data presented here, we believe that the discussion regarding the purpose of extended follow-up and its value for the individual patient initially treated with curative intend should be intensified.

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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.

Included subtypes based on ICD-O-3 coding and grade.

Sarcoma subtype (WHO 2013)	Morphology code
High-grade (2/3) chondrosarcoma	
Chrondrosarcoma NOS	9220/3 + 9231/3
Dedifferentiated chondrosarcoma	9243/3
Surface osteosarcoma	
Parosteal osteosarcoma	9192/3
Periosteal osteosarcoma	9193/3
High-grade surface osteosarcoma	9194/3
High-grade osteosarcoma	
Osteosarcoma NOS	9180/3
Chondroblastic osteosarcoma	9181/3
Fibroblastic osteosarcoma	9182/3
Teleangiectatic osteosarcoma	9183/3
Osteosarcoma in Paget's disease	9184/3
Small-cell osteosarcoma	9185/3
Central osteosarcoma	9186/3
Intracortical osteosarcoma	9195/3
Ewing sarcoma	9260/3
Angiosarcoma of bone	
Epithelioid hemangioendothelioma NOS	9133/3
Hemangiosarcoma	9120/3
Sarcoma of bone NOS	
Sarcoma	8800/3
Splindle cell sarcoma	8801/3
Small-cell sarcoma	8803/3
Chordoma	9370
Dediferentiated Chordroma	9372
Adamantinoma	9261

Grade: 3 = high

Excluded subtypes based on ICD-O-3 coding and grade.

Sarcoma subtype (WHO 2013)	Morphology code
Giant cell sarcoma	8802
Epithelioid sarcoma	8804
Fibrous histiocytoma	8830
Leomyoma / Leomyosarcoma	8890
Fibrous mesothelioma	9051
Chondroblastoma	9230
Giant cell tumour of bone	9250
Ameloblastoma	9310
Clear cell odontogenic carcinoma	9341
Chondroid chordoma	9371
Atypical Cartilaginous Tumour	9220 / Low-grade
Low-grade central osteosarcoma	9186 / Low-grade
Clear-cell chondrosarcoma	9242 / Low-grade
Periosteal chondrosarcoma	9221 / Low-grade

CHAPTER 8

General discussion

Aims of this thesis

The overall aim of this thesis is assessment of bone sarcoma care. First, bone sarcoma care was assessed in terms of incidence. Second, the impact of centralisation was assessed regarding time to diagnosis and organisation of care. Third, follow-up of bone sarcoma was assessed to ultimately improve the clinical approach towards bone sarcoma care.

Efforts aimed at emphasising the need for centralisation and multidisciplinary treatment

The first part of the thesis assessed the incidence of bone sarcoma, given its rarity. Centralisation of care in terms of clinical assessment, biopsy and treatment is the cornerstone of bone sarcoma care. The need for centralisation is emphasised by the comprehensive low incidence estimates as presented in the study of **Chapter 2**. The study showed increasing centralisation over the years in terms of biopsy and treatment. However, around 33% of biopsies and 15% of surgical resections were performed outside of a bone sarcoma centre. A future challenge thus remains to minimise biopsy and treatment outside of bone sarcoma centres. Oncological outcome for patients with rare cancers is worse than for common entities, (1) and the cut-off value for adherence to treatment of rare cancers is difficult to determine. (2) The Netherlands is a relatively small yet densely populated country, which facilitates centralisation. Unfortunately, virtually all bone sarcoma patients are primarily seen in a local hospital at first presentation, which imposes challenges for swift referral to a bone sarcoma centre. Improvements to facilitate maximum centralisation could be achieved by creating awareness of the regional function of every bone sarcoma centre with a low threshold for consultation and referral. Repetitive schooling of peripheral general surgeons, orthopaedic surgeons and radiologists could be a valuable tool to keep relevant knowledge up to date.

> Comprehensive incidence figures for all the main primary bone sarcomas in the Netherlands were provided.

Centralisation of care does result in increased travel distances, which has a profound negative influence on a patients' quality of life and personal finances. (3) After referral to a bone sarcoma centre, a diagnostic workup is performed. This workup consists of additional imaging with a contrast-enhanced MRI of the tumour and nuclear imaging with PET to screen for distant metastases. Simultaneously, a tumour biopsy is performed to confirm the diagnosis. Guidance on types of imaging and lead time regulations are grounded in the national bone tumour guideline and SONCOS standardisation report.

(4,5) Multidisciplinary decision-making after diagnosis is mandatory in the Netherlands according to SONCOS and embodied as the Dutch bone tumour committee. The combined experience of this committee results in alteration of a diagnosis and subsequent treatment strategy in approximately 20% of the discussed cases. (6) This emphasises the importance of multidisciplinary decision-making in bone sarcoma care.

An international trend is seen away from centralisation towards networking for treating patients with rare cancers. (7) A hub-and-spoke model for networking is used for several oncological entities to minimise health migration without loss of quality of care. A spoke or peripheral hospital with good facilities for managing cancer patients could facilitate a limited part of the diagnostic workup. (3) For bone sarcoma patients, the radiological workup with X-ray, contrast-enhanced MRI and PET could be performed outside of a bone tumour centre. Assessment of the radiological studies could still be done in a hub, i.e. bone tumour centre, as it is already set up nowadays. Tumour biopsy and treatment should stay centralised and always be performed in this hub, since the biopsy trajectory is excised during the subsequent tumour resection, including the affected muscle compartments. In recent years digital transfer of radiological images has emerged, further facilitating this type of networking. Travel distances in the Netherlands are short and bone sarcoma care is centralised in four centres for adult patients, so the benefit for patients in terms of health migration seems limited. A Dutch survey study among adult cancer patients showed that 14% of patients with a rare cancer reported negative experiences when treated at different hospitals. These are patients who were willing to travel as far as necessary to receive optimal care in specialised centres. (8) Last, networking is costly due to the extra administrative burden and efforts of medical professionals. This is difficult to reimburse, therefore proper funding is one of the main concerns for implementation of a hub-and-spoke model. (3) Alternatively, all bone sarcoma care could be centralised in a single centre in the Netherlands, given the relative short travel distances. This would optimise multidisciplinary care by an experienced team with extensive exposure. However, all knowledge and expertise of biological reconstruction and reconstruction with tumour prostheses would also be centralised in this single bone sarcoma centre. We believe that this would compromise care for other non-sarcoma patients that need these reconstructions in cases of infection or complex trauma. Centralisation of bone sarcoma towards a single centre in the Netherlands is therefore undesirable.

Centralisation of bone sarcoma care has improved over the last two decades in terms of biopsy and treatment. However, survival has not significantly improved.

In our study in **Chapter 3** we described the largest series so far of a rare sarcoma subtype: periosteal chondrosarcoma. We recommended that staging for metastatic disease should be performed in histologically grade II lesions and higher based on clinical and radiological data. This concords with a recent narrative review where the authors advised that treatment and follow-up of periosteal chondrosarcoma should be equal to conventional chondrosarcoma of the same grade. (9) However, radiological differentiation between a benign entity and malignancy for this surface lesion remains difficult. Tumour dimensions larger than 3 cm were found as the most important indicator of a malignancy. (10) Notably, a subsequent histological interpretation on the same case series as our study revealed a discrepancy with our study. After histological analysis of the same patients, histological gradation was not determined as a prognostic factor. (11) Hence **Chapter 3** of this thesis is an example of the difficulties in interpretation of imaging and histology. Conclusions cannot be based solely on clinical and radiological parameters, despite a nationwide study for an extremely rare entity like periosteal chondrosarcoma. As known from literature, multidisciplinary decision-making by an experienced team of clinicians, radiologists and pathologists is essential towards obtaining the correct diagnosis for chondrosarcoma. (12) This chapter emphasises the need for centralisation of care for bone sarcomas. Misdiagnosis could result in death of the affected patient.

> The complex interpretation of imaging and histology requires a multidisciplinary approach with clinicians, radiologists and pathologists, especially for rare bone sarcoma subtypes.

Efforts aimed at analysing and shortening delay in diagnosis

The second part of this thesis focused on the impact and potential benefits of centralisation in terms of organisation and follow-up of bone sarcoma care. In the Netherlands, a potential bone sarcoma patient is first seen by a general practitioner (GP). After initial referral, virtually all patients with such rare diseases are primarily seen in a local hospital. This imposes challenges for swift referral of bone sarcoma patients. In **Chapter 4** we quantified and analysed patient- and doctor-related delays and their effects on clinical outcome. Most delays were seen at the GP's office. Prolonged delay in diagnosis did not result in lower survival though. More aggressive, fast-growing tumours are detected earlier and do result in higher mortality. For example, aggressive tumour behaviour in osteosarcoma and Ewing sarcoma patients evidenced shorter delays in our study. These results imply that tumour location and resectability are more important for survival than delay in diagnosis in patients with osteosarcoma and Ewing sarcoma.

Prolonged delay in diagnosis does not result in lower survival probably due to more aggressive tumour behaviour, which results in shorter delays.

Only few studies have been conducted on delay of diagnosis and treatment for bone sarcoma patients. A recent Dutch cross-sectional study examined patient-related delays and diagnostic (doctor-related) delays, looking for associations between diagnosis and delay. (13) Osteosarcoma was mildly associated with a diagnostic delay longer than one month with an odds ratio (OR) of 1.5. No associations with prolonged delays were seen for Ewing sarcoma. Chondrosarcoma was associated with a diagnostic delay longer than one month (OR 2.0) and mildly associated with a diagnostic delay longer than three months (OR 1.3). The prolonged delay seen for chondrosarcoma patients concords with our findings, and can be explained by the slower growth pace, which results in fewer and later onset of symptoms. Chondrosarcoma is often diagnosed in the pelvis and around the hip, where it can grow extensively without alarming symptoms. A British survey study among young adult cancer patients also focused on patient and healthcare delays. Among other cancers, delay was analysed for 22 sarcoma patients. Sarcoma was strongly associated with healthcare delay longer than one month compared to other malignancies. Almost a quarter of the sarcoma patients were seen over four times by a GP before referral, associated with prolonged delay. Based on our study and the literature, evidence is lacking on the effect of delay on oncological outcome. Still, swift referral for bone sarcoma patients is important to offer them the best available care within the existing lead time regulations.

Another aim of our study was to identify novel strategies for shortening delays. As most delays are seen at the GP's, most gains can be achieved there. Minimising GP-related delays could be achieved by adopting a lower threshold for obtaining plain radiographs at the pre-hospital stage. Given the low incidences of these tumours, however, low-threshold plain radiographs would cause a serious financial burden on healthcare expenses with minimal gains at the population level. An alternative would be repetitive schooling for GPs and making available a simple hand-out or website with alarm symptoms. Along with the existing guidelines these tools could be valuable for optimisation of referral patterns towards a bone sarcoma centre. (4,5)

Efforts aimed to identify potential benefits of organisation of care and follow-up beyond borders

The Netherlands is a small country with only a few oncological orthopaedic surgeons. Organisation of bone sarcoma care is centralised in only five bone sarcoma centres, including a specialised centre for paediatric sarcoma patients. With clear guidelines and lead time regulations, organisation of care in the Netherlands results in satisfactory quality for our patients. A European society such as EMSOS provides the opportunity to benefit from a larger sarcoma network for improving knowledge and exchanging best practices. In **Chapter 5**, we assessed organisation of care in several bone sarcoma centres in Europe to identify potential benefits beyond borders. Geographical and political differences between European countries made comparisons difficult, yet satisfactory quality of care can be achieved by following essential requirements as defined by the European CanCer Organisation (ECCO). (14) In geographically large countries where bone sarcoma centres are expertise-based, a lack of exposure could result in an inadequate diagnostic workup and treatment. These bone sarcoma centres with little adherence would benefit from a national bone tumour board for extensive case evaluation including classification and advice for treatment from a team with more experience. A recent British study showed that a virtual multidisciplinary sarcoma meeting is sufficient to present cases with adequate decision-making. (15) Wider use of this modality would facilitate attendance of healthcare professionals from bone sarcoma centres with little adherence or difficult geographical location. A national registry is essential for adequate storage and reproduction of oncological data. The Netherlands Cancer Registry (NCR) is a database that is filled retrospectively and receives primary notification from the Dutch Pathology Network (PALGA). A national prospective registry including patient-reported outcome measures is being developed. Based on the varying experiences across borders in our study, a vision of an ideal bone sarcoma centre has become clearer. This would be a centre with sufficient adherence and well-functioning regional network capabilities with low-threshold digital consultation for regional hospitals. An experienced multidisciplinary team for decision-making and treatment would be mandatory, and adequate data storage for quality and research purposes seems worthwhile. The Dutch bone tumour committee can currently be consulted by every orthopaedic surgeon in the Netherlands without prior consultation with the nearest bone sarcoma centre. The committee reviews radiological images as well as whole cases for advice. The referring orthopaedic surgeon receives a letter with recommendations after a radiological review or committee meeting. The committee meetings are only attended by members, which limits the opportunity for referring surgeons to receive feedback or gain relevant knowledge. Digital participation in the bone tumour committee meeting of eager and

enthusiastic referring orthopaedic surgeons could prove valuable. Residents and medical students could also gain knowledge from such meetings in order to educate and motivate the next generation of bone sarcoma caregivers.

> A national bone tumour board gives European bone sarcoma centres with little adherence the opportunity to gain from knowledge from a more experienced team.

With the same interest and intention as for organisation of care, we asked our European colleagues affiliated to EMSOS to provide us with data on follow-up. Their input helped us assess follow-up in several European bone sarcoma centres, identifying potential benefits beyond borders in **Chapter 6**. We saw clear variations in follow-up intervals and imaging modalities among European bone sarcoma centres. Unsurprisingly, only low-quality evidence is available for follow-up in existing guidelines like EMSOS and NICE. (16,17) In the latest EMSOS guidelines, we believe that rather conservative follow-up intervals are recommended solely based on expert opinion. (16) Unexpectedly though, the majority of respondents found these guidelines sufficient to base their follow-up protocols on. There is a clear lack of evidence regarding follow-up intervals and duration of follow-up. Based on the available literature, survival of bone sarcoma patients depends on strong prognostic factors such as location, metastatic disease, tumour size and grade. (18–20) However, the effects of follow-up on survival are not known at present and therefore remain relevant for further research.

> Sufficient evidence is lacking in the existing follow-up guidelines on frequency and type of imaging modalities.

Efforts aimed at improving follow-up by providing evidence

The third and last part of the thesis focused on follow-up. Based on the findings in **Chapter 6**, additional evidence is needed to assess current follow-up strategies for high-grade bone sarcomas in the Netherlands. A follow-up regimen with prolonged intervals without bargaining on survival could benefit sarcoma patients. Disadvantages for patients from a conservative follow-up regimen are frequent outpatient visits, psychological distress and stochastic effects of repeated imaging. (21,22) In **Chapter 7** we evaluated oncological events occurring after index treatment with curative intent during follow-up, including time to local recurrence and distant metastasis using nationwide data from the NCR. A plateau in local recurrences and distant metastatic events after four years of treatment

for patients with high-grade osteosarcoma and Ewing sarcoma was seen during follow-up. Unfortunately, based on the low number of patients left in follow-up we were unable to provide a recommendation for extended follow-up after five years. Still, this study could ignite a discussion about the purpose of extended follow-up and its value for the individual patient. To provide a solid scientific basis for future recommendations for follow-up intervals and duration, larger international multicentre studies are needed due to the low incidence figures of these tumours. Artificial intelligence models could prove valuable in facilitating the much-needed big data in bone sarcoma research.

A plateau in new local recurrences and distant metastatic events after four years of treatment for patients with high-grade osteosarcoma and Ewing sarcoma was seen during follow-up.

Clinical implications, considerations and future perspectives

The goal of this thesis was to assess, and ultimately improve, the clinical approach towards the organisation of bone sarcoma care and follow-up. The main findings of this thesis indicate that bone sarcoma care is of satisfactory quality for our patients in the Netherlands. Bone sarcoma care has become more centralised over the last two decades. With the concentration of all paediatric oncology in one specialised centre in the Netherlands, maximum effort has been made to combine the available expertise in order to improve organisation of care. The concentration of all paediatric oncology in this single centre has resulted in approximately a 10% decrease of exposure of bone sarcoma patients in the other four centres. It is therefore debatable whether this paediatric concentration will prove beneficial for the quality of bone sarcoma care nationally. The concentration could lead to decreased regional knowledge about paediatric sarcoma care, potentially resulting in more delays and so-called whoops procedures. The diminished exposure in the remaining bone sarcoma centres could have a negative effect on surgical reconstructive capabilities. Tumour prostheses are often used for reconstruction after radical resection, with additional and extensive soft-tissue reconstruction needed in most cases. Given the complexity of these procedures, sufficient exposure is crucial for multidisciplinary teams of orthopaedic oncologists and plastic surgeons. Increased survival for the individual patient must be found in improving systemic treatment, as delay in diagnosis does not seem to affect survival of bone sarcoma patients. Various research initiatives are focused on improving survival by optimising systemic treatment. (23,24) A prospective national registry including patient-reported outcome measures could prove valuable in terms of better outcome and organisation of care. Regarding follow-up, sufficient evidence in the

existing guideline is lacking. At present, follow-up intervals for adults with high-grade chondrosarcoma, high-grade osteosarcoma and Ewing sarcoma are every 3 months in the first year after treatment, every 4 months in the second year, and then prolonged to a 6-month-interval until 5 years of follow-up. A one-year-interval is used until 10 years of follow-up. Although it is difficult to provide a solid recommendation, we advocate that the follow-up intervals after 5 years could be elongated to 2 years. A proposal to end follow-up after 5 years is not evidence-based at present, and neither is the rationale and added value of extended follow-up up to 10 years.

> The discussion about the purpose of extended follow-up and its value for the individual patient, initially treated with curative intent, should be intensified because of the negative effects of a conservative follow-up regimen.

Several considerations and limitations regarding this thesis are worth mentioning. Due to the low incidence of these tumours, it was difficult to acquire sufficient patient cohorts for statistical analysis even though several studies in this thesis were based on national registries. This resulted in several recommendations with a limited quality of evidence. Most research initiatives in the field of orthopaedic oncology focus on surgical or systemic treatment and the quantitative effects on survival. This thesis, however, focuses on the clinical approach towards bone sarcoma care, including two international collaborative studies with more qualitative results. The available literature for comparison with our findings was scarce. This is why the findings in this thesis are highly relevant and of practical value for clinicians, to evaluate and potentially improve the organisation of bone sarcoma care locally and across borders.

Future efforts in organisation of care should be aimed at improving referral patterns of patients towards bone sarcoma centres. Intensification of regional networking care could prove valuable to create awareness among healthcare professionals, facilitate low thresholds for consultation and provide repetitive education. Regarding follow-up, future research should aim towards the effects of follow-up strategies on health outcomes based on larger patient cohorts generated through international collaboration. Cost-effectiveness studies and individualised follow-up algorithms based on prognostic factors are subjects of interest for future research. With the application of artificial intelligence, these algorithms should be incorporated into electronic health records to facilitate both clinicians and patients in shared decision-making.

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SUMMARY

English summary
Nederlandse samenvatting

English summary

For over two decades now, bone sarcoma care has been centralised in the Netherlands.

This seems rational, given the low incidence of these tumours: inappropriate histological diagnosis, treatment delays and inappropriate care (so-called whoops surgeries) are known factors with a negative effect on survival for the individual patient. Recently, bone sarcoma care for paediatric patients has been centralised to a single centre in close collaboration with the other four Dutch bone sarcoma centres.

To obtain a clear picture of bone sarcoma care and the effect of centralisation in the Netherlands it is important to evaluate the way we treat these patients. Apart from centralisation of care, organisation and follow-up are important parameters to review as well.

The overall aim of this thesis is the assessment of optimal care for bone sarcoma patients. First, bone sarcoma care was assessed in terms of incidence. Second, the impact of centralisation was assessed for time to diagnosis and organisation of care. Third, follow-up of bone sarcoma was assessed to ultimately improve the clinical approach towards bone sarcoma care.

Chapter 1 is a general introduction providing an overview of the most common high-grade bone sarcomas and their clinical behaviour. The foundations of this thesis and key concepts are explained. These key concepts include centralisation of care, international collaboration and data storage. Last, the aims and contents of this thesis are outlined.

Part 1 Bone Sarcoma Incidence

Chapter 2 is a nationwide registry study that provided comprehensive incidence estimates for all main primary bone sarcomas over a 15-year period. Data for this study were derived from the Netherlands Cancer Registry, which receives primary notification from the national pathology database. Increased centralisation over the years was seen in terms of biopsy and treatment. We also assessed the effect of centralisation of care on oncological outcome in terms of tumour biopsy and treatment. Treatment at a bone tumour centre was found to be associated with better outcome for patients with high-grade central osteosarcoma.

In **Chapter 3**, another nationwide registry study focused on the presentation, treatment and outcome of periosteal chondrosarcoma over a 59-year period. Periosteal chondrosarcoma is known as a rare subtype of chondrosarcoma with difficulties in

diagnosis. Data for this study were derived from the archive of the Dutch bone tumour committee. Based on the clinical data, we found that staging for metastatic disease should be performed in histologically grade II lesions and higher. The results in this chapter illustrate how multidisciplinary decision-making with clinicians, radiologists and pathologists is essential towards obtaining the correct diagnosis.

Part 2 The impact of centralisation

In **Chapter 4**, a retrospective single bone sarcoma centre study quantified time to diagnosis and its effect on clinical outcome in high-grade bone sarcoma. Patient-related delay as well as the different types of doctor-related delay were singled out and analysed. Prolonged delay in diagnosis did not result in lower survival, while metastatic disease had a pronounced effect on survival. We believe that aggressive tumour behaviour resulted in shorter delays. Efforts to minimise delays could include adopting a lower threshold for obtaining plain radiographs at the pre-hospital stage along with guideline optimalisation to improve referrals to a bone sarcoma centre.

In **Chapter 5**, a cross-sectional study described the organisation of care in several European bone sarcoma centres. Data for this observational cross-sectional study was obtained through healthcare professionals affiliated with EMSOS. Ten questions were formulated, focused on guidance, multidisciplinary decision-making and data storage. The questionnaires revealed that the provision of oncological care differed between the bone sarcoma centres. A major increase in adherence per centre could result in a low referral and treatment percentage. A national bone tumour board gives bone sarcoma centres with little adherence the opportunity to gain knowledge from a more experienced team. The optimal size for a bone sarcoma centre in terms of patient adherence is unknown at present.

Part 3 Follow-up of bone sarcoma

In **Chapter 6**, a cross-sectional study analysed follow-up procedures in several European bone sarcoma centres. Data was obtained from analysis of several follow-up protocols and a nine-question digital questionnaire returned by professionals affiliated with EMSOS. Based on the questionnaires, all participating bone tumour centres reached a minimum follow-up period of ten years. Variations in follow-up intervals and use of repeated imaging were seen between European bone sarcoma centres as well as in the various national guidelines. The majority of the participating centres follow existing international guidelines and find them sufficient as basis for a follow-up surveillance programme despite a clear lack of evidence.

In **Chapter 7**, a nationwide registry study evaluated the oncological events occurring after index treatment with curative intent during follow-up. The aim was to obtain additional evidence to assess current follow-up strategies. Data for this study were derived from the Netherlands Cancer Registry. Local recurrence and distant metastasis were analysed along with overall survival for high-grade chondrosarcoma, high-grade osteosarcoma, Ewing sarcoma and chordoma. This study showed a plateau in local recurrences and distant metastatic events after four years of treatment for patients with high-grade osteosarcoma and Ewing sarcoma. Due to a lack of reliable evidence, however, we were unable to provide additional guidance on follow-up intervals and duration. Collaborative research with larger groups is needed to provide a solid scientific recommendation for follow-up in the heterogenous patient population with bone sarcoma.

The general discussion in **Chapter 8** is structured around the three themes covered in this thesis. The results of the individual studies are discussed along with the main findings of this thesis. Last, clinical implications, considerations and future perspectives are provided.

Nederlandse samenvatting

Al ruim twee decennia is de zorg voor botsarcomen in Nederland gecentraliseerd. Dit lijkt verstandig gezien de lage incidentie van deze tumoren. Bekend is dat een verkeerde histologische diagnose, uitgestelde behandeling of een verkeerde behandeling factoren zijn met een negatief effect op de overleving van de patiënt.

Om een goed beeld te krijgen van de zorg voor botsarcomen en het effect van centralisatie van zorg in Nederland, is het belangrijk om de manier waarop we deze patiënten behandelen te evalueren.

De studies die in dit proefschrift zijn beschreven, hebben als doel de zorg voor patiënten met een botsarcoom te optimaliseren. Deze studies zijn gestructureerd aan de hand van drie thema's. In deel 1 van het proefschrift wordt voor de belangrijkste botsarcomen de incidentie beschreven. Vervolgens wordt in deel 2 de impact van centralisatie beoordeeld op het gebied van doorlooptijden voor diagnostiek en organisatie van zorg. Tenslotte wordt in deel 3 de nazorg (follow-up) voor patiënten met een botsarcoom geanalyseerd.

Hoofdstuk 1 bevat een algemene inleiding, die een overzicht geeft van de meest voorkomende hooggradige botsarcomen. Daarnaast worden de aanleiding en het doel van dit proefschrift uiteengezet samen met enkele belangrijke concepten: centralisatie van zorg, internationale samenwerking en gegevensbeheer.

Deel 1 Incidentie van botsarcomen

Hoofdstuk 2 beschrijft een landelijke registerstudie, waarin voor alle belangrijke primaire botsarcomen de incidentie is vastgesteld over een periode van 15 jaar. De gegevens voor dit onderzoek zijn afkomstig van het Integraal Kankercentrum Nederland (IKNL). Voor zowel biopsie als behandeling werd gedurende de studieperiode een toename van centralisatie waargenomen. Het effect van deze centralisatie van zorg op de oncologische uitkomst werd ook beoordeeld. Voor biopsie werd geen verschil aangetoond. Behandeling in een botsarcomencentrum resulteerde in een betere overleving voor patiënten met hooggradig osteosarcoom. Voor patiënten met hooggradig chondrosarcoom en Ewing sarcoom kon dit niet worden aangetoond.

In **hoofdstuk 3** wordt een zeldzaam subtype van het chondrosarcoom beschreven en geanalyseerd: het periostaal chondrosarcoom. Gegevens voor dit onderzoek zijn afkomstig uit het archief van de Nederlandse Commissie voor Beentumoren. In dit landelijke archief vonden we 36 patiënten met periostaal chondrosarcoom over een periode van 59 jaar. Het stellen van de juiste diagnose bij zo'n zeldzame tumor is lastig. De resultaten van deze studie laten zien dat, na tumorbiopsie, er voor afwijkingen vanaf

graad II verder onderzoek nodig is naar eventuele afstandsmetastasen. De bevindingen in dit hoofdstuk illustreren dat multidisciplinaire besluitvorming door chirurgen, oncologen, radiologen en pathologen essentieel is voor het verkrijgen van de juiste diagnose.

Deel 2 De impact van centralisatie

In **hoofdstuk 4** worden in een retrospectieve studie de doorlooptijden voor diagnostiek en het effect hiervan op overleving bij hooggradige botsarcomen geanalyseerd. De doorlooptijden voor diagnostiek en vertraging werden opgedeeld in patiënt-delay en drie soorten dokters-delay: bij de huisarts, het algemene ziekenhuis en in het botsarcomencentrum. In deze studie resulteerde vertraagde diagnostiek niet in een verminderde overleving. Patiënten met gemetastaseerde ziekte hadden wel een slechtere overleving. Wij concluderen, op basis van de resultaten van deze studie, dat agressieve hooggradige botsarcomen snel groeien waardoor er weinig vertraging in de diagnostiek optreedt. Een aanbeveling voor het verder verminderen van diagnostische vertraging in de huisartsenpraktijk zou een laagdrempelige röntgenfoto zijn bij een niet-pluis gevoel. Daarnaast is het belangrijk de richtlijn te optimaliseren voor versnelling van het verwijstraject naar een botsarcomencentrum.

Hoofdstuk 5 omvat een cross-sectioneel onderzoek, waarin de organisatie van de zorg in verschillende Europese botsarcomencentra werd geanalyseerd. De gegevens voor deze observationele studie werden verkregen via zorgprofessionals aangesloten bij de European Musculo-Skeletal Oncology Society (EMSOS). Er werden tien vragen geformuleerd gericht op het mandaat van botsarcomenzorg, multidisciplinaire besluitvorming en dataopslag. Uit de vragenlijsten bleek dat het mandaat voor het verlenen van botsarcomenzorg niet eenduidig was. In een aantal landen was dit overheidsgedreven, terwijl in andere landen dit op basis van (eigen) expertise werd uitgevoerd. Enkele grote landen met veel inwoners hadden weinig botsarcomencentra. Wij concluderen dat dit, door reisafstanden, kan leiden tot een laag verwijs- en behandelpercentage per centrum. Voor behandelcentra met weinig patiëntenaanbod kan een landelijke commissie voor beentumoren de mogelijkheid geven te profiteren van een meer ervaren team. De hoogte van een kwantitatieve volumenorm met kritische ondergrens voor het verlenen van zorg voor botsarcomen is op dit moment niet goed wetenschappelijk te onderbouwen.

Deel 3 Follow-up

In **Hoofdstuk 6** worden in een cross-sectioneel onderzoek de follow-up procedures in verschillende Europese botsarcomencentra bestudeerd. De informatie vanuit de beschikbare follow-up protocollen werd aangevuld met een digitale vragenlijst met negen vragen. Deze vragen werden beantwoord door zorgprofessionals aangesloten bij de EMSOS. Uit deze studie bleek dat alle deelnemende bottumorcentra een minimale follow-up periode van tien jaar aanhouden. Er was een variatie zichtbaar in follow-up-intervallen en het gebruik van herhaalde beeldvorming tussen de verschillende centra. Ook was er geen eenduidigheid in de verschillende nationale richtlijnen over het gebruik van herhaalde beeldvorming en follow-up intervallen. Geconcludeerd kan worden dat de meerderheid van de deelnemende centra volgt de bestaande internationale richtlijnen, en vindt deze voldoende als onderbouwing voor een follow-up protocol, ondanks een duidelijk gebrek aan bewijs.

Hoofdstuk 7 beschrijft een landelijke registerstudie met aandacht voor de timing van lokaal recidief en afstandsmetastasen gedurende follow-up na de initiële behandeling van hooggradige botsarcomen. Daarnaast werd de overleving geanalyseerd. Het doel van dit onderzoek was om het huidige protocol te kunnen toetsen en eventueel een aanbeveling te kunnen geven over de duur en intervallen van follow-up. De gegevens voor dit onderzoek zijn afkomstig van het IKNL. Deze studie toonde een plateau aan in lokaal recidief en afstandsmetastasen na vier jaar follow-up voor patiënten met hooggradig osteosarcoom en Ewing-sarcoom. Vanwege een gebrek aan sluitend bewijs kunnen we echter geen aanbeveling geven over de duur en intervallen van follow-up. Toekomstig internationaal opgezet onderzoek met een grotere groep is nodig om een goede wetenschappelijke aanbeveling te kunnen geven voor follow-up van botsarcomen.

De algemene discussie in **Hoofdstuk 8** is gestructureerd aan de hand van de drie thema's die in dit proefschrift worden behandeld. De resultaten van de afzonderlijke onderzoeken worden besproken samen met de belangrijkste bevindingen van dit proefschrift. Als laatste worden klinische implicaties, overwegingen en toekomstperspectieven beschreven.

APPENDICES

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Lectures

2014
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Clinical characteristics, therapeutic regimen and outcome of periosteal chondrosarcoma in the Netherlands.
Oral presentation

2015
28th Annual Meeting of the EMSOS: 29 april–1 may, Athens
Delay in diagnosis and its effect on clinical outcome in high-grade sarcoma of bone; a referral oncological center report and review of the literature.
Oral presentation

2016
29th Annual Meeting of the EMSOS: 25-27 may, La Baule.
Complications of percutaneous sclerosing therapy for aneurysmal bone cysts using ethanol and polidocanol.
Poster presentation

2018
31st Annual Meeting of the EMSOS: 9-11 may, Amsterdam
Bone Sarcoma Incidence in the Netherlands
Oral presentation

2019
32nd Annual Meeting of the EMSOS: 15-17 may, Florence
Organization of bone sarcoma care: a cross-sectional study from a European group
Poster presentation

2021
33rd Annual Meetings of the EMSOS: 1-3 december, Graz
Follow-up of bone sarcoma care: a cross-sectional study from a European group
Oral presentation

Magazine

2020

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Incidentie van botsarcomen in Nederland
Magazine Patiëntenplatform Sarcomen: Leven met sarcomen december 2020

Book chapter

2023 (Expected)

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Curriculum vitae

Louren Matthias Goedhart was born on October 26th 1988 in Harderwijk, the Netherlands. He attended the Atheneum at Christelijk College Nassau Veluwe between 2001 and 2007. After completing high school he moved to Groningen and started studying Medicine in 2007. A junior internship at the Orthopaedic surgery department sparked his enthousiasm for Orthopaedic oncology. This marked the beginning of his scientific career under the supervision of Dr. J.J.W. Ploegmakers. Their first project formed the foundation of this thesis with a publication in 2014. His enthousiasm for Orthopaedics was confirmed during his senior internships in Medisch Spectrum Twente Enschede.

After completing Medical School in 2014, Louren started working as a resident Orthopaedic surgery not in training in Enschede, supervised by Dr. A.V.C.M. Zeegers. As a result of this opportunity, he was admitted to the residency program in ROGO Noord-Oost in 2016. He completed his basic surgical training in Treant (Emmen - Stadskanaal - Hoogeveen), supervised by Dr. M. van den Berg. He continued his residency with Orthopaedic surgery at Martini hospital Groningen, supervised by Dr. J.J.A.M. van Raaij. For his fourth residential year, he returned to Medisch Spectrum Twente Enschede in 2019. The final two years of his residency were spent at University Medical Center Groningen, supervised by Prof. Dr. P.C. Jutte and Dr. J.J.W. Ploegmakers. During his residency Louren continued persueing his scientific career, ultimately leading to the completion of this thesis in 2022. Parallel to this, he completed his Orthopaedic surgical training in December 2022. From January 2023 onwards, he will take his first steps as an Orthopaedic surgeon and Knee fellow at Martini Hospital Groningen supervised by Dr. R.W. Brouwer.

Louren lives together with Florine (resident OBGYN) and their daughter Rosalie (2021) at the Typografengasthuis in Groningen.