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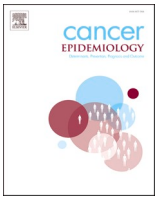

Incidence and centralization of chordoma in the Netherlands: A nationwide study between 1991 and 2020

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ABSTRACT

Introduction: Chordomas are rare malignant bone tumors arising in the axial skeleton, with an incidence of 0.3–0.88 per million inhabitants. We studied the annual incidence rate and centralization of treatment for chordoma in the Netherlands.

Methods: We retrieved pathology excerpts from the PALGA nationwide Dutch Pathology Registry between 1991 and 2019 for patients with a chordoma to calculate incidence rates. From pathology reports we extracted patient age at diagnosis, sex, year of diagnosis, localization of primary tumor, histologic chordoma subtype (conventional including chondroid, poorly differentiated or dedifferentiated), center of diagnosis (bone tumor referral center (BTC) or other hospital), and partial identification of the BTCs.

Results: A total of 420 individual chordoma patients were identified in the given time period. The incidence of chordoma increased from 0.593 per million inhabitants between 1991–1995 to 1.111 from 2015–2019 ($P = 0.001$). Median age at diagnosis was 63 years (range 1–95), 252 patients (60%) were male. The proportion of samples analyzed in a BTC either primarily or secondary, as a consultation, revision or referral, increased significantly from 29.3% to 84.4% ($P < 0.001$). Most primary and secondary samples were analyzed at the Leiden University Medical Center (LUMC, 54.4% and 57% respectively).

Conclusions: This study shows an increase in the standardized incidence of pathology proven chordoma in the Netherlands. We observed an increase in samples being analysed in the specialized BTCs as well, which is in line with current guidelines and will hopefully lead to more accurate diagnoses and optimal treatment plans for chordoma patients in specialized treatment centers.

1. Introduction

Chordomas are ultra rare bone tumors which can affect the whole axial skeleton from skull base (30%), to mobile spine (20%), to sacrum (50%) and rarely extra-axial [1], that show notochordal differentiation [2]. They represent 1–4% of all bone malignancies and although rare they are the 4th most common malignant primary bone tumour [3]. Chordomas are believed to arise from cellular remnants of the notochord that persist during fetal development [2].

Chordomas can be categorized as conventional (which includes the chondroid variant), poorly differentiated and dedifferentiated. Conventional or classical chordomas represent 95% of the total, whereas poorly differentiated and dedifferentiated chordoma represent only 5% of all chordomas [4]. The diagnosis can be made based on histology and expression of cytokeratin, S100 protein and brachyury. Dedifferentiated chordomas show a lost expression of brachyury [1,5].

These tumors are malignant and although rarely metastatic, may lead to great morbidity and mortality. Prognosis is highly dependent on resectability, presence of metastases and dedifferentiated component. While the median survival of chordoma overall is 7.7 years [6], this is only 16–26 months in case of dedifferentiated chordoma [7,8]. The mainstay of treatment is surgical resection, which can be challenging depending on tumor extension and anatomical site [1]. The high rate of local relapse of the disease is strongly related to resection margins at primary surgery [9,10]. High dose radiotherapy, preferable with particles (protons or carbon ions) is recommended as adjuvant therapy or

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definitive treatment when surgical resection is not feasible [1]. Definitive Proton beam (PB) therapy for mobile spine and sacral chordomas show relatively good clinical results in patients refusing surgery given the burden of surgical resection [11]. Given the low incidence and prevalence and the challenging technical aspects of surgery and radiotherapy for this malignancy the treatment of chordoma should be centralized.

Incidence data for chordomas in Europe and the United States of America (USA) collected from different national health database were previously published, and report an incidence of 0.30–0.88/1.000.000 [6,12–20]. Chordomas are considered among the ultra rare sarcoma subtypes [21]. Chordoma incidence increases with age and the median age lies between 55–58.5 years, [6,14] with a lower median age for patients with a cranial chordoma (47.5 years) compared to sacral chordoma (64 years) [22,23]. Males are more often diagnosed compared to females with a male to female ratio of 1.6:1 [6,14,24]. The primary location of the tumor is cranial in 32%, spinal in 33%, sacral in 29% and extra-axial or ill-defined in the remaining 6% of patients [14].

Five-year overall survival rates range from 62,5 to 72% and no differences were seen according to sex or primary tumor site [12,14]. Survival is improving over time given the advancements made in surgical and radiotherapy techniques [12].

We performed a study to estimate the annual incidence rate of chordoma in the Netherlands. For data collection we used the nationwide Pathological Anatomical National Automated Archive (PALGA) registry that covers 100% of pathology reports in the Netherlands [25]. Our primary objective was to estimate the annual incidence of chordoma in the Netherlands from 1991 to 2020. We hypothesized that the annual incidence rate of chordoma has increased during the past four decades in the Netherlands, given the annual rise in incidence seen in previous studies [15,19]. The secondary objective was to estimate the incidence of chordoma by age, sex, histologic subtype and center of diagnosis (either a Dutch bone tumor referral center or other hospital) and to evaluate centralization of care for chordoma patients.

2. Materials and methods

2.1. Patients

All patients with a chordoma diagnosed between January 1 1991 and January 1 2020 were selected from the PALGA database [25]. A search request in PALGA for all patients with the following diagnoses was performed: chordoma, chordoma metastasis and free text search for ‘chordoma’. The standardized excerpts contain specific subject identification numbers, age at diagnosis, sex, date of pathology specimen, clinical information, conclusion of the pathology report and whether the analysis was done in a Dutch bone tumor referral center (defined below) or not. Patients with a first diagnosis of chordoma were included. To prevent registration of multiple excerpts from one single patient we excluded excerpts that described revisions or consultations, residual or recurrent disease and metastatic lesions.

The Dutch Ministry of Health has indicated four Dutch expertise centers as Bone Tumor Referral centers (BTCs); Leiden University Medical Center (LUMC), Amsterdam University Medical Center (AMC), University Medical Center Groningen (UMCG) and Radboud University Medical Center (Radboud UMC). For this study the 3 BTCs other than the LUMC will remain partially blinded and will be referred to as BTC-A, BTC-B and BTC-C.

2.2. Ethics

Since fully anonymized pathology reports were used and individualized patient outcome data were not used, no informed consent was obtained.

2.3. Data collection

Data was collected on age at diagnosis, sex, year of diagnosis, localization of primary tumor, histologic subtype of chordoma (conventional including chondroid, poorly differentiated or dedifferentiated), center of diagnosis (a BTC or other hospital), and identification of the BTCs (other hospitals were anonymized). The BTCs have given explicit consent for de-blinding of laboratory identification data.

2.4. Statistical analysis

For each 5-year study period (1991–1994, 1995–1999, 2000–2004, 2005–2009, 2010–2014 and 2015–2019) we calculated incidence rates per million inhabitants subdivided by age, sex, tumor localization and center of diagnosis. Incidence rates are given as crude rates, standardized rates using the Dutch population in 2019 as a standard population and age-standardized to the WHO and European (ESR) standard population [26–28].

For statistical testing Pearson’s chi-squared test and one way ANOVA were used. Time trends for incidence were tested with linear regression analysis.

3. Results

A total number of 420 individual patients were included for incidence analysis and analysis of clinical data from the excerpts. Fig. 1 illustrates the result of the search strategy and number of patients included and excluded from the analysis.

A total of 75 patients were excluded from the analysis due to an uncertain diagnosis. The percentage of samples with an uncertain diagnosis was not evenly distributed over time ($P = 0.049$) and uncertain diagnoses were more frequent in the period from 1991–1999 (Fig. 7 supplementary materials).

The median age of chordoma patients was 63 years (range 1–95) and 252 patients (60%) were male. The localization of chordoma was in the skull base in 34.3%, cervical spine in 8.8%, thoracic spine in 4.8%, lumbar spine in 8.6%, sacrum in 41.4% and unknown for 1.4% of patients (Table 1). Fig. 2 illustrates chordoma localization per age group. The peak incidence of chordoma of the skull base is 50–59, for mobile spine (cervical, thoracic and lumbar) 70–79 and sacral 60–69 years of age. Skull base chordomas are the most common chordoma localization in children and young adults (< 30 years of age).

3.1. Incidence rates

The standardized incidence rate increased from 0.593 per million inhabitants in the period 1991–1994 to 1.111 in the period 2015–2019

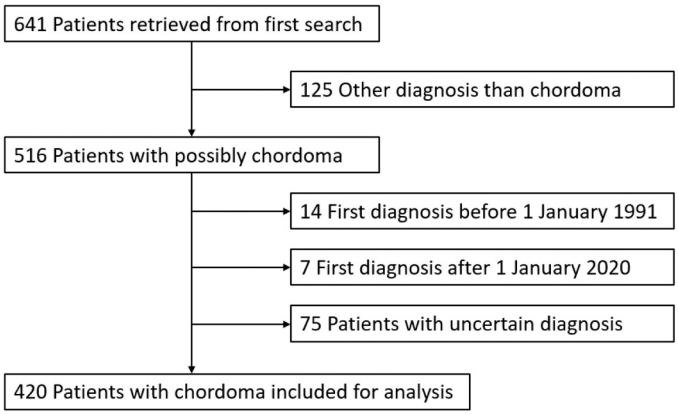

Fig. 1. Diagram of inclusion and exclusion of patient samples.

Table 1
Disease characteristics of all chordoma patient samples retrieved from the nationwide PALGA registry in the Netherlands between 1991–2019.

	Year						
	1991-1994	1995-1999	2000-2004	2005-2009	2010-2014	2015-2019	All
Total number of patients per time period	41	59	73	68	83	96	420
Gender, male no. (%)	25 (61.0)	33 (55.9)	39 (53.4)	41 (60.3)	52 (62.7)	62 (64.6)	252 (60)
Age, median (range)	65 (14-91)	63 (17-85)	57 (17-93)	61 (5-84)	63 (1-95)	65 (6-90)	63 (1-95)
Localization, no. (%)	9 (22.0)	22 (37.3)	24 (32.9)	28 (41.2)	36 (43.4)	25 (26)	144 (34.3)
– Skull base	6 (14.6)	9 (15.3)	6 (8.2)	5 (7.4)	3 (3.6)	8 (8.3)	37 (8.8)
– Mobile spine	2 (4.9)	-	4 (5.5)	3 (4.4)	4 (4.8)	7 (7.3)	20 (4.8)
– Cervical	4 (9.8)	3 (5.1)	8 (11.0)	5 (7.4)	7 (8.4)	9 (9.4)	36 (8.6)
– Thoracic	19 (46.3)	25 (42.4)	31 (42.5)	26 (38.2)	32 (38.6)	41 (42.7)	174 (41.4)
– Lumbar	-	-	-	1 (1.5)	-	2 (2.1)	3 (0.7)
– Sacrum	1 (2.4)	-	-	-	1 (1.2)	4 (4.2)	6 (1.4)
– Other							
– Unknown							
Subtype chordoma, no (%)	39 (95.1)	54 (91.5)	67 (91.8)	64 (94.1)	81 (97.6)	85 (88.5)	390 (92.9)
– Conventional	1 (2.4)	4 (6.8)	6 (8.2)	4 (5.9)	2 (2.4)	4 (4.2)	21 (5.0)
– Chondroid	-	-	-	-	-	1 (1.0)	1 (0.2)
– Poorly differentiated	1 (2.4)	1 (1.7)	-	-	-	6 (6.3)	8 (1.9)
– Dedifferentiated							

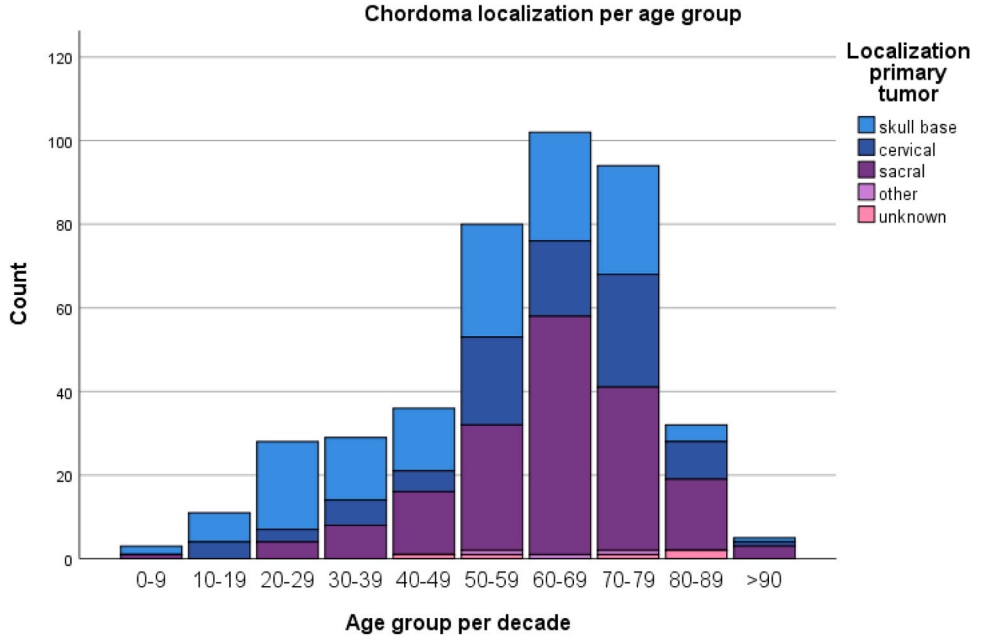

Fig. 2. Chordoma localization per age group.

Table 2
Incidence rates of chordoma in the Netherlands.

Year	Absolute number of patients	Crude incidence (Dutch population / million / year inhabitants)	WHO age standardized incidence per million inhabitants	Standardized incidence (Dutch population 2019) per million inhabitants	European standardized rate per million inhabitants
All	420			0.838	
1991-1994	41	0.675	0.352	0.593	0.576
1995-1999	59	0.757	0.374	0.683	0.595
2000-2004	73	0.908	0.431	0.845	0.636
2005-2009	68	0.830	0.381	0.787	0.539
2010-2014	83	0.993	0.412	0.961	0.615
2015-2019	96	1.124	0.411	1.111	0.651

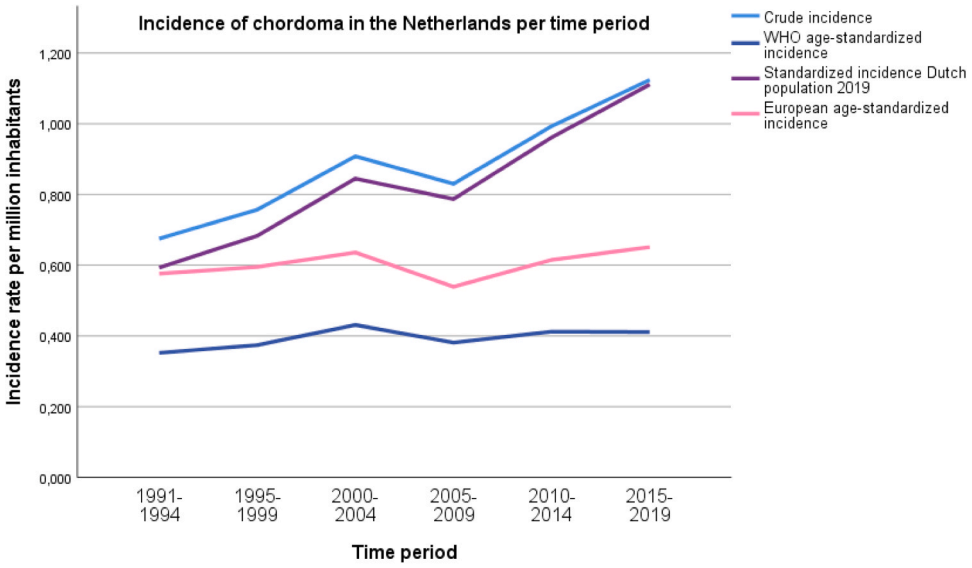

Fig. 3. Incidence rates of chordoma for the Dutch population, crude incidence per 10^6 inhabitants/year, standardized incidence per 10^6 inhabitants Dutch population 2019/year, WHO age-standardized incidence and European age-standardized incidence.

(P = 0.001) (Table 2 and Fig. 3).

Age of peak incidence was 60–69 years, with 24.3% of all chordomas diagnosed in the study period 1991–2019 occurring in this age group (Table 5 supplementary materials). A chordoma diagnosis before the age of 20 was rare (0.4%). Median age at diagnosis did not significantly increase over the 5-year study periods (P = 0.361).

Standardized incidence rate among males was 1.013 per million and for females 0.666 per million over the entire study period 1991–2019 (Table 3). No significant change in gender distribution was seen over the 5-year study periods (P = 0.727).

No significant changes were seen in distribution of chordoma subtypes (P = 0.123) or localization (0.301) over the 5-year study periods.

3.2. Centers of diagnosis

A total of 45 laboratories diagnosed chordomas, among which the four Dutch bone tumor referral centers (BTCs). The proportion of samples primarily analyzed in the pathology laboratory of a BTC increased significantly from 22% over 1991–1994 to 56.3% over 2015–2019 (P < 0.001). The proportion of samples that was either primarily analyzed in a BTC or secondary, as a consultation, revision or referral, also increased significantly from 29.3% to 84.4% (P < 0.001). (Fig. 4 below and Table 6 supplementary materials).

Table 3
Standardized chordoma incidence males versus females (Dutch population of 2019), No: number.

Period	No	Standardized incidence (Dutch population 2019) per million inhabitants	No	Standardized incidence (Dutch population 2019) per million inhabitants
1991-2019	252	1.013	168	0.666
1991-1994	25	0.728	16	0.460
1995-1999	33	0.769	26	0.598
2000-2004	39	0.909	34	0.782
2005-2009	41	0.956	27	0.621
2010-2014	52	1.212	31	0.713
2015-2019	62	1.445	34	0.782

Most primary and secondary samples were analyzed at the LUMC (54.4% and 57% respectively), followed by BTC-A (20.8% and 18.3%), BTC-B (10.7% and 13.0%) and lastly BTC-C (12.1% and 11.6%) (Fig. 4 and Fig. 6 supplementary materials).

Apart from the four BTCs, four other diagnosing laboratories analyzed large volumes of chordoma samples for primary analysis (> 20 samples during the study period) (Fig. 5). These centers remained anonymous but, in comparison to the BTC's, these centers analyzed a larger proportion of chordoma samples originating from the skull base, and smaller proportion originating from the sacrum (Table 5 and Table 6 supplementary materials).

4. Discussion

This study shows an increase in the standardized incidence of pathology proven chordoma in the Netherlands from 0.593 per million inhabitants between 1991–1994 to 1.111 between 2015 and 2019. This increase is seen in the crude incidence as well, and to a lower extent in the WHO age-standardized incidence and European age-standardized incidence rates. The incidence rise was expected based on several previous reports from population studies in Europe and the USA that report an annual percentage increase of 1.29–1.88% [15,19]. This is the first population based study of chordoma in the Netherlands.

In older population studies a higher incidence is reported in populations from the USA compared to those from the rest of the world [6,14,16–20,29]. See Table 4 for an overview. Population studies using data from national cancer registries in Finland, Sweden, England and Taiwan reported incidence rates between 0.18 and 0.51 per million [16–19]. In contrast, the studies by McMaster and Smoll, based on the Surveillance, Epidemiology and End Results programme (SEER) database in the USA, found incidences of 0.80–0.84 per million [6,14]. It was hypothesized that this might be due to incidence variation between races, however patient numbers were not sufficient to show significant differences between race [29]. Another explanation could be the underreporting of skull base chordomas due to diagnostic difficulties and distinction from chondrosarcoma for example [30]. Since the discovery of brachyury as a diagnostic marker for chordoma in 2006, this distinction has become easier to make [31]. This is reflected by our finding of an inequal distribution of uncertain diagnoses with a higher number of uncertain diagnoses in the earlier time frames. The incidence of skull base chordomas specifically was lower in the European studies

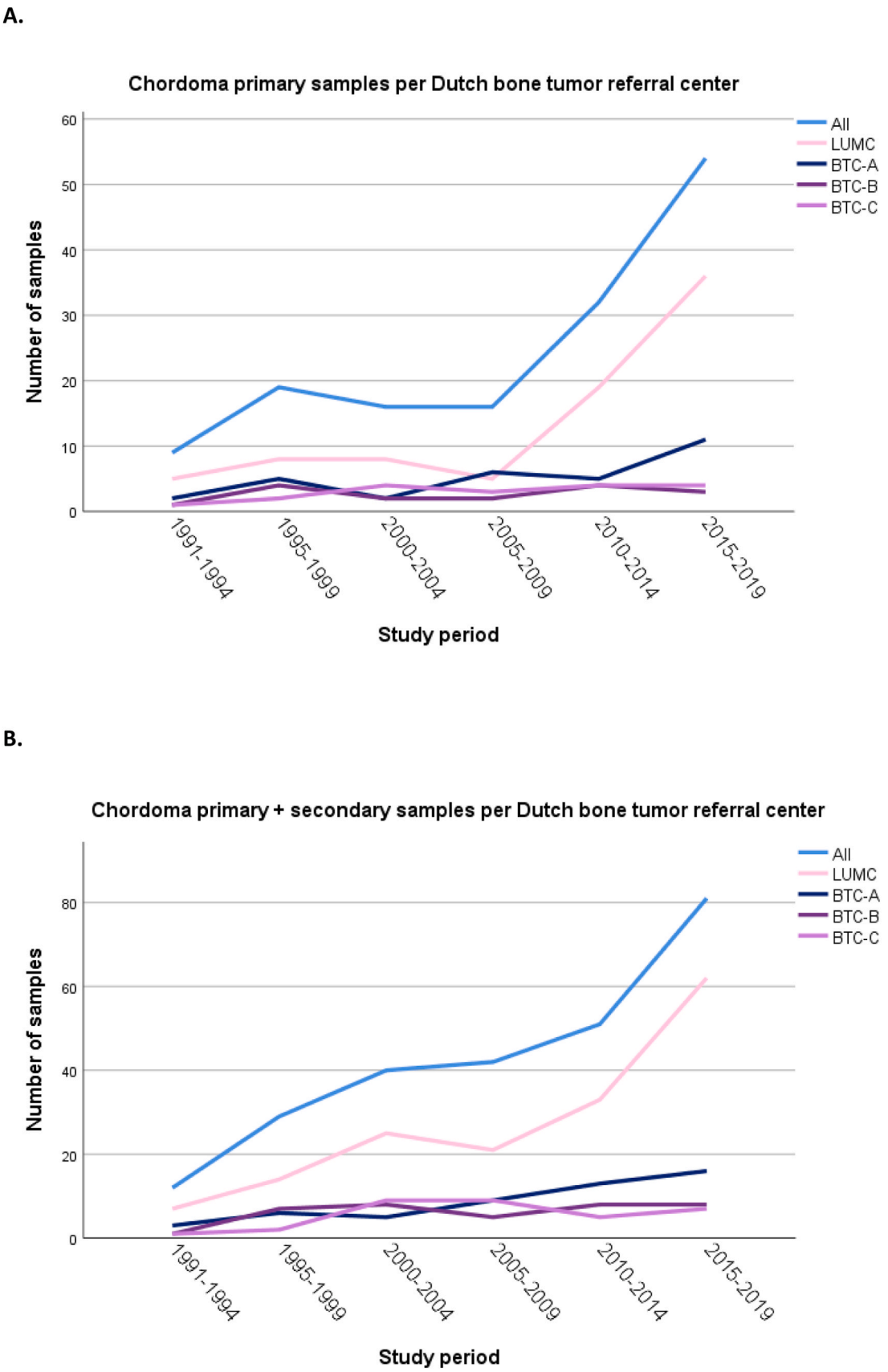

Fig. 4. Samples per Dutch bone tumor referral center. A. Primary samples B. Primary + secondary (referral, revision, consultation) samples. LUMC: Leiden University Medical Center, BTC-A: bone tumor center A, BTC-B: bone tumor center B, BTC-C: bone tumor center C.

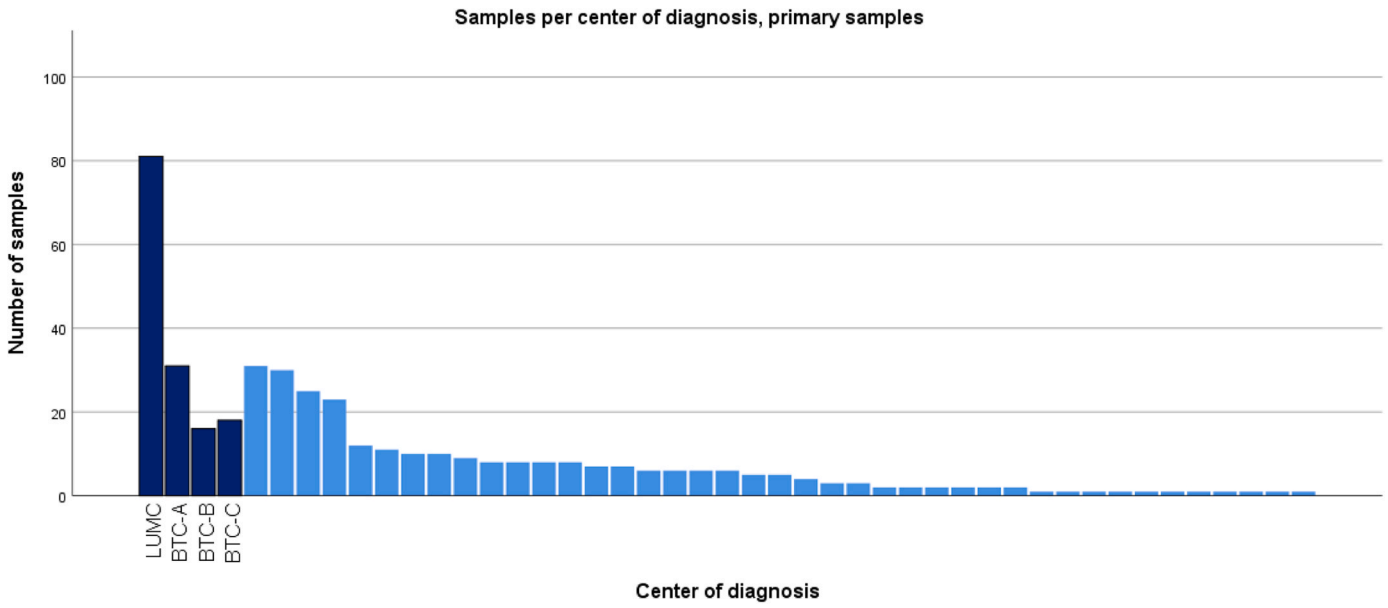

Fig. 5. Samples per diagnosing center, primary samples all centers 1991–2019. LUMC: Leiden University Medical Center, BTC-A: bone tumor center A, BTC-B: bone tumor center B, BTC-C: bone tumor center C.

[16,18,19].

Two more recent studies by Gatta and Das from Europe and the USA show an incidence rate more comparable to our study. Gatta et al. collected data from the RARECARE project, using 94 cancer registries across Europe, and found an incidence of 0.7 per million [13]. Das et al. reported an incidence of 0.88 per million retrieved from data from the Centers for Disease Control and Prevention and National Program of Cancer Registries [15]. These incidence rates are in line with the rates reported in our study.

The overall increase in chordoma incidence might be multifactorial. Diagnostic procedures have improved over the last decades, including better imaging methods and the introduction of immunohistochemical staining with brachyury which can distinguish chordoma from other histological mimics [31,32]. It is likely that more imaging is performed in general, and therefore more asymptomatic chordomas might be detected that would have otherwise remained occult. Especially patients with skullbase and craniocervical destructive lesions were not treated regularly before the year 2000. A very high complication rate, early recurrent disease after partial removal probably caused diagnostic and treatment "nihilism" Furthermore, data collection in the national cancer registries might have improved over time. And lastly, cancer incidence in general is increasing due to our increasing lifespan.

The higher incidence of poorly differentiated and dedifferentiated chordoma is probably due to their later addition to the WHO classification as a separate entity [33].

The male predominance of chordoma and peak incidence between 50 and 70 years old are confirmed by all population studies [6,14–20]. The median age in this report is higher compared to previous studies, which might be due to the relatively old population in the Netherlands [34]. With regards to the incidence of chordoma subtypes, chondroid chordomas are expected to be underreported since not all pathologists make the distinction between conventional and chondroid chordoma, also given the lack of clinical relevance [35,36].

Over time we observed an increase in samples being analysed in the BTCs, which is according to recent guidelines and as such a positive development. Both the number of primary samples as well as the number of samples that were evaluated as referrals, consultations or revisions increased in the BTCs during the study period. Increased awareness on the importance of referral and multidisciplinary evaluation in an expert BTC is probably the cause for this increase. Confirmation of the diagnosis in one of these referral centers by a specialized pathologist that has access to brachyury immunohistochemistry will consequently allow the multidisciplinary team to draft the best suitable treatment plan, with knowledge of the latest developments and the possibility of taking part in clinical trials. According to European and global guidelines a suspected chordoma case should be diagnosed and treated in a referral center or within reference networks with access to the required facilities and disease-specific knowledge [1,37,38].

The four centers, apart from the BTCs, that diagnosed >20 chordomas during the study period are likely to be large neurosurgical centers, as these were enriched for skull base tumors. These centers fall outside of the scope of the BTCs but diagnose and treat relatively many chordomas, especially those localized in the skull base.

The strength of this study is the use of the PALGA database, which is an automated pathology archive founded in 1971 [25]. The database has complete national coverage of all pathology reports since 1991, therefore we chose this start date for our study. In contrast to national cancer registries, with data collection through the PALGA database untreated chordomas will not be missed, therefore this is the most complete and accurate way to collect data in the Netherlands. On the other hand, radiologically suspected chordomas that never get pathologically confirmed will not appear in the PALGA database.

Unfortunately, we had to exclude 75 out of 516 excerpts of possible chordoma due to an uncertain diagnosis. In many cases there was a differential diagnosis of a chordoma, chondrosarcoma or metastasis of a renal cell carcinoma. There was no further follow-up available for these cases to confirm the diagnosis, any follow-up samples that might be performed leading to an alternative diagnosis would not be found with in the current search strategy. It is therefore most likely these cases were either not chordomas or not followed up with another biopsy.

5. Conclusions

This population based study on chordoma in the Netherlands has shown an increase in the incidence of pathology proven chordoma from 0.593 per million inhabitants between 1991–1994 to 1.111 between 2015 and 2019. Age of peak incidence was 60–69 years old, and chordoma has a male predominance. Primary localization of most chordomas was the sacrum (41.4%), followed by skull base (34.3%) and mobile

Table 4
Incidence chordoma – previously puplished papers on epidemiology. This is an update of a previously published table on chordoma epidemiology by Bakker et al. in European spine Journal 2018 [29]. M: male, F: female, NR: not reported, SB: skull base, MS: mobile spine, SC: sacrococcygeal.

Authors	Year of publication	Country / region	Time period	Registry	Number of cases	Incidence rate/ 10^6/ year	Age	Gender	Localization distribution	Comments
Paavolainen	1976	Finland	1953-1970	Finnish Cancer Registry	20	M: 0.30 F: 0.18	Mean 55.5	M: 60% F: 40%	SB: 10% MS: 15% SC: 75%	
Eriksson	1981	Sweden	1958-1970	Swedish Cancer Registry	51	0.51	Mean 57 (range 6-87)	M: 51% F: 49%	SB: 27% MS: 16% SC: 57%	
McMaster	2001	USA	1973-1995	Surveillance, Epidemiology and End Results (SEER) programme	400	0.80 M: 1.0 F: 0.6 (P = 0.0002)	Median 58.5 (range 3-95)	NR	SB: 32% MS: 32.8% SC: 29.2% Other: 6%	
Whelan	2012	England	1979-2009	National Cancer Data Repository and the Office of National Statistics	544	1979-1987: 0.3 1988-1997: 0.3 1998-2007: 0.4	NR	NR	SB: 26% MS: 23% SC: 45% Missing: 6%	
Smoll	2013	USA	1973-2009	Surveillance, Epidemiology and End Results (SEER) programme	1062	0.84 M: 1.06 F: 0.66	Median 58 (interquartile range 29 years)	NR	NR	Update on publication by McMaster 2001
Stiller	2013	Europe	1995-2002	RARECARE project, using 64 cancer registries across Europe	352	< 1 M: 1 F: < 1	0-14: < $1/10^6$ 15-24: < $1/10^6$ 25-64: < $1/10^6$ 65 + : $1/10^6$	NR	NR	
Hung	2014	Taiwan	2003-2010	Taiwan Cancer Registry	83	0.40 M: 0.52 (0.38-0.66) F: 0.25 (0.15-0.35)	0-24: 6 25-59: 48 ≥ 60: 29	M: 67% F: 33%	NR	
Gatta	2017	Europe	2000-2007	RARECARE project, using 94 cancer registries across Europe	1145	0.7	NR	NR	NR	
Das	2020	USA	2004-2014	United States Cancer Statistics (USCS)	3670	0.88 M: 1.09 F: 0.71	NR	M:F IRR 1.54	SB: 38.7% MS: 27% SC: 34.3%	USCS entails: - SEER - National Program of Cancer Registries (NPCR)
Klangjorhor	2022	Thailand	2001-2015	Population-based cancer registries	37	M: 0.3 F: 0.2	NR	M: 57% F: 43%	SB: 24% MS: 8% SC: 47% Other: 3% Unknown: 23%	
Lipplaa	2023	Netherlands	1991-2019	PALGA pathology database	420	0.84 M: 1.01 F: 0.67	Median 63 (range 1-95)	M: 60% F: 40%	SB: 34.3% MS: 22.2% SC: 41.4% Other: 0.7%	

spine (22.2%). We observed an increase in samples being analysed in the specialized BTCs, which is in line with current guidelines and will hopefully lead to more accurate diagnoses and optimal treatment for patients with this ultra rare tumor.

More centralization of future chordoma patients is necessary as diagnosis and treatment are complex. Our patients, suffering from these extremely rare tumors have the right to receive expert care and an optimal treatment plan.

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CRediT authorship contribution statement

A. Lipplaa: Conceptualization, Methodology, Formal analysis, Investigation, Writing – original draft. **R.J.P. van der Wal:** Writing – review & editing. **A.D.G. Krol:** Writing – review & editing. **W.C. Peul:** Writing – review & editing. **J.V.M.G. Bovée:** Conceptualization, Methodology, Writing – review & editing, Supervision. **H. Gelderblom:** Conceptualization, Methodology, Writing – review & editing, Supervision.

Declaration of Competing Interest

The authors declare that they have no known competing financial interests or personal relationships that could have appeared to influence the work reported in this paper.

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AL, HG and JB designed the study. The PALGA group provided the data for this analysis. AL collected the data and performed data analysis.

AL wrote the first manuscript. RW, AK, WP, JB and HG carefully read the manuscript and commented on the manuscript. All authors read and accepted the final manuscript. We received no financial support for this work.

Appendix A. Supporting information

Supplementary data associated with this article can be found in the online version at doi:10.1016/j.canep.2024.102527.

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