

Chordoma: incidence and survival patterns in the United States, 1973–1995

Mary L. McMaster*, Alisa M. Goldstein, Christina M. Bromley, Naoko Ishibe & Dilys M. Parry
Genetic Epidemiology Branch, Division of Cancer Epidemiology and Genetics, National Cancer Institute, National Institutes of Health, Bethesda, Maryland, USA

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Abstract

Background: Chordoma, a rare tumor arising from notochordal remnants, has been described to date only by single-institution case series or small population-based surveys.

Methods: We used data from the Surveillance, Epidemiology, and End Results (SEER) program of the National Cancer Institute, 1973–1995, to calculate age-adjusted incidence and survival rates for 400 cases of microscopically confirmed chordoma and to derive information regarding case distribution and risk of second cancer.

Results: The age-adjusted chordoma incidence rate (IR) of 0.08 per 100,000 was age-dependent, more common in males (IR 0.10) than females (IR 0.06) and rare among patients aged <40 years and blacks. Within the axial skeleton 32% of cases were cranial, 32.8% spinal and 29.2% sacral. Young age (<26 years; $p = 0.0001$) and female sex ($p = 0.037$) were associated with greater likelihood of cranial presentation. There was no overall increased risk for second primary cancers after chordoma. Median survival was 6.29 years; 5- and 10-year relative survival rates were 67.6% and 39.9%, respectively. Comparison with other bone sarcomas revealed racial disparities in incidence for the two developmental tumors, chordoma and Ewing's sarcoma.

Conclusions: This study provides new data regarding incidence and survival patterns of chordoma in the US. Additional epidemiologic studies are required to elucidate the genetic and environmental determinants underlying this rare, distinctive neoplasm.

Introduction

Chordoma is a rare tumor believed to arise from vestigial or ectopic notochordal tissue [1, 2]. Although more than 1000 cases have been reported since chordoma was characterized by Ribbert in 1894, individual case reports and small single-institution case series comprise most of the literature. Furthermore, because it is so rare, chordoma is frequently considered in combination with other rare bone neoplasms rather than as a separate pathologic entity. A few population-based surveys of chordoma exist,

including national or regional data for Finland (20 cases between 1953 and 1971) [3], Sweden (51 cases between 1958 and 1970) [4], and Scotland (34 cases between 1953 and 1971) [5]. In addition, some data on chordoma are reported as a subset of data on bone tumors from the United Kingdom (11 cases between 1946 and 1974 and 13 cases between 1958 and 1989, from the Bristol [6] and Leeds [7] registries, respectively) and the United States (221 cases between 1973 and 1987) [8]. However, most of these population-based studies are limited by small numbers of cases. To clarify the epidemiologic patterns of chordoma in the general US population we evaluated 400 cases reported to nine population-based registries within the Surveillance, Epidemiology, and End Results (SEER) program over a 22-year period from 1973 through 1995.

* Correspondence to: Mary L. McMaster, MD; Executive Plaza South, Room 7010; 6120 Executive Boulevard, MSC 7236; Bethesda, MD 20892-7236, USA; Ph.: 301.402.9726; Fax: 301.402.4489; E-mail: mcmastem@exchange.nih.gov

Methods

The Surveillance, Epidemiology, and End Results (SEER) program

The SEER program of the National Cancer Institute compiles incidence and survival data for patients with malignant neoplasms. Consistent data beginning in 1973 on chordoma were available from nine population-based cancer registries across the United States that together represent approximately 9.5% of the US population. The nine registries include five states (Connecticut, Hawaii, Iowa, New Mexico, and Utah) and four standard metropolitan areas (Atlanta, Detroit, San Francisco–Oakland, and Seattle–Puget Sound); they were included in SEER because they are based on broad geographic and racially diverse populations that reflect the composition of the overall US population. To provide complete ascertainment, data are collected by trained SEER abstractors from hospital records and death certificates, as well as private laboratories, radiotherapy units, nursing homes and other medical service units that provide cancer diagnostic services. Patient demographics, primary cancer site, histology, methods of diagnostic confirmation, details of initial treatment modality and survival data are among the specific variables routinely compiled. Because the data are population-based they avoid the selection biases associated with referral and treatment patterns.

Chordoma case definition

For this analysis we used chordoma cases diagnosed during the period 1973 through 1995; cases were identified using the World Health Organization's *International Classification of Diseases for Oncology, Version Two* (ICDO-2) [9] morphology code for chordoma (9370/3). Of the 412 chordoma cases diagnosed between 1 January 1973 and 31 December 1995 we excluded 12 cases that lacked microscopic confirmation; one additional case of unknown race was excluded from the racial analyses. Overall, the histologic confirmation rate was 97.1%.

Incidence and distribution

We calculated age-adjusted (1970 US standard) incidence rates using the public use program provided by SEER; incidence rates are expressed as new cases per 100,000 population and analyzed by age, gender, race, anatomical site of presentation, year of diagnosis, geographic area and initial treatment modality. Initial treatment is defined as any anticancer therapy received

within 4 months of diagnosis. Sites of presentation were compiled according to ICDO-2 topography codes. Cranial sites included the nasopharynx (ICDO-2 codes 112, 119), pharynx (140, 148), nasal cavity or sinuses (300, 313, 319), bones of the skull and face (410), connective, subcutaneous and soft tissues of the head, face and neck (490), cerebral meninges (700), any structure in the brain (710, 712, 714, 716, 717, 719, 751, 753), and other ill-defined sites of the head (760). Spinal sites included bones of the spine exclusive of sacrum and coccyx (412), the spinal cord (720), posterior mediastinum (382), and connective, subcutaneous, and soft tissue of the thorax or trunk (493, 496). Included within sacral sites were bones of the sacrum and coccyx (414), connective, subcutaneous and soft tissue of the pelvis (495), and pelvis not otherwise specified (763). Extra-axial sites included long bones of the lower limb (402), skin of the trunk (445), and connective, subcutaneous and soft tissues of upper limb and shoulder, abdomen, or other unspecified sites (491, 494, 499). A few sites could not be categorized satisfactorily on the basis of the ICDO-2 coding, including 728 (overlapping lesion of brain and central nervous system), 729 (nervous system, not otherwise specified), and 809 (unknown primary site). Limited incidence data were described previously for 221 of these patients [8].

Similar methods were used to calculate the age-adjusted incidence of other morphologically and clinically distinct primary bone tumors reported to SEER during the same period, including osteosarcoma (ICDO-2 codes 9180, 9181, 9182, 9183, 9185, and 9190), chondrosarcoma (ICDO-2 codes 9220, 9221, 9231, and 9240), and Ewing's sarcoma (ICDO-2 code 9260).

Treatment

The SEER database contains information regarding treatment offered to chordoma patients during the first 4 months following diagnosis. We used these data to assess patterns of first treatment for chordoma. All patients underwent surgical biopsy for diagnosis. If more extensive surgery, *e.g.* debulking or partial resection, occurred during the diagnostic procedure, the procedure was coded as surgical treatment. Patients were regarded as having received radiation alone if they had no surgery beyond the initial diagnostic biopsy. Treatment status was classified as unknown if all details of either surgery or radiotherapy were not known. For this analysis, if a particular therapy was recommended but not given or not known to be given, then the patient was considered to have received the treatment. SEER codes do not differentiate between different methods of external beam radiotherapy, so that the type of radio-

therapy administered, *i.e.* charged particle therapy, could not be assessed.

Multiple primary analysis

We examined the data on chordoma cases for invasive primary malignancies that developed after the initial chordoma diagnosis. Cancer sites were grouped according to ICDO-2 classification. In order to estimate the risk of second cancers we calculated numbers of person-years at risk from the date of chordoma diagnosis to one of the following events: diagnosis of a second cancer, death, last-known follow-up, or end of study, whichever occurred first. SEER incidence rates were multiplied by the total number of person-years to estimate the expected number of cancer cases. The observed number of second cancers following chordoma was compared with the expected number of those cancers in the general population by applying age-, gender-, calendar year-, and region-specific population-based incidence rates to the appropriate person-years at risk [10].

Survival calculations

Survival is defined as the time from date of diagnosis to one of the following: date of death, loss to follow-up, or study cutoff date. Relative survival of a group is defined as the ratio of observed survival of the group to the expected survival based on the age- sex- and race-comparable mortality of the general population. For these analyses, observed and relative survival rates were calculated using the survival module of the public use database. Standard SEER exclusion criteria for the survival analyses included unknown race ($n = 3$); diagnosis of other cancer prior to diagnosis of chordoma ($n = 33$); and patients for whom survival information was not available ($n = 3$). The remaining 361 cases were used for survival analysis. Five-year, 10-year and median observed survival rates were calculated for all patients. Long-term observed and relative survival rates, with up to 20 years of follow-up, were calculated when the data permitted. There were insufficient numbers of nonwhite patients ($n = 31$) to allow meaningful racial subset analyses.

Statistical analysis

Age and year of diagnosis were divided into four equal groups (quartiles). The measures of association between site of presentation and age quartile, gender and race were analyzed through PROC FREQ of SAS (Version 6.12 of Windows), using Pearson's chi-square test. All variables with a probability of less than 0.05 to commit

Type I errors were regarded as significant. A further distinction was drawn at 0.01 and 0.001 to identify highly significant differences. All statistical tests were two-sided.

Ninety-five percent confidence intervals (CI) for the second cancer analysis were calculated based on the assumption that the numbers of second cancers observed followed a Poisson distribution.

Kaplan–Meier estimates were used to compare survival between different age groups, types of cancers, year of diagnosis quartiles and gender. This method is most suitable for small data sets with precisely measured event times. To test for differences in survivor functions, PROC LIFETEST of SAS was used to calculate the Wilcoxin test.

Results

Incidence and demographic data

Four hundred cases of microscopically confirmed chordoma were diagnosed among residents of nine SEER registry areas during the 22-year period between 1 January 1973 and 31 December 1995, yielding an overall incidence rate of 0.08 per 100,000 (Table 1); the gender-specific incidence rate was higher in males (0.10) than in

Table 1. Age-adjusted incidence rates and rate ratios for chordoma based on race and gender for the period 1973–1995

	n	%	Incidence ^a	Ratio of incidence rates ^b
Overall	400		0.08	n.a.
Race ^c				
White ^d	364	91.2	0.08	1.0
Black	9	2.2	0.02	0.2
Other ^e	26	6.5	0.07	0.9
Gender				
All races, male	238	59.5	0.10	1.0
All races, female	162	40.5	0.06	0.6
White males	214	58.8	0.10	1.0
White females	150	41.2	0.06	0.6

^a Incidence rates are expressed per 100,000 population and age-adjusted to the 1970 US standard.

^b The incidence rate in whites was used as the denominator for the calculation of ratios of incidence rates between races; the incidence rate in males served as the denominator for similar calculations between genders; n.a. = not applicable.

^c One case of unknown race was excluded.

^d White cases include 20 patients of Spanish surname or origin.

^e Other races include Chinese ($n = 6$), Japanese ($n = 6$), Filipino ($n = 6$), Hawaiian ($n = 4$), Native American ($n = 1$), other, not specified ($n = 2$) and unknown ($n = 1$).

females (0.06; risk ratio 0.6; $\chi^2 = 14.26$; $p = 0.0002$). Of the 399 cases of known race, 364 (91.2%) were white, 9 (2.2%) were black, and 26 (6.5%) were persons of other races/ethnicities. Among whites there were 20 patients with Hispanic surnames or origin. Chordoma was distinctly unusual in African-Americans; the incidence rate in whites was four times that in blacks but approximated the incidence rate in persons of other racial origin. Analysis of the distribution of cases by race and gender revealed that white males comprised 53.6% ($n = 214$), white females, 37.6% ($n = 150$), black males, 1.8% ($n = 7$), black females, 0.5% ($n = 2$), males of other races, 4.3% ($n = 17$) and females of other races, 2.2% ($n = 9$).

Among white males the estimated annual percent change in age-adjusted incidence was 3.80 (CI 0.9–6.8); among white females it was 4.10 (CI 0.5–7.8). There was no significant difference in the estimated annual percent change in age-adjusted incidence for the period after 1985, compared to the prior 10-year period (data not shown).

The median age at chordoma diagnosis was 58.5 years (range 3–95 years), and there was a generally progressive increase in incidence with age (Figure 1). Although chordoma was reported in all age groups it was especially uncommon at younger ages, with a cumulative incidence rate in persons less than age 40 years of 0.02 per 100,000, and distinctly rare in the first decade. Moreover, whereas 77 of 374 cases (20.5%) in whites occurred at ages younger than 40, seven of nine cases (78%) in blacks were diagnosed prior to age 40 years. Median age at diagnosis was 59 years (range 3–95 years) among whites and 27 years (range 11–71 years) in blacks. There was slight geographic variation, with relatively low rates (0.05) reported from the Atlanta and Detroit Metropolitan registries compared to the highest rate (0.10), reported from Iowa.

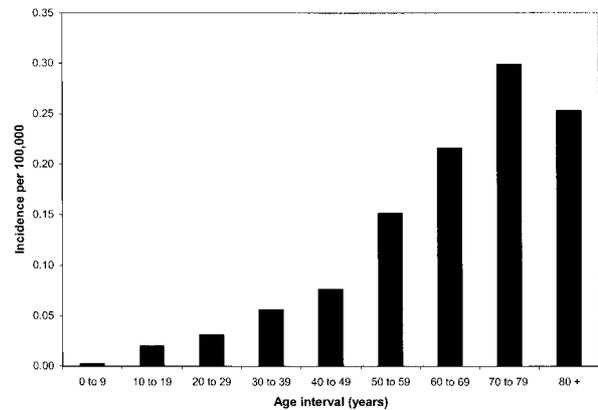


Fig. 1. Age-adjusted incidence of chordoma by decade during the period from 1973 through 1995. See 'Methods' section for a description of the incidence data of the Surveillance, Epidemiology, and End Results program. Incidence rates are reported per 100,000 population and age-adjusted to the US 1970 standard.

Characteristics of disease and treatment

As shown in Table 2, 128 cases (32.0%) of chordoma presented at cranial sites, 131 cases (32.8%) were spinal, and 117 cases (29.2%) were sacral; 24 cases (6.0%) presented at extra-axial or ill-defined sites. Site of presentation varied significantly by age and gender. The youngest age quartile was associated with a propensity toward cranial presentation (54.5%), whereas in the oldest patients sacral tumors were more common (41.3% vs. 15.2%, $p = 0.001$). One-quarter (25.8%) of cranial tumors presented prior to age 35, whereas only 7.7% of sacral tumors presented before age 35; the median age at cranial presentation was 49 years, nearly two decades earlier than median sacral presentation at 69 years. Female sex was associated with a greater likelihood of cranial presentation ($p = 0.037$; Table 2). Although cranial tumors (55.6%) exceeded

Table 2. Distribution of major anatomic sites of chordoma presentation by category of age quartile and gender, 1973 through 1995

Presenting site	All ages and genders		Age quartile (years)								Gender			
	n	%	3–25		26–48		49–71		72–95		Male		Female	
			n	%	n	%	n	%	n	%	n	%	n	%
Cranial	128	32.0	18	32.0	44	45.4	52	29.2	14	15.2	66	27.7	63	38.9
Spine	131	32.8	11	32.8	30	30.9	60	33.7	30	32.6	80	33.6	51	31.5
Sacrum	117	29.2	2	29.2	18	18.6	59	33.1	38	41.3	79	33.2	38	23.4
Other ^a	24	6.0	2	6.0	5	5.2	7	3.9	10	10.9	13	5.5	10	6.2
Total ^b	400	100.0	33	100.0	97	100.1	178	99.9	92	100.0	238	100.0	162	100.0

^a "Other" sites include extra-axial and ill-defined sites as described in the Methods section.

^b Because of rounding error, percentages may not total 100.0.

sacral lesions (22.2%) in blacks, the numbers were small, and the difference was not significant.

Data regarding initial treatment were available for 376 (94%) cases (Table 3). Of these, 365 (97%) received treatment, usually surgery alone (48.5%) or in combination with external-beam radiotherapy (37.8%). A small subset (13.7%) received only radiotherapy. Older patients were more likely than younger patients to be treated with radiotherapy. Likewise, sacral lesions were more likely than cranial tumors to be treated with radiotherapy alone (31.9 % and 11.0%, respectively). When treatment modality was analyzed as a function of year of diagnosis, surgery was consistently the mainstay of treatment; use of dual modality therapy did not increase with time.

Second primary cancers

The individual case records of all chordoma patients were examined for the occurrence of additional primary neoplasms. Fifty-two patients (13.0%) had a history of another primary cancer; in 10 of these patients (2.5%) there was a history of multiple (*i.e.* >2) primary cancers. Second primary cancers were defined as primary malignant neoplasms diagnosed at least

2 months after the diagnosis of chordoma. Of the 52 cases with at least two primary neoplasms, 13 were excluded because they lacked microscopic confirmation ($n = 5$), were diagnosed within 2 months of chordoma diagnosis ($n = 5$), were recorded solely on the basis of death certificate or autopsy information ($n = 2$), or had incomplete follow-up information ($n = 1$). In the remaining 39 cases, chordoma occurred as the first primary neoplasm in 20 cases; however, in one of these cases the second cancer was of unknown primary site and was not considered in the subsequent analysis.

Observed and expected numbers of second cancers among patients with chordoma are shown in Table 4. Overall there were 19 observed and 17.1 expected cancers (observed-to-expected ratio [O/E] = 1.11; CI 0.7–1.7). Significantly elevated risks were seen only for cancers of bone, but with only two cases, power to detect significant risk was low. Review of the individual case files revealed that the two observed bone cancers included one case each of chondrosarcoma and malignant fibrous histiocytoma. The chondrosarcoma occurred in the bones of the skull 73 months after the initial diagnosis of chordoma of the pituitary gland. The malignant fibrous histiocytoma was diagnosed in the spine 83 months after the initial diagnosis of

Table 3. Treatment modalities employed in the first 4 months following chordoma diagnosis according to categories of age quartile, presenting site and year of diagnosis quartile during the period 1973 through 1995

	n	Treatment unknown ^a		Treatment known ^b		No treatment		Surgery alone		Surgery and radiation		Radiation alone ^c	
		n	%	n	%	n	%	n	%	n	%	n	%
Age quartile (years)													
1 (3–25)	33	2	6.1	31	93.9	2	6.4	15	48.4	13	41.9	1	3.2
2 (26–48)	97	7	7.2	90	92.8	3	3.3	50	55.5	36	40.0	1	1.1
3 (49–71)	178	24	13.5	154	86.5	4	2.6	74	48.0	70	45.4	6	3.9
4 (72–95)	92	25	27.2	67	72.8	3	4.5	30	44.8	24	35.8	10	14.9
Total	400	58	14.5	342	85.5	12	3.5	169	49.4	143	41.8	18	5.3
Presenting site													
Cranial	128	16	12.5	112	87.5	2	1.8	58	51.8	50	44.6	2	1.8
Spine	131	13	9.9	118	90.1	3	2.5	52	44.1	56	47.4	7	5.9
Sacrum	117	26	22.2	91	77.8	5	5.5	48	52.7	30	33.0	8	8.8
Other	24	3	12.5	21	87.5	2	9.5	11	52.4	7	33.3	1	4.8
Total	400	58	14.5	342	85.5	12	3.5	169	49.4	143	41.8	18	5.3
Year of diagnosis quartile													
1 (1973–1978)	71	22	31.0	49	69.0	0	0.0	25	51.0	24	49.0	0	0.0
2 (1979–1984)	93	20	21.5	73	78.5	0	0.0	36	49.3	37	50.7	0	0.0
3 (1985–1990)	127	15	11.8	112	88.2	3	2.7	55	49.1	50	44.6	4	3.6
4 (1991–1995)	109	1	0.9	108	99.1	9	8.3	53	49.1	32	29.6	14	13.0

^a Treatment status is categorized as unknown if all details regarding either surgery or radiotherapy are not known.

^b For this analysis, patients were included within various treatment groups if the specific therapy had been given or if specific therapy was recommended but not given, or not known to be given. No patients were treated with chemotherapy in the first 4 months following diagnosis.

^c In every case of radiotherapy the radiation was coded as beam radiation; there was no distinction between conventional beam radiation and charged particle therapy.

Table 4. Observed and expected numbers of second cancers among patients with chordoma (person-years: 1476)

Site of tumor	No. observed	No. expected	Observed/ expected	CI	Clinical details				
					Sex	Age at chordoma diagnosis: (years)	Time to second cancer (months)	Type of second cancer: histology	Age at second cancer (years)
All second cancers	19	17.08	1.11	0.7–1.7					
Digestive system	6	3.91	1.54	0.6–3.3					
Esophagus	1	0.20	4.95	0.1–27.6	M	44	185	Adenocarcinoma	59
Stomach	1	0.44	2.29	0.0–12.7	M	45	65	Adenocarcinoma	51
Large intestine	2	1.74	1.15	0.1–4.2	M	81	29	Adenocarcinoma	84
					F	67	58	Adenocarcinoma	72
Liver	1	0.25	3.94	0.0–21.9	F	53	86	Hepatocellular carcinoma	60
Pancreas	1	0.46	2.19	0.0–12.2	M	65	80	Adenocarcinoma	71
Respiratory system	1	3.20	0.31	0.0–1.7					
Trachea, bronchus, lung	1	2.88	0.35	0.0–1.9	M	68	131	Squamous cell carcinoma	79
Female breast	1	1.39	0.72	0.0–4.0	F	52	101	Infiltrating duct carcinoma	61
Female genital tract	1	0.66	1.52	0.0–8.5					
Corpus uteri, uterus NOS	1	0.33	3.05	0.0–17.0	F	51	88	Adenocarcinoma	58
Prostate gland	3	3.40	0.88	0.2–2.6	M	66	2	Adenocarcinoma	66
					M	65	20	Adenocarcinoma	67
					M	81	35	Adenocarcinoma	84
Kidney, renal pelvis, ureter, other and unspecified urinary	1	0.42	2.38	0.0–13.2	F	87	7	Transitional cell carcinoma	88
Brain	1	0.19	5.30	0.1–29.5	F	52	4	Chordoma ^a	52
Bone	2	0.02	113.64	12.8–410.3	M	57	73	Chondrosarcoma ^b	63
					F	57	83	Malignant fibrous histiocytoma ^c	64
Lymphatic, hematopoietic system	2	1.25	1.60	0.2–5.8					
Multiple myeloma	1	0.21	4.67	0.1–26.0	M	68	37	Multiple myeloma	71
Leukemia	1	0.45	2.25	0.0–12.5					
CML	1	0.06	16.42	0.2–91.3	F	34	63	Chronic myeloid leukemia	39
Unknown primary site	1	n.a.	n.a.	n.a.	M	64	39	Squamous cell carcinoma	68

CI = 95% confidence interval; CML = chronic myelogenous leukemia. NOS = not otherwise specified.

^a The site of the first primary, chordoma, was the lateral wall of the nasopharynx; the site of the second chordoma was the brainstem.

^b The site of the first primary, chordoma, was the pituitary; the site of the second primary, chondrosarcoma, was the bones of the skull, face and associated joints, excluding the mandible.

^c The site of the first primary, chordoma, was the vertebral column, excluding the sacrum and coccyx; the site of the second primary, malignant fibrous histiocytoma, was the vertebral column, excluding the sacrum and coccyx.

chordoma in the spine. In addition, a second primary chordoma of the brainstem was diagnosed 4 months following the first diagnosis of chordoma in the lateral wall of the nasopharynx.

Survival

There were sufficient data available to analyze survival in 361 cases of first primary chordoma. The median survival for all races and genders was 6.29 years. Median survival was longer for females (7.25 years) than for males (5.93 years), but there was no significant difference in observed survival based on gender ($p = 0.32$). When cranial chordoma was considered alone, median survival for females (7.70 years)

again exceeded that of males (6.42 years), but the difference was not statistically significant ($p = 0.07$). The median observed survival in whites was 6.33 years. As expected, age was associated with risk of death ($\chi^2 = 42.13$; $p = 0.0001$). There were no significant differences in survival based on primary site at presentation ($p = 0.26$) although median survival was slightly lower in spinal chordomas (5.88 years) compared to cranial (6.94 years) and sacral (6.48 years) presentations.

Five-, 10-, and 15-year relative survival rates were also computed (Table 5). The overall 5- and 10-year relative survival rates were 67.6% and 39.9%, respectively; relative survival at 20 years was 13.1%. Although there were insufficient follow-up data to calculate 20-year

Table 5. Relative survival (percentages) of chordoma cases based on gender, race, anatomic site of presentation and age of diagnosis quartile in the US during the period 1973–1995

	5-year survival	10-year survival	15-year survival	20-year survival
All races, all genders	67.6	39.9	39.2	13.1
Males	65.1	38.0	34.5	13.0
Females	71.4	43.4	50.5	n.a.
Whites ^a	68.9	40.9	39.8	12.9
Site of presentation				
Cranial	64.7	46.6	48.4	n.a.
Spinal	67.2	37.8	30.6	0.0 ^b
Sacral	73.6	32.2	34.4	18.5
Age at diagnosis quartile (years)				
3–25	62.1	56.6	38.0	n.a.
26–48	44.1	62.1	60.3	48.7
49–71	69.2	31.4	30.9	0.0 ^c
72–95	50.7	18.4	19.0	0.0 ^b

n.a. = Not available, based on insufficient follow-up data.

^a Relative survivals are given only for whites because the small numbers of black cases (n = 9) precludes meaningful survival analysis in blacks.

^b 0.0 based on longest follow-up of 18 years.

^c 0.0 at 20 years of follow-up.

relative survival for all subsets, survival continued to decline beyond 15 years.

Comparison with other bone primary tumors

Because bone sarcomas comprise a diverse, though small, set of neoplasms, we were interested in comparing the various tumors within the group. All bone tumors were relatively uncommon; however, the incidence rates for chordoma were two- to four-fold lower than for Ewing's sarcoma, chondrosarcoma, and osteosarcoma (Table 6). Chondrosarcoma and malignant fibrous histiocytoma (MFH), like chordoma, tend to occur in older patients, whereas osteosarcoma and Ewing's sarcoma are predominantly diseases of youth. All bone tumors occurred more often in males than females, and all but osteosarcoma and MFH were more frequent in whites than blacks. Like chordoma, Ewing's sarcoma was particularly underrepresented in blacks, with a black:white rate ratio of 0.1. Chondrosarcoma is known to be a more indolent neoplasm; survival for patients with this disease was significantly longer than that for the other bone tumors ($p = 0.0001$). Median survival for chordoma was intermediate between that of chondrosarcoma (14.88 years) and osteosarcoma (4.36 years), Ewing's sarcoma (4.27 years), and MFH (2.31 years). Osteosarcoma, Ewing's sarcoma and MFH have shown steady

improvements in 5-year survival in nearly every 5-year period since 1973. Although chordoma has shown no consistent trend in 5-year survival rates over time, there was a significant increase in survival for those patients diagnosed during the 1985–1990 quartile (Figure 2; $\chi^2 = 9.98$; $p = 0.02$).

Discussion

Chordoma exhibited a strong age-related variability in incidence, with age-adjusted incidence rates peaking in the eighth decade. Conversely, it was distinctly rare in young patients, especially in the first decade of life. Equally striking was the rarity of chordoma in blacks. Our data indicate that chordoma is one-fourth as common in blacks compared to whites, confirming an earlier observation [8]; however, the reasons for this racial disparity are not clear. Black patients tended to be younger than white cases, but conclusions about race and age were limited by the small numbers of black patients.

The frequently reported anatomic distribution of chordoma, *i.e.* sacral ~50%, spheno-occipital ~35%, spinal ~15%, was based primarily on 262 patients from the Mayo Clinic experience [11, 12]; similar distributions have been reported in smaller registry series [3–5]. Site distributions, however, appear variable and dependent upon the expertise of the reporting institutions [3, 13–18]. Our results showed relatively even distribution between cranial, spinal and sacral sites. These distribution differences may be attributable to the population-based nature and larger size of our study, which is less likely to reflect regional and/or tertiary practice and referral patterns inherent in smaller single-institution case series. Earlier series noted an association between gender or age and site of presentation [11]. This study confirmed a statistically significant association between sacral presentation and male gender, whereas female sex was associated with cranial presentation. The association between site and age is consistent with the expectation that a given tumor volume is more likely to cause symptoms in an intracranial location relative to a sacral origin, and would thus be diagnosed earlier. However, this observation does not completely explain the discrepancies between site distribution at various ages. Cranial presentation was also the most common primary site in blacks, but there were too few cases to assess this association. The relatively young age at diagnosis of blacks, rather than race, may account for the preponderance of cranial tumors.

Chordoma remains largely a surgical disease, despite advances in radiotherapy techniques, including charged-

Table 6. Incidence rates (based on race, gender and period of diagnosis), median age at diagnosis, and survival rates for microscopically confirmed primary bone tumors diagnosed in the US from 1973 through 1995

	Chordoma	Chondrosarcoma	Osteosarcoma	Ewing's sarcoma	MFH of bone
Total number of cases	400	1310	1569	695	127
Incidence ^a					
Overall	0.08	0.24	0.33	0.16	0.02
White	0.08	0.26	0.32	0.18	0.02
Black	0.02	0.15	0.36	0.02	0.02
Rate ratio, whites:blacks ^b	4.0	1.7	0.9	9.0	1.0
Male	0.10	0.32	0.37	0.19	0.03
Female	0.06	0.20	0.29	0.12	0.02
Incidence trends over time					
1973–1978	0.06	0.23	0.30	0.13	0.01
1979–1984	0.07	0.23	0.33	0.17	0.03
1985–1990	0.09	0.22	0.34	0.15	0.03
1991–1995	0.08	0.29	0.36	0.18	0.02
Median age at diagnosis (years)	58.5	51	22	16	56
Median survival (years)	6.29	14.88	4.36	4.27	2.31
5-year relative survival trends over time (%)					
1973–1978	61.2	71.7	41.9	38.2	23.9
1979–1984	57.9	70.2	47.3	45.2	34.2
1985–1990	78.4	77.6	56.5	52.6	45.7
1991–1995	50.4	82.8	57.6	63.6	63.2

MFH = malignant fibrous histiocytoma.

^a Incidence rates are expressed per 100,000 population and age-adjusted to the 1970 US standard.

^b The incidence rate in blacks was used as the denominator for calculation of incidence rate ratios between whites and blacks.

particle (proton beam) radiotherapy for cranial disease, which is available predominantly on an investigational basis [19]. SEER treatment coding does not differentiate between standard fractionated radiation and other modalities, so we cannot determine whether patients received an alternative form of radiotherapy. The use of radiotherapy as a single modality was highest in the oldest age quartile and in patients with sacral primaries, an observation complicated by the finding that sacral lesions were more likely to be diagnosed in older patients. Elderly patients are more likely to have comorbid conditions that preclude curative surgical intervention, and those with sacral tumors may present with more extensive or metastatic disease, resulting in less aggressive palliative therapy.

There was no observed overall excess of second primary cancers in this series, but there were specific second neoplasms of interest. One case had a second primary cranial chordoma diagnosed in the brainstem 4 months after the first chordoma was diagnosed in the lateral wall of the nasopharynx. Assuming diagnostic accuracy, the second tumor may have been a metachronous primary or intracranial metastasis, rather than a local recurrence. However, intracranial chordoma metastasis is an extremely rare event, and

all reported cases but one have had additional systemic metastases [20]. There were also two reported second primaries of bone. A chondrosarcoma arose in the skull 73 months following a pituitary chordoma. Since, prior to refinement of immunohistochemical criteria, chondrosarcoma was one of the chief entities in the differential diagnosis of chordoma [21], these tumors could have been misclassified, and the second may represent clival recurrence of either chordoma or chondrosarcoma. Finally, a malignant fibrous histiocytoma (MFH) arose in the vertebral column 83 months following a surgically treated spinal chordoma. Rarely, high-grade sarcomatous lesions have been reported to coexist with conventional chordoma [22]. The pathogenesis of these lesions is not established, but may represent either a transformation from chordoma to sarcoma due to a dedifferentiation process [22–25] or radiation-induced transformation [26–29]. Because the initial chordoma was not irradiated, the subsequent MFH was not likely treatment-related. Thus, the MFH in this study most likely represents either a distinct second primary cancer or sarcomatous transformation of recurrent chordoma.

Long-term survival for chordoma is limited; the 5-year relative survival rate of 67.6% dropped to

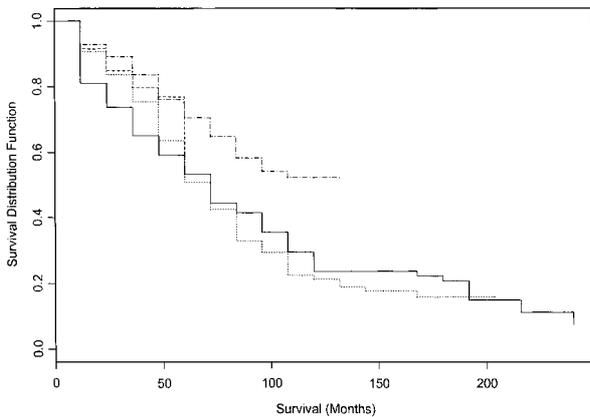


Fig. 2. Survival distribution estimates stratified by year of diagnosis quartile. Survivals were evaluated using the Kaplan–Meier method (Wilcoxin test). Solid line (—) = 1973–1978, $n = 71$; dotted line (·····) = 1979–1984, $n = 93$; dot-dash (– · – · –) = 1985–1990, $n = 127$; dashed line (– – – –) = 1991–1995, $n = 109$. Survival in the third year of diagnosis quartile (1985–1990) was significantly better than other groups ($p = 0.0015$). Because the period was divided into quartiles by whole years, the fourth quartile encompasses a 5-year, rather than a 6-year interval. For the 94 patients diagnosed during 1991 through 1995 there were only 16 deaths during the follow-up period that ended with the 31 December 1995 study cutoff date, whereas nearly 80% had insufficient follow-up data available for a meaningful survival analysis for this group.

13.1% at 20 years. Survival may be improving over time, however, as there was a significant improvement in survival for patients diagnosed from 1985 to 1990 relative to cases diagnosed earlier. Longer follow-up will be required to determine whether the improvement in survival is sustained.

A few reports suggest that chordoma may have a worse prognosis in very young patients, *i.e.* less than 20 years [30–34], because of greater histologic variability with heightened histologic aggressiveness [34, 35]. Survival in the first quartile (33 patients aged ≤ 25 years) was no different from that of the second or third quartile. However, because there were few cases in the very youngest subsets, the statistical power was insufficient to draw definitive conclusions.

Female sex has been suggested to be a poor prognostic feature, particularly for cranial chordoma, in some studies [36–39], although other series have not found a significant association [40–43]. Our study revealed no difference in survival based on gender or site of presentation. Clearly more research is required to resolve this question. No other population-based survey has considered the effect of gender; however, two found no relationship between anatomic site and survival [4, 5], consistent with our results.

Chordomas comprise 2–4% of bone tumors [44] and are seldom considered separately in large reviews of

bone cancers. Our comparison of chordoma to other bone primaries reveals a diverse and heterogeneous group of diseases that share some common themes. Most bone primaries demonstrate a strong age-specific predilection, though peak age of onset differs among different pathologic entities [8, 44]. Small increases in incidence over time may reflect growing use of improved diagnostic and imaging modalities [45–48] rather than true biologic changes in disease patterns. All bone tumors are somewhat more common in males than females. Chordoma and Ewing's sarcoma (ES) are exceptionally rare among blacks, whereas other histologies have a more equal racial distribution. Overall relative 5-year survival has improved steadily in nearly all cases, largely attributable to advances in surgical and radiation techniques.

In the past, chondrosarcoma has frequently been misdiagnosed as chordoma, particularly in cranial sites [37]. Some cases in the present series may be misclassified chondrosarcomas, as illustrated by the reported second primary chondrosarcoma discussed earlier. On inspection, however, there is no convincing reciprocal change in incidence patterns over time for the two tumors, as might be expected if improved immunohistochemical techniques [49–51] were leading to a change in diagnostic accuracy. Also, whereas survivals for the two neoplasms are clearly distinct, there is no difference in survival for cranial chordoma compared to other chordoma sites. Thus, we believe that although misclassification is a legitimate issue, it does not appear to have a serious impact in this series.

The similar racial incidence patterns of chordoma and ES raise some intriguing questions. Chordoma is believed to arise from vestigial notochordal remnants or ectopic notochordal tissue, whereas ES is thought to be of neural origin related to, but less differentiated than, peripheral primitive neuroectodermal tumors. A characteristic translocation resulting in a fusion gene is thought to contribute to ES pathogenesis. No consistent nonrandom cytogenetic changes have been reported for chordoma, although various abnormalities of chromosome 1p have been described in about one-third of cases [52–59]. Unlike ES, which has not been convincingly described among multiple relatives, there are rare reports of familial chordoma [59–63]. Detailed studies of such families may help elucidate the molecular mechanisms underlying the pathogenesis of chordoma.

The small numbers of cases in certain demographic subsets in this study limited the statistical power of some analyses. In addition, SEER registry coding practices limit the nature and quantity of some kinds of clinical information available for study; however, as SEER

continues to accrue cases, larger numbers will be available in the future to address the questions raised by this survey. Despite these limitations this survey provides new, population-based data regarding the incidence, treatment and survival patterns of chordoma in the US in the largest series of cases in the literature to date. Future epidemiologic studies will continue to elucidate the genetic and environmental determinants underlying this rare, distinctive neoplasm.

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