Original Article

Twenty Years of Follow-Up of Survivors of Childhood Osteosarcoma

A Report From the Childhood Cancer Survivor Study

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BACKGROUND: Osteosarcoma survivors have received significant chemotherapy and have undergone substantial surgeries. Their very long-term outcomes (20 year) are reported here. **METHODS:** The authors assessed the long-term outcomes of 733 5-year survivors of childhood osteosarcoma diagnosed from 1970 to 1986 to provide a comprehensive evaluation of medical and psychosocial outcomes for survivors enrolled in the Childhood Cancer Survivor Study (CCSS). Outcomes evaluated included overall survival, second malignant neoplasms (SMNs), recurrent osteosarcoma, chronic health conditions, health status (general and mental health and functional limitations), and psychosocial factors. Outcomes of osteosarcoma survivors were compared with general-population statistics, other CCSS survivors, and CCSS siblings. **RESULTS:** Survivors had a mean follow-up of 21.6 years. The overall survival of children diagnosed with osteosarcoma who survived 5 years at 20 years from original diagnosis was 88.6% (95% confidence interval [CI], 86.6%-90.5%). The cumulative incidence of SMNs at 25 years was 5.4%, with a standardized incidence ratio of 4.79 (95% CI, 3.54-6.33; $P<.01$). Overall, 86.9% of osteosarcoma survivors experienced at least 1 chronic medical condition, and >50% experienced ≥2 conditions. Compared with survivors of other cancers, osteosarcoma survivors did not differ in their reported general health status (odds ratio [OR], 0.9; 95% CI, 0.7-1.2), but were more likely to report an adverse health status in at least 1 domain (OR, 1.9; 95% CI, 1.6-2.2), with activity limitations (29.1%) being the most common. **CONCLUSIONS:** Childhood osteosarcoma survivors in this cohort did relatively well, considering their extensive treatment, but are at risk of experiencing chronic medical conditions and adverse health status. Survivors warrant life-long follow-up. ***Cancer*** **2011;117:625–34.** © *2010 American Cancer Society.*

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There are approximately 400 individuals younger than 20 years diagnosed with osteosarcoma each year in the United States.[1] The treatment for patients with osteosarcoma includes the use of multiagent chemotherapy and complete surgical resection. The type of surgical intervention depends on the site, age of the patient, extent of disease, and expertise/preference of the orthopedic surgeon. The 5-year overall survival rates approach 70%.[2,3] However, outcomes have been associated with disease- and treatment-related sequelae,[4] which can have a negative impact on patients' quality of life and need for continued access to healthcare services.[5]

Given that childhood cancer is relatively rare, and young adult survivors do not always return to their treatment center for long-term follow-up, a single institution will not have sufficient numbers of patients to draw firm conclusions about long-term outcomes. The Childhood Cancer Survivor Study (CCSS),[6] a multi-institutional study of individuals surviving ≥5 years after treatment for childhood cancer, provides a unique opportunity to assess the outcomes of long-term survivors of pediatric osteosarcoma. This report provides a comprehensive evaluation of survival, medical and psychosocial outcomes, and health status.

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MATERIALS AND METHODS

Study Design and Participants

The study design and cohort characteristics of CCSS have been previously described in detail.[6] The 26 CCSS collaborating institutions initially identified 20,631 eligible 5-year cancer survivors diagnosed at an age of <21 years between 1970 and 1986; 14,357 (69.6%) were successfully located and completed a baseline survey during 1995 to 1996. Additional follow-up surveys were conducted in 2000 and 2003. Copies of surveys are available from www.stjude.org/ccss. Informed consent was obtained from all participants.

A total of 733 (68.1%) of 1077 eligible osteosarcoma survivors completed the baseline questionnaire. Nonparticipants included survivors who refused (n = 194), were lost-to-follow-up (n = 148), or were non-English speakers (n = 2). Overall in the CCSS, participants, refusers, and subjects lost to follow-up were found similar with regard to the distributions of sex, age at diagnosis, age at the entry to CCSS, diagnosis type, and type of cancer treatment.[6,7]

To compare survivors with cancer-free individuals, a random sample of siblings of the CCSS survivors were selected and asked to complete the CCSS questionnaires. There were 3899 (81.4% of eligible) siblings who completed the baseline questionnaire, 2540 siblings and 552 survivors who completed the 2000 follow-up survey, and 2875 siblings and 488 survivors who completed the 2003 follow-up survey. All of the outcomes used all available data from the 3 surveys except for chronic health conditions and adverse health status, which was available only from the baseline questionnaire.

The US National Death Index (NDI) was used to ascertain the vital status of all 1068 eligible osteosarcoma survivors as of December 31, 2002, with causes of death being identified through death certificates (causes of 9 Canadians' deaths could not be ascertained).[8]

Treatment Data

Treatment information including tumor location was collected from the treating institution. Data regarding exposure to 42 chemotherapeutic agents (yes/no) were abstracted from the medical record, with cumulative doses abstracted for 22 specific agents.[6] Cancer-related surgical procedures and fields/doses of radiation therapy were also collected. As described previously,[9] for alkylating agent, the total dose received per body surface area (mg/m^2) was summed for each agent received, and the overall distribution of the nonzero doses among all participants was divided into tertiles. Among patients exposed to an alkylating agent, the dose score was calculated by adding the tertile score (1, 2, or 3) for each of the alkylating agents given to a particular patient. A score of 0 was assigned to nonexposed patients. The total anthracycline dose and platinum agent dose were scored and grouped into tertiles by total dose levels.[10,11]

Second Malignant Neoplasm/Recurrence Assessment

Second malignant neoplasms (SMNs) and recurrences (local or distant) were ascertained initially through self-report via the questionnaires. Cohort members were asked to report occurrences of any cancer (either relapse or new cancer) since the diagnosis of original cancer. The pathology reports of positive responses were obtained and SMNs validated by the CCSS pathologist.[9] Nonmelanoma skin cancers, nonmalignant meningiomas, and other nonmalignant central nervous system tumors were excluded from the SMN analysis. SMNs were coded by histology using the International Classification Diseases for Oncology.[12] Diagnostic groupings of SMNs were constructed after the International Classification of Childhood Cancer.[13]

Chronic Medical Conditions

Chronic medical conditions were assessed for participants of age ≥18 years using the Common Terminology Criteria for Adverse Events.[14] As described earlier,[15] grades 1 to 4 of chronic medical conditions represent, respectively, mild, moderate, severe, and life-threatening or disabling.

Hearing and cardiovascular outcomes were individually evaluated for incidence and associations with risk factors.

Health Status

Six domains of health status (general health, mental health, functional status, activity limitations, pain as a result of the cancer or its treatment, and anxiety as a result of the cancer or its treatment) were assessed among survivors who were alive when they completed the baseline questionnaire using the same method as an earlier report.[16] Brief Symptom Inventory (18 items)[17,18] was used to assess mental health. Functional status and activity status were classified based on answers to questions adapted from the National Health Interview Survey and the Behavioral Risk Factor Surveillance System Survey Questionnaire.[19,20] To compare osteosarcoma survivors

to the other CCSS survivors, Ewing sarcoma survivors were excluded, because their treatment similarity may have lessened any noted differences. No comparison for osteosarcoma survivors versus siblings was made for pain and anxiety, because the questions on cancer-related pain and anxiety were not asked of siblings.

Psychosocial Status

Psychosocial outcomes were compared among living osteosarcoma survivors and CCSS siblings of age ≥25 years (time at which one generally completes schooling and transition to independence from parents) at the time of the most recent survey. This included marital status, education, employment, and health insurance.

Statistical Analysis

Descriptive statistics for demographic variables and treatment exposures (radiotherapy, chemotherapy, surgery including amputation) were tabulated for the 733 osteosarcoma survivors and the 3899 siblings who participated in the CCSS study.

Standardized mortality ratios (SMRs) for all cause and cause-specific deaths of 1068 eligible osteosarcoma survivors, stratified by sex, were calculated using age-, sex-, and calendar year-specific US mortality rates.[21] The person time at risk for death was taken as the time from the cohort entry (5 years from cancer diagnosis) to the earlier of death or the follow-up end date of December 31, 2002 (NDI cutoff date). The Kaplan-Meier method[22] was used to estimate survival curve after study entry, and compared with a hypothetical survival curve that assumed the age-, sex-, and calendar year-matched US population mortality rates for the osteosarcoma survivors. To identify factors associated with mortality risk in the 733 osteosarcoma survivors, a multivariate Poisson regression model was used with a prespecified set of potential risk factors.

The cumulative incidence of SMNs and that of recurrence of original cancer were calculated separately, taking death as a competing risk event. Vital status of the survivors was described in relation to early (within 5 years since osteosarcoma diagnosis) and late (after 5 years after diagnosis) recurrence. SMNs were enumerated by type initially, followed by Poisson regression analysis of standardized incidence ratios (SIRs) for developing SMNs, using sex, age at diagnosis, time since diagnosis, and radiation exposures as explanatory variables. The person time at risk for SMN was taken as the time from the cohort entry to the earliest of SMN development, date of death, and the most recent questionnaire completion date. Age-, sex-, calendar year-specific cancer incidence rates from the National Cancer Institute's Surveillance, Epidemiology, and End Results registry[23] were used as reference rates in the SIR calculation.

Numbers and percentages of osteosarcoma survivors, CCSS siblings, and other CCSS survivors for chronic medical conditions, health status, and psychosocial outcomes were reported. Multivariate log-binomial regression for relative risks and logistic regression for odds ratios (ORs), adjusting for age, sex, and amputation were used for comparisons of these outcomes in the osteosarcoma survivors with the CCSS siblings and other CCSS survivors.

Prevalence of tinnitus and/or vertigo, and that of deafness and/or use of hearing aid were tabulated and assessed by multivariate logistic regression. Incidence of cardiovascular outcomes was evaluated using multivariate Poisson regression. Each of these analyses of specific chronic conditions was performed with respect to a set of prespecified risk factors.

For the osteosarcoma survivors, psychosocial outcomes were tabulated and compared with the CCSS siblings, using polytomous logistic regression, adjusting for age and sex, while taking into account the potential within-family correlation between survivors and siblings using nonparametric bootstrap of families.[24]

All statistical analyses were conducted with SAS version 9.1.3, using 2-sided inference including standard asymptotic 95% confidence intervals (CIs) associated with each regression analysis.

RESULTS

Demographics

Table 1 lists the characteristics of the osteosarcoma survivor study population and CCSS sibling cohort. The 733 osteosarcoma survivors had a mean age at diagnosis of 13.7 years (range, 2-20 years), mean age at last contact of 35.3 years (range, 13-51 years), and mean length of follow-up of 21.6 years (range, 5.1-33.8 years). At last contact, the sibling cohort was younger than the cases, with an average age of 31.3 years (range, 3-58 years).

Survival

Among ≥5-year survivors of osteosarcoma, subsequent survival at 10, 15, and 20 years since diagnosis was 93.5% (95% CI, 92.1%-95.0%), 90.4% (95% CI, 88.7%-92.2%), and 88.6% (95% CI, 86.6%-90.5%), respectively. Figure 1 compares the observed overall survival of

Table 1. Demographic, Cancer/Treatment, and Vital Status of Osteosarcoma Survivors and CCSS Siblings

Characteristic	Osteosarcoma, n=733		Siblings, n=3899		*P*
	No.	%	No.	%	
Sex (baseline)					
Male	380	51.8	1878	48.2	.07
Female	353	48.2	2021	51.8	
Year of diagnosis (treatment era)					
1970-1974	110	15.0	NA	NA	—
1975-1979	250	34.1	NA	NA	
1980-1984	268	36.6	NA	NA	
1985-1986	105	14.3	NA	NA	
Age at diagnosis, y					
<4	12	1.6	NA	NA	—
5-9	88	12.0	NA	NA	
10-14	295	40.3	NA	NA	
≥15	338	46.1	NA	NA	
Cancer site (baseline)					
Upper extremity	73	10.0	NA	NA	—
Lower extremity, pelvis	587	80.0	NA	NA	
Head, trunk, other	73	10.0	NA	NA	
Treatment					
Surgery only	62	8.5	NA	NA	—
Chemotherapy and surgery	493	67.3	NA	NA	
Surgery and radiation	8	1.1	NA	NA	
Chemotherapy, surgery, and radiation	74	10.1	NA	NA	
Missing	94	12.8	NA	NA	
Anthracycline score					
1-209 mg/m^2	50	6.8	NA	NA	—
210-358 mg/m^2	138	18.8	NA	NA	
≥359 mg/m^2	289	39.4	NA	NA	
No dose	98	13.4	NA	NA	
Unknown dose	158	21.6	NA	NA	
Alkylator score					
Score 1	261	35.6	NA	NA	—
Score 2	43	5.9	NA	NA	
Score 3	21	2.9	NA	NA	
No dose	265	36.2	NA	NA	
Unknown dose	143	19.5	NA	NA	
Platinum score					
1-362 mg/m^2	41	5.6	NA	NA	—
363-489 mg/m^2	73	10.0	NA	NA	
≥490 mg/m^2	108	14.7	NA	NA	
No dose	383	52.3	NA	NA	
Unknown dose	128	17.5	NA	NA	
Amputation					
Yes	531	72.4	18	0.5	<.001
No	187	25.5	3875	99.4	
Unknown	15	2.1	6	0.2	
Survival status					
Dead	80	10.9	NA	NA	—
Alive	653	89.1	NA	NA	

CCSS indicates Childhood Cancer Survivor Study; NA, not available.

the osteosarcoma survivor cohort with overall survival for the age- and sex-adjusted US population. There were sex differences in overall survival ($P = .04$), with an advantage for females at 10 years (94.9% vs 92.4%), 15 years (92.3% vs 88.9%), and 20 years (90.0% vs 87.3%).

Of the 1068 eligible survivors, 138 (12.9%) died after entry into the cohort (Table 2). Seventy-five of those deaths were because of recurrent or persistent osteosarcoma. The overall SMR was 5.85 (95% CI, 4.91-6.91), with females having a higher SMR at 8.40 compared with males at 4.92; the higher SMR in females was because of the lower mortality rates of females, relative to males, in the US population. Significant SMR (Table 2) elevations are seen with SMN and cardiac etiologies. Risk factors for mortality, determined in regression models (data not shown) included exposure to cisplatin, radiation therapy, and the development of a second malignancy or recurrent disease.

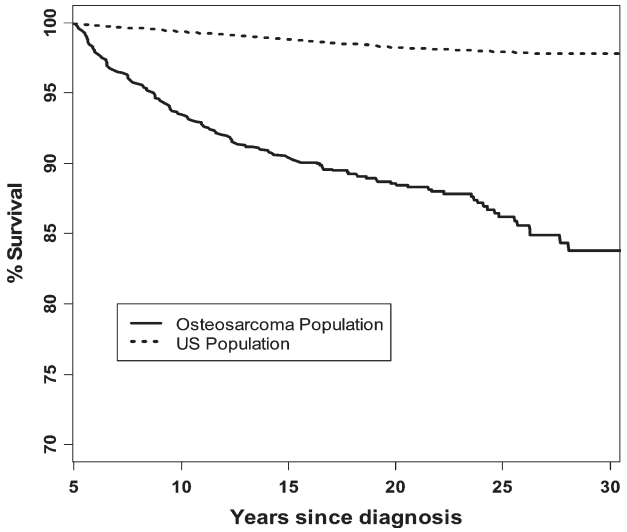

Figure 1. The survival curve of Childhood Cancer Survivor Study osteosarcoma survivors versus US population is shown.

Recurrences

Only 24 first recurrences (local and distant) occurred after 5 years from diagnosis. The cumulative incidence of recurrences at 5, 10, 15, 20, and 25 years were 24.5%, 27.2%, 27.6%, 28.0%, and 28.1%, respectively (Fig. 2). In contrast to the SMNs, whose rates continued to increase across time, the majority of recurrences occurred within 10 years after diagnosis (Fig. 2).

SMNs

There were a total of 49 SMNs (Table 3) (in 37 survivors) among the 733 osteosarcoma survivors who participated; 61.2% occurred among female survivors. The most common SMNs was female breast cancer. The majority (85.7%) of SMNs occurred >10 years from diagnosis (Fig. 2), and the SIRs were significantly elevated (Table 3) regardless of sex. The cumulative incidence of SMNs at 25 years from OS diagnosis was 5.4% (males 4.1%, females 7.1%) (Fig. 2). The SIRs were elevated for female breast cancer, thyroid cancer, and gastrointestinal cancer (Table 3). Multivariate Poisson regression analysis did not identify any particular demographic- or treatment-related risk factors for developing an SMN. Eight of the 37 patients who were diagnosed with an SMN after entry into the cohort subsequently died.

Health Conditions

The prevalence of tinnitus/vertigo and deafness/hearing aid requirement at the baseline survey in this group of osteosarcoma survivors was 14.7% and 7.0%, respectively.

Table 2. All-Cause and Cause-Specific SMRs for Osteosarcoma Survivors[a]

Death Categories	All			Male			Female		
	Deaths	SMR	95% CI	Death	SMR	95% CI	Deaths	SMR	95% CI
All deaths	138	5.85	4.91-6.91[b]	85	4.92	3.93-6.08[b]	53	8.40	6.29-10.99[b]
SMN	20	8.05	4.92-12.44[b]	7	5.38	2.16-11.09[b]	13	10.99	5.84-18.79[b]
Cardiac	7	3.91	1.56-8.05[b]	4	3.12	0.84-7.98	3	5.89	1.18-17.20[c]
Pulmonary	2	3.58	0.40-12.94	1	3.03	0.04-16.83	1	4.40	0.06-24.46
External	14	1.13	0.62-1.90	13	1.31	0.70-2.24	1	0.41	0.01-2.27
Other	11	1.72	0.86-3.07	6	1.34	0.49-2.92	5	2.58	0.83-6.03
Unknown (DCO)	9	—	—	5	—	—	4	—	—

SMR indicates standardized mortality ratio; CI, confidence interval; DCO, death certificate only; CCSS, Childhood Cancer Survivor Study.
There are an additional 75 deaths due to recurrent or persistent osteosarcoma. The SMN deaths include 12 survivors who developed an SMN within 5 years of their osteosarcoma diagnosis, survived for ≥5 years from the osteosarcoma diagnosis (thus entered the CCSS cohort), and subsequently died.
[a] All eligible osteosarcoma survivors in the CCSS.
[b] $p<0.01$, [c] $0.01 \leq p < 0.05$.

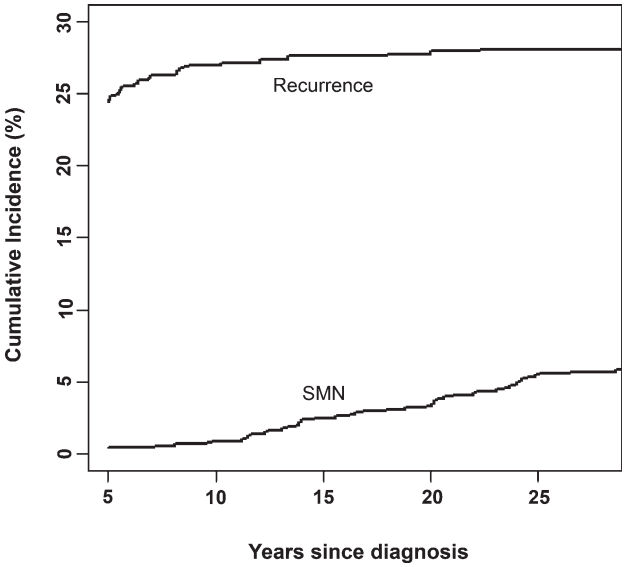

Figure 2. Cumulative incidence curves of second malignant neoplasm (SMN) and recurrence are shown.

The prevalence of these complications increased with increasing doses of platinum for both tinnitus and deafness: no platinum (7.8%, 3.7%), platinum dose 1 to 362 mg/m^2 (14.6%, 9.8%), platinum dose 363 to 489 mg/m^2 (23.3%, 8.2%), and platinum dose >490 mg/m^2 (29.6%, 15.7%). After adjusting for sex, age at diagnosis, and platinum dose, females were more likely to have deafness or need hearing aids ($P = .03$), or to report tinnitus or vertigo ($P = .07$) than were males. Survivors diagnosed with osteosarcoma at early age (0-9 years) were less likely to report tinnitus or vertigo compared with those who were older (≥15 years) at diagnosis (OR, 0.42; 95% CI, 0.19-0.93; $P = .03$).

Eleven (1.5%) of the 733 osteosarcoma survivors reported having coronary heart disease >5 years from diagnosis. The prevalence of coronary heart disease was similar across all time frames from the time of diagnosis. After adjusting for sex, current age, time since diagnosis, and anthracycline cumulative exposure, no significant predictors were identified. Nineteen survivors reported having congestive heart failure >5 years from diagnosis. Survivors' sex, age at diagnosis, time since diagnosis, and anthracycline were not predictive of this complication, although more events occurred in patients who were exposed to higher doses of anthracyclines.

Chronic Medical Conditions

Eighty-seven percent of osteosarcoma survivors reported at least 1 chronic medical condition. Greater than 50% experienced ≥2 chronic medical conditions, and 76.1% experienced grade 3 or 4 conditions. When compared with siblings, osteosarcoma survivors were more likely to have any grade, multiple grades (≥2), and high grades (3 or 4) of chronic medical conditions. Relative to other childhood cancer survivors, osteosarcoma survivors were more likely to have higher grade conditions (risk ratio, 1.4; 95% CI, 1.2-1.6; $P<.001$), even after adjusting for amputation status, sex, and age. No difference in the prevalence of chronic medical conditions was seen between the osteosarcoma survivors and survivors of other childhood cancers (Table 4).

Table 3. SIRs of SMNs

SMN	No. (%)	SIR	95% CI
Any cancer site	49	4.79	(3.54-6.33)[a]
Male	19 (38.8)	4.25	(2.56-6.63)[a]
Female	30 (61.2)	5.21	(3.51-7.43)[a]
Breast	16 (32.7)	9.73	(5.56-15.80)[a]
Skin	8 (16.3)	4.84	(2.09-9.55)[a]
GI	6 (12.2)	5.84	(2.13-12.70)[a]
Thyroid	6 (12.2)	7.03	(2.57-15.30)[a]
STS/bone	4 (8.2)	13.72	(3.69-35.12)[a]

SIR indicates standardized incidence ratio; CI, confidence interval; GI, gastrointestinal; STS, soft tissue sarcoma.
[a] $P<01$.Nine other SMNs include 2 brain, 2 lung, 2 leukemias, 1 cervical, 1 kidney, and 1 lymphoma.

Health Status

More than half of the osteosarcoma survivors aged ≥18 years reported having had some adverse heath outcome, compared with 1/3 of other survivors and 17.7% of siblings. Approximately 10.3% of osteosarcoma survivors reported having adverse general health, 15.8% reported adverse mental health, and 15.6% impaired functional status. In addition, among the osteosarcoma survivors, 29.1% reported a physical limitation, and 22.1% reported having pain from their osteosarcoma and its treatment; 12.2% reported still having anxiety/fear as a result of their diagnosis and treatment. When compared with siblings, osteosarcoma survivors were more likely to have impaired health status across all measures. But when osteosarcoma survivors are compared with other survivors of childhood cancer, osteosarcoma survivors were only more likely to experience functional limitations, activity limitations, and pain (Table 4).

Psychosocial Outcomes

Overall, 25.4% of survivors reported having never been married compared, with 20.3% of siblings; 7.2% of survivors did not graduate from high school, whereas 2.7% of

Table 4. Chronic Health Conditions, Adverse Health Status, and Socioeconomic Outcomes of Osteosarcoma Survivors Compared to Other Survivors and CCSS Siblings

Outcomes	Osteosarcoma Survivors, No. (%)	Other Survivors, No. (%)	CCSS Siblings, No. (%)	Osteosarcoma Survivors vs Siblings		Osteosarcoma Survivors vs Other Survivors	
Chronic health conditions[a,b]				**RR (95% CI)**	***P***	**RR (95% CI)**	***P***
Any grade 1-4	622 (86.9)	5646 (60.6)	1164 (37.8)	1.8 (1.7-2.0)	<.001	1.0 (0.99-1.07)	.18
Grade 3 or 4	545 (76.1)	2218 (23.8)	179 (5.8)	6.5 (5.3-8.0)	<.001	1.4 (1.2-1.6)	<.001
≥2 in grades 1-4	366 (51.1)	3412 (36.6)	433 (14.0)	3.0 (2.4-3.6)	<.001	1.1 (0.9-1.2)	.25
Adverse health status[a,c]				**OR (95% CI)**		**OR (95% CI)**	
Any domain	386 (53.9)	3523 (37.8)	547 (17.7)[d]	3.6 (3.0-4.3)[e]	<.001	1.9 (1.6-2.2)	<.001
General health	74 (10.3)	941 (10.1)	157 (5.1)	2.3 (1.7-3.1)	<.001	0.9 (0.7-1.2)	.53
Mental health	113 (15.8)	1392 (14.9)	302 (9.8)	1.9 (1.5-2.4)	<.001	1.0 (0.8-1.3)	.89
Functional status	112 (15.6)	1002 (10.8)	79 (2.3)	7.9 (5.9-10.8)	<.001	1.5 (1.2-1.9)	<.001
Activity limitation	208 (29.1)	1122 (12.0)	178 (5.8)	7.2 (5.8-9.1)	<.001	2.9 (2.4-3.5)	<.001
Pain	158 (22.1)	727 (7.8)	—[d]	—	—	3.2 (2.6-3.9)	<.001
Anxiety	87 (12.2)	1075 (11.5)	—[d]	—	—	1.0 (0.8-1.3)	.9
Psychosocial outcomes[f]				**OR (95% CI)**		**OR (95% CI)**	
Marital status							
Never married (single)	168 (25.4)	—	576 (20.3)	1.9 (1.5-2.3)	<.001	—	—
No longer married	80 (12.1)	—	315 (11.1)	1.2 (0.9-1.6)	.23	—	—
Married (or living as married)	413 (62.5)	—	1948 (68.6)	1.0	—	—	—
Education							
Not high school graduate	48 (7.2)	—	78 (2.7)	3.0 (2.0-4.4)	<.001	—	—
High school graduate	307 (46.0)	—	1275 (45.0)	1.2 (1.0-1.4)	.06	—	—
College graduate	312 (46.8)	—	1483 (52.3)	1.0	—	—	—
Employment							
Unemployed	21 (3.1)	—	6 (0.2)	17.2 (7.7-62.8)	<.001	—	—
Employed	651 (96.9)	—	2843 (99.8)	1.0	—	—	—
Health insurance							
No health insurance	174 (25.9)	—	689 (24.2)	1.4 (1.2-1.7)	<.001	—	—
Public insurance	84 (12.5)	—	75 (2.6)	5.7 (4.1-8.0)	<.001	—	—
Private health insurance	413 (61.6)	—	2089 (73.2)	1.0	—	—	—

CCSS indicates Childhood Cancer Survivor Study; RR, relative risk; CI, confidence interval; OR, odds ratio.
[a] Restricted to baseline and age ≥18 years (716 survivors, 9317 other survivors, and 3083 siblings).
[b] Adjusted RRs for age, sex, and amputation.
[c] Adjusted ORs for age and sex.
[d] Pain and anxiety were not available for CCSS siblings.
[e] Pain and anxiety were excluded. The number of osteosarcoma survivors with any domain excluding pain and anxiety was 309 (43.2%).
[f] Restricted to age ≥25 years, and adjusted ORs for age and sex (676 survivors and 2870 siblings).

siblings did not. Unemployment rates were low, but more survivors (3.1%) were unemployed versus siblings (0.2%). In terms of health insurance, both groups had a significant number without insurance (Table 4).

DISCUSSION

Because of the relatively low incidence (approximately 400 per year) of childhood osteosarcoma in the United States,[1] conducting a large comprehensive study of osteosarcoma survivors at any 1 institution is very difficult. However, the CCSS, with its large multi-institutional cohort enables comprehensive assessments of various sequelae of a large number of ≥5-year osteosarcoma survivors. This is an important subset of patients to examine in detail, as these patients receive very invasive surgeries and multimodal chemotherapy with known significant toxicities.

Mortality estimates in this cohort of 5-year survivors of osteosarcoma were elevated when compared with the US population, with a 20-year survival probability of 88.6%, which is similar to the reported overall CCSS mortality.[25] Females had a slight survival advantage compared with males (90.0% vs 87.3%); however, females had a higher SMR compared with males, because of the lower mortality rates of females (compared with males) in the US population coupled with the increased risk of an SMN in females. The development of an SMN or

recurrent disease was predictive of death, as was the use of radiation and exposure to cisplatin, which may be a marker for extent or aggressiveness of disease. In data not shown, it was noted that radiation therapy was predominately given to older cohorts, for whom survival was likely poorer and systemic therapy was limited. When cisplatin exposure was further examined, higher cumulative exposure was associated with death attributed to recurrences, SMNs, and cardiac toxicity. However, cumulative cisplatin exposure is correlated with other exposures, such as higher cumulative dose of anthracycline. Thus, the exact contribution of cisplatin to the observed increase in risk of death is not clear, and it is possibly a surrogate for more aggressive disease or disease recurrence necessitating more chemotherapy exposure.

When comparing our survival rates of 5-year survivors with those reported in other studies, caution must be used, as the majority of the survivorship studies report survival from diagnosis as compared with survival of those alive 5 years from diagnosis. In 1 large study of 1702 patients with newly diagnosed osteosarcoma between 1980 and 1998 from the German Cooperative Osteosarcoma Study Group, the overall survival at 5 years from diagnosis was 65.3%. Survival rates continued to decline, with 10- and 15-year survival rates of 59.8% and 57.3%. These rates approximate this study's survival rates of 5-year survivors at 10 and 15 years from diagnosis.[2]

The cumulative incidence of recurrences in our study was relatively stable after 5 years (24.5% at 5 years and 28.1% at 25 years), with only 24 subjects experiencing a recurrence >5 years after diagnosis. This is comparable to a large study of 576 patients with relapsed osteosarcoma, where only 5.7% of the relapses occurred after 5 years.[26]

In contrast to the recurrences, the majority of SMNs occurred ≥10 years from diagnosis. A prior report from CCSS showed that bone tumor survivors had a cumulative incidence of 3.3% at 20 years.[9] The current report extends these data and focuses on osteosarcoma patients. The SIR for all SMNs was 4.8, with a cumulative incidence of 1.0% at 10 years and 5.4% at 25 years, which is consistent with a 10-year cumulative incidence reported by Goldsby et al.[27] Several other studies have reported on the incidence of SMNs, with rates ranging from 2% to 5% at 10 years.[28-31]

The literature reports that the incidence and magnitude of hearing loss increases with increasing cumulative cisplatin doses, with a threshold between 240 and 400 mg/m^2 and younger age associated with greater risk.[32,33] In the current study, we confirmed increased hearing loss and increased prevalence of vertigo with increasing cumulative cisplatin dose. However, younger age at diagnosis was not predictive of this late sequelae, which may be because of the small number of children who were diagnosed at a very young age among the osteosarcoma group (12 survivors younger than 4 years at diagnosis) in this cohort.

Although anthracyclines are known to have cardiac toxicity, they are an integral part of osteosarcoma therapy, and the majority of patients with osteosarcoma now receive close to what is considered the maximum cumulative dosing (450 mg/m^2). Recent studies[34] have demonstrated a cumulative incidence of 10% at 20 years for acute congestive heart failure for those who received >300 mg/m^2, but even those with lower cumulative anthracyclines doses may be at risk.[35] In our study, 19 reported having congestive heart failure, with 13 of the 19 having received >360 mg/m^2 of anthracyclines. Reports of congestive heart failure are important to note in this cohort, as nearly 86% received anthracyclines, with 58.2% receiving >210 mg/m^2 of anthracyclines. Congestive heart failure tended to be more common in patients farther from treatment. In addition to congestive heart failure, 11 reported having cardiovascular disease. One limitation of these data is that they rely on self-reporting, which is an underestimation, and also it is unknown how well surveillance imaging and follow-up were performed in this group of survivors.

As previously identified, bone sarcoma survivors were more likely than the siblings to have chronic and adverse health conditions.[15,16] Because survivors of osteosarcoma in the current study had a large number of grade 3 or 4 chronic health conditions because of the high number of amputations (72%) performed in this treatment era (1970-1986), we adjusted for amputations when comparing against siblings and other survivors. This is reflected in decreased relative risks when compared with Oeffinger et al.[15] Interestingly, osteosarcoma survivors had more grade 3-4 conditions (even after adjusting for amputation) compared with other survivors, likely reflecting the effects of extensive surgery and chemotherapy received by this group of survivors.

When general health status was examined, osteosarcoma survivors were more likely than the sibling cohort to report adverse health status. When osteosarcoma survivors were compared with survivors of other tumors, general health, mental health, and anxiety were not different, but functional status, activity limitations, and pain were more

likely to be a problem. Given the use of amputation and surgeries in this osteosarcoma cohort compared with other survivors, this would be expected. However, with 72% of the CCSS osteosarcoma survivors having an amputation, one would expect a greater number reporting impaired functional status (15%) or activity limitation (29%). This is remarkable and is likely because of adaptation to their limitations. The increased incidence of chronic conditions and limitations and pain seen in osteosarcoma survivors is especially concerning, given the relative lack of health insurance of this osteosarcoma cohort (25.9%). Survivors of osteosarcoma also seemed to compare reasonably in terms of marital status, employment, and education, despite the impact therapy had on the development of chronic illnesses and general health. However, differences exist when compared with siblings, and additional support services may allow for improved integration.

When interpreting the results of this study, there are some limitations that must be considered. The majority of the outcomes were based on self-report and thus may be subject to over- or under-reporting. Exceptions to the self-report included the occurrence of second malignancies, where pathology reports were obtained to verify and classify cases. Causes of death were determined using death certificate information. Assessments of chronic health conditions were restricted to individuals aged >18 years at the time of enrollment in CCSS. Although the vast majority of osteosarcoma patients were older than 18 years, our results can not be applied to younger survivors. Lastly, we used the CCSS sibling cohort to compare with the osteosarcoma survivors for several outcomes. Because siblings of pediatric cancer survivors may experience a variety of stressors resulting from the psychosocial and familial impact of having a sibling with cancer, the magnitude of risk observed may be an underestimate. Although this group of survivors was treated differently in terms of surgery (more amputations), more varied chemotherapy regimens, and supportive care compared with current osteosarcoma patients, this serves as a baseline for future comparisons.

Overall, the childhood osteosarcoma survivors in this cohort did relatively well, considering their extensive treatment; however, they are an at-risk population and warrant life-long follow-up for SMNs, adverse medical conditions, and issues related to general health, disability/function, and pain. Prospective evaluation of current patients with osteosarcoma will be important to assess both acute and long-term effects of current osteosarcoma therapy and their impact on survivorship.

CONFLICT OF INTEREST DISCLOSURES

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