1. Title

Long-term outcomes in survivors of pediatric primary tumors of the vertebral column and spinal canal.

2. Working group and investigators

a. Chronic Disease (primary)
b. Epidemiology and Biostatistics (secondary)
c. Psychology (secondary)

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3. Background and Rationale

Pediatric vertebral column and spinal cord tumors are difficult to study because of their rarity and histologic heterogeneity. Spinal tumors are much less common than intracranial tumors accounting for just 5-10% of central nervous system (CNS) malignancies with an overall incidence of between 1-2.7 per 1 million children.[1,2] Intramedullary tumors account for ~30% of spinal tumors anatomically, intradural extramedullary tumors account for ~25%, extradural tumors ~35%, and the remaining 10% emanate from the paraspinal soft tissues.[3] Intramedullary tumors are typically astrocytomas and ependymomas, most of which are low grade having good long term survival outcomes. Sarcomas, neuroblastoma, and lymphoma are the most common extradural tumors.[2] The overall incidence of spinal sarcomas based on SEER registry data is 0.019 cases per 100,000 persons, although these tumors are generally more common in adults than in the pediatric population.[4] Of the two most common pediatric primary bone sarcomas, less than 5% of osteosarcomas and ~10% of Ewing sarcomas present in the mobile spine.[5] While lymphomas and leukemias are common pediatric malignancies, primary spine involvement including having compressive myelopathy as a presenting symptom is seen in only ~4% of these patients.[6,7]

Further complicating the longitudinal study of these tumors and their survivors is the poor survival statistics associated with these histologies. Neuroblastoma – the most common source of epidural spinal cord compression in children – has an overall 5-year survival of 83% for infants, 55% for children 1-5 years old, and just 40% for children older than 5 years.[8] 5-year survival for spinal osteosarcoma and Ewing sarcoma in the pediatric population is 60%.[4] Intramedullary astrocytomas overall can have a 5-year survival of almost 75%, but this outcome is highly dependent on tumor grade.[9] Fortunately, lymphoma involving the spine has an excellent prognosis, approaching 100% survival at 10 years.[7]

It is well known that these tumors can cause pain, as well as motor, sensory, bowel, and bladder dysfunction from spinal cord compression. Much less well documented is the impact of these tumors and their treatments on the social, psychological, functional, and quality of life (QoL) outcomes of their survivors. Scheineman et al. retrospectively reviewed all of the spinal low-grade gliomas (LGG) sent to their regional referral center from 1985-2007, a number which accounted for <5% of all LGGs treated at the institution during this period.[10] Of the 29 patients included, median age at diagnosis was 6 (range 1-15) with 8 years (range 0-14) of follow up. 83% of survivors overall reported persistent neurologic or orthopaedic morbidity, including 52% having weakness or bowel/bladder dysfunction and 66% with spinal deformity. 35% of survivors required additional surgery, mostly to address spinal deformity. Despite these complications, 79% of the children were rated as a grade of 1 or 2 out of 4 on the McCormick Functional Scale,[11] which correlated to only mild or moderate disability. This was not affected by the extent of surgery, radiation, or chemotherapy. To the authors' credit, they highlighted the apparent disconnect between the extent of post-treatment morbidity and the acceptable functional outcomes as determined by the McCormick Scale and emphasized that this scale – regularly used in the assessment of spinal tumors – may be inadequate for capturing the daily difficulties of these survivors and highlighted the need for improved outcome metrics in this population.[10]

Poretti et al. reported complications and QoL of 20 survivors of pediatric spinal tumors including both extradural and intramedullary sites. Median age at diagnosis was 3 years, and median follow up was 8.4 years. The Functional Independence Measure (FIM) and the FIM for Children <7yo (WeeFIM) were used to determine the disability associated with daily living. The Youth Self Report (YSR) and the Child Behavior Checklist (CBCL) were used to assess behavioral and emotional problems, and the Pediatric Quality of Life Inventory (PedsQL) was used to assess health-related QoL (HRQoL). Survivor outcomes were compared to those from a standardized population in the PedsQL previously reported in the literature.[12] Not all patients were eligible to complete each of these outcome scores, so the data pools were further limited. Despite this limitation, 50% of survivors reported persistent weakness (mono or paraparesis) or bowel/bladder dysfunction. 8 of 8 assessed survivors reported normal scores on the YSR scale, although parents' reports on the CBCL indicated higher incidences of anxiety and depression (3 of 8). Only 4 of 20 patients assessed had functional scores <90% of normal on the FIM or weeFIM. Low functional scores were correlated to neurologic deficits at diagnosis. HRQoL scores for the tumor cohort were not different in the assessed survivors as compared to healthy controls, although correlations were found in survivors who did report impaired overall QoL with impaired weeFIM/FIM scores and with persistent neurologic deficits. Overall, this study reported a good prognosis (10yr OS = 96% in this series) with minimally-impaired QoL in survivors of pediatric spinal tumors. Given the high percentage of survivors with residual neurologic deficits and the association of neurologic deficits with worse functional outcomes, it is not immediately clear how overall scores were as good as reported. Certainly, these data are limited by the size of the population and the even-more-limited

number of survivors assessed per outcome. Nonetheless, this represents one of the largest outcomes studies of survivors of pediatric spinal malignancies currently available in the literature.

Another study also used the PedsQL to assess outcomes of surgically-treated high- and low-grade intramedullary spinal cord tumors in children reporting the results from 10 survivors diagnosed at a mean age of 7 with 4 years of follow up.[13] A fraction of the cohort received chemotherapy and/or radiation, for which the analyses were not controlled. The authors found no significant differences in the study cohort versus the normative scores in the PedsQL instrument.

In a study that most closely mimics the methods of the modern CCSS, Mostow et al. described the quality of life in 342 survivors of central nervous system (CNS) tumors diagnosed before the age of 20 between 1945-1975 who had survived at least 5 years and compared them to 479 healthy sibling controls in a collaborative study amongst the National Cancer Institute and 5 cancer registries.[14] Average age at diagnosis was 11 years, and survivors had an average age of 32 years at assessment. However, only 7% of these survivors had an extracranial malignancy preventing direct comparison with our proposed cohort. Survivors exhibited significantly greater odds of death at any given age, of being unable to work, and of having adverse physical and emotional health conditions compared to the sibling controls. These effects were more severe in survivors of supratentorial tumors. Additional more modern[15] studies on long-term outcomes in survivors of pediatric brain tumors have also been reported.[16-18]

Thus, while CNS malignancies account for the second leading cause of cancer incidence and mortality in childhood, <10% of cases affect the spinal column. Given their rarity and the poor survivorship from high grade lesions, there are very few studies on long-term outcomes for survivors of these tumors. The studies that exist have small sample sizes, and there remains some question as to what outcomes metrics can adequately capture the disability that may accompany the long-term health impact of these tumors and their treatments on survivors. Our study is proposed to help address these gaps in knowledge by investigating long-term outcomes in survivors of pediatric primary tumors of the vertebral column and spinal canal diagnosed between 1970-1999 who underwent any form of local or systemic control including resection, locally-delivered radiotherapy, and/or chemotherapy. We will report psychosocial, functional, and HRQoL outcomes, overall and cause-specific mortality, and incidence of chronic health conditions in these survivors and compare them to the CCSS sibling cohort. With an estimated ~140 spinal column tumor survivors available within CCSS, this analysis would represent the largest study of spinal column tumor survivors ever reported with the longest follow up having robust outcomes measures.

4. Specific aims/objectives/research hypotheses

Specific Aim 1

Determine overall late mortality and cause-specific late mortality (heath-related and external cause), late (>5 years from diagnosis) recurrence, and subsequent malignant neoplasms (SMN) for survivors of tumors of the vertebral column and spinal cord.

Hypothesis: Survivors of spinal tumors will be at an increased risk of overall mortality at any age compared to siblings and will be at an increased risk of developing SMNs. In risk stratified-analyses, survivors exposed to radiotherapy will have a higher incidence of SMN, while surgical treatment will not be associated with any increased risk.

Specific Aim 2

Estimate the cumulative incidence of relevant CTCAE chronic health conditions (CHCs) and scoliosis among spine tumor survivors according to tumor and treatment characteristics and local control methods. Specifically estimate the incidence of adverse neurologic CHCs (eg: numbness, weakness) reported on the CCSS follow up surveys and identify demographic and treatment-related factors associated with adverse neurologic sequelae.
Hypothesis: Survivors of spine tumors will be at an elevated risk of grade 3 or 4 CHCs compared to siblings. Survivors treated with surgery for the primary tumor will be at an elevated risk of developing scoliosis. Factors associated with reported neurologic sequelae may include age at diagnosis, tumor location (intramedullary versus extramedullary), and treatment with surgery and/or radiation

Specific Aim 3
Describe the rate of late-occurring spine surgery (>5 years from diagnosis) as a group and partitioned by tumor characteristics and local control methods.
Hypothesis: Survivors of spine tumors will undergo significantly elevated rates of late spine surgery compared to sibling controls. Survivors initially treated with surgery will undergo still higher rates of subsequent spine surgery compared to survivors not treated with surgery for their primary tumor.

Specific Aim 4
Describe the health-related quality of life (HRQoL), functional impairment, activity limitations, and psychosocial outcomes of spine tumor survivors according to tumor and treatment characteristics stratified by local control modality while controlling for systemic (chemotherapy) exposures.
Hypothesis: Survivors will exhibit significant HRQoL and functional impairments as compared to siblings. Survivors will exhibit impaired mental health outcomes compared to siblings. Survivors of higher-grade tumors will exhibit greater degrees of functional and QoL limitations than will survivors of lower grade malignancies.

Specific Aim 5
Describe socioeconomic outcomes including ability to work, ability to drive, ability to manage routine needs of daily living, and educational attainment among spine tumor survivors as compared to siblings.
Hypothesis: Survivors will exhibit more substantial impairment including decreased educational attainment, lower levels of employment/income, and greater dependency for activities of daily living compared to siblings

5. Analysis Framework
a. *Subject population*
Inclusion criteria –. We will include all childhood cancer survivors of malignant tumors of the vertebral column (cervical, thoracic, and lumbar vertebral levels), spinal cord, and associated meninges diagnosed between 1970-1999 who underwent any form of local or systemic control including resection, locally-delivered radiotherapy, and/or chemotherapy. Survivors will be identified based on ICD diagnosis codes for tumors of cervical, thoracic, or lumbar spine (ICD dx site C41.2 = vertebral column) or spinal cord (C72.0) and exclude tumors of the sacrum/pelvis

(C41.4). All extradural, intradural extramedullary, and intramedullary solid tumors and hematopoietic malignancies – such as lymphoma – with primary presentation in the vertebral column will be included.

Exclusion criteria – Any survivor who did not receive tumor-directed therapy.

b. Outcomes of interest

Overall late mortality and cause-specific late mortality (heath-related and external cause), late (>5 years from diagnosis) recurrence, subsequent malignant neoplasms (SMN), and Grade 3 or 4 chronic health conditions for spine tumor survivors. Specific analyses will focus on the development of chronic neurologic conditions in survivors (memory problems, seizure, balance problems, etc).

- All-cause mortality rates will be calculated as described in the *Statistical methods* section, below
    - Vital status is determined using linkage with the National Death Index
- Incidence of subsequent malignant neoplasms (based on LTFU 2019 #R1, R6 or similar depending on LTFU survey
- Relative risk of developing a National Cancer Institute's Common Terminology for Adverse Events v4.3 (CTCAE)[19] Grade 3 or higher chronic health condition in survivors versus siblings
- Prevalence of adverse neurologic sequelae (any Grade) as assessed by the relevant CCSS survey questions (eg. LTFU 2019 #J5-J6, J8-J12) and codified by the CTCAE-based chronic health condition dataset.
    - Specifically:
        - Memory problems
        - Seizures
        - Balance problems
        - Tremors
        - Weakness in leg
        - Paralysis
        - Weakness in arm
        - Sensory neuropathy
        - Other neurologic condition

Additional late health-related quality of life (HRQoL), functional impairment, activity limitations, and psychosocial outcomes of these spine tumor survivors according to tumor type. Additional analyses will stratify outcomes by treatment exposure including surgery and/or radiation while controlling for chemotherapy. Data will be abstracted from the most recent survey completed by the survivor and sibling cohorts.

- HRQoL as assessed by Short Form 36 (SF-36) survey
    - The SF-36, which provides subscale scores for eight domains of HRQOL: mental health, physical health, emotional role function, physical role function, social health, pain, vitality and energy, and health perceptions. Raw scores from the SF-36 will be converted to T scores (range, 0-100) and dichotomized so that a score at

or below 40 (1 SD below the population mean) was classified as a poor HRQOL outcome.

- Psychosocial outcomes (Depression vs. no depression; anxiety vs. no anxiety; etc) as assessed by the Brief Symptom Inventory (BSI) survey
    - The BSI-18 is a measure of depression, somatization, anxiety, and global mental health. Participants with T-scores of 63 or more on a particular scale will be classified as having poor emotional health[20]
- Functional status and activity status classified based on answers to questions adapted from the National Health Interview Survey and the Behavioral Risk Factor Surveillance System Survey Questionnaire.
    - Questions on physical limitation assess the duration of such limitation (none, 3 months or less, or more than 3 months) based on six questions, where scores range from 6 (most physical limitation) to 18. Respondents with scores in the 10th percentile of a healthy control group (score ≤ 15) are defined as having physical limitation.[20]
- Ability to work, drive, to live independently, and to manage routine needs of daily living independently (all binary outcomes) are assessed by the relevant CCSS follow up survey questions (example: LTFU 2019 #M25-28)
- socioeconomic outcomes such as education attained, most recent employment status, income level, health insurance status, and marital status (e.g., based on LTFU 2019 #A6-A10, A15 or similar items from the last survey answered)
    - These analyses will be restricted to survivors aged 25 years and older at the time of latest follow up
- Late-occurring spine surgery for scoliosis or other surgery of the spine or spinal cord (based on LTFU 2019 #K2, 3 or similar depending on LTFU survey)

c. *Exploratory variables*

- Demographic variables
    - Age at diagnosis and time of follow-up (continuous and categorical)
    - Sex (categorical; Baseline #A2; ExpBaseline #A2)
    - Race/ethnicity (categorical; Baseline #A4; ExpBaseline #A5)
- Cancer variables
    - Initial diagnosis
        - By histologic group (sarcoma, glioma)
    - Tumor location
        - Cervical, thoracic, lumbar
    - Local tumor recurrence (Baseline & ExBaseline #K1 and K4, LTFU 2019 #R1/R5/R10)
- Treatment variables
    - Decade of diagnosis (1970-1979, 1980-1989, 1990-1999)
    - Surgery variables
        - Type of surgery if available
    - Any chemotherapy (binary)
        - Antimetabolits - methotrexate
        - Anthracyclines - doxorubicin
        - Alkylating agents – cyclophosphamide, ifosfamide

        - Platinum agents - cisplatin
        - Epipodophyllotoxins – etoposide
        - Vinca alkyloid – vincristine
    - Any spine-directed radiation therapy
        - XRT exposure divided into tertiles
        - Any-spine radiation will be defined as yes to the neck, chest, abdomen, and pelvis. The maximum target dose (maxTD) to the treated region will be used in analyses. When multiple regions were irradiated, the highest maxTD will be used. Radiation data are available in the body region dosimetry file.
        - Note that the spine-dose variable will not be used to define spine dose because it only considers patients treated with spine fields, as opposed to any RT directed at the spine.

d. *Statistical methods*

Aim 1: We will tabulate cumulative incidence curves for subsequent malignant neoplasms (SMN). The overall survival rate will be estimated using the Kaplan-Meier method. Unadjusted risk-ratios for all-cause late mortality will be calculated for spine tumor survivors compared to siblings. Additional comparison will be made to survivors of other CNS malignancies (i.e. brain tumors) in the CCSS cohort. Vital status will be determined using linkage with the National Death Index.

- Survival: Table 2, Figure 1
- SMN: Table 3, Figure 2

Aim 2: We will tabulate cumulative incidence of relevant CTCAE chronic health conditions, particularly cardiac, GI, MSK, nervous system, and renal/GU conditions. Information about chronic health conditions will be obtained from organ-specific questions covering cardiovascular, endocrine, respiratory, gastrointestinal, renal, neurologic, immunologic, and hematologic systems. These conditions will be graded for severity using the National Cancer Institute's Common Terminology for Adverse Events v4.3, including Grade 1 (mild or asymptomatic), Grade 2 (moderate), Grade 3 (severe and/or disabling), and Grade 4 (life-threatening).[19] We will specifically tabulate the cumulative incidence of adverse neurologic sequalae from survivor report on CCSS follow up surveys. We will identify demographic and treatment-related factors associated with long-term adverse neurologic sequaela. A univariable Cox proportional hazards model will be used to examine the impact of demographic and treatment variables, cancer recurrence, and Grade 3 and 4 chronic health conditions on the hazard ratio (HR) of a neurologic sequelae in survivors of spine tumors. Cancer recurrence and Grade 3 and 4 chronic health conditions will be treated as time-varying covariates. Factors from the univariable analysis with a p value <0.1 will be included in a multivariable regression analysis.

- Table 4 (CHC)
- Table 5 (neurologic sequelae)
- Table 6 (factors associated with any neurologic sequelae)

Aim 3: We will tabulate the cumulative incidence and cumulative count of late-occurring spine surgery (for scoliosis and for all other spine surgeries) in all survivors of spine tumors and evaluate for differences due to tumor type and location and local control treatment modalities. Analyses

will proceed according to published methods.[21] Relative risk of late spine surgery will be estimated using CCSS siblings as the reference.

- Table 7, Figure 3

Aim 4: HRQOL will be evaluated using the SF-36, which provides subscale scores for eight domains of HRQOL: mental health, physical health, emotional role function, physical role function, social health, pain, vitality and energy, and health perceptions. Raw scores from the SF-36 will be converted to T scores (range, 0-100) and dichotomized so that a score at or below 40 (1 SD below the population mean) will be classified as a poor HRQOL outcome. Mental health outcomes / emotional distress will be measured with the BSI-18, a measure of depression, somatization, anxiety, and global mental health. Participants with T-scores of 63 or more on a particular scale will be classified as having poor emotional health.[20] A modified Poisson regression approach [22] will be used to estimate the relative risk (RR) of HRQOL, psychosocial, physical or functional impairments (binary outcomes defined earlier) between survivors and siblings, adjusted for age at the time of evaluation. Additionally, comparisons will be made against survivors of other CNS malignancies in the CCSS cohort.

- Table 8, Table 9

Aim 5: We will evaluate for differences between survivors and siblings for functional and socioeconomic outcomes including ability to work, educational attainment, ability to drive and manage routine needs of daily living, as well as measures of impaired physical performance, which will be obtained from survivors' responses to CCSS follow-up surveys. Physical performance will be determined based on published methods. [20] Questions on physical limitation assess the duration of such limitation (none, 3 months or less, or more than 3 months) based on six questions, where scores range from 6 (most physical limitation) to 18. Respondents with scores in the 10th percentile of a healthy control group (score ≤ 15) will be defined as having physical limitation. Demographic and treatment variables will be controlled for in multivariate analysis. Risk ratios will be reported where appropriate using the CCSS sibling cohort as the reference.

- Table 10

6. Sample Tables/Figures:

Table A: CCSS primary diagnoses in the vertebral column or spinal cord

Primary Diagnosis	**ICD Site Diagnosis Code**		**Total**
	C41.2 (Vertebral Column)	**C72.0 (Spinal Cord)**	
Extradural			
Neuroblastoma	0	0	0
Soft tissue sarcoma	3	1*	4
Ewing sarcoma	18	1*	19
Osteosarcoma	0	0	0
Other bone malignancy	4	1*	5
Intramedullary			

Astrocytoma	0	67	67
Medulloblastoma, PNET	1*	15	16
Other CNS malignancy	0	36	36
Lymphatic			
Non-Hodgkin's lymphoma	0	0	0
Total	25	118	143

* exclude as these diagnosis locations must be miscoded

Table 1: Demographic and treatment-related variables in survivors of pediatric spinal tumors

	Spine Tumor Survivors (n=*)**
	n (%)
Sex	
Male	
Female	
Race	
White, Non-Hispanic	
Black, Non-Hispanic	
Asian/Pacific Islander	
Other	
Age at Diagnosis (yrs)	
<5	
5-9	
10-14	
15+	
Age at last follow up or death (yrs)	
Mean(SD)	
Decade of Diagnosis	
1970s	
1980s	
1990s	
Diagnosis	
Extradural	
Ewing sarcoma	

Other bone malignancy	
Intramedullary	
Astrocytoma	
Other CNS Malignancy	
Chronic medical condition	
Any Grade 3-4	
No	
Yes	
Cancer recurrence	
Yes	
No	
Treatment	
Surgery Only	
Radiation Only	
Surgery+Chemo	
Surgery+XRT	
Surgery+Chemo+XRT	
Chemotherapy exposure	
None	
Any	
Anthracycline	
Yes	
No	
Alkylating agent	
Yes	
No	
Platinum	
Yes	
No	
Vinca alkaloid	
Yes	
No	
Antimetabolites	
Yes	
No	

Topoisomerase inhibitor/Anti-tumor antibiotic	
Yes	
No	

Table 2: All-cause and cause-specific standardized mortality ratios (SMR)* for spine tumor survivors. A) vertebral column tumors B) spinal cord tumors

Death Category	All			Male			Female		
	# Death	SMR	95% CI	# Death	SMR	95% CI	# Death	SMR	95% CI
All-cause									
SMN									
Cardiac									
Pulmonary									
External									
Other									
Unknown									

*calculated using age-sex-calendar year-specific US mortality rates. See Nagarjan et al., *20 Years Osteosarcoma*[23]

Table 3: Standardized incidence ratios of SMNs in spine tumor survivors. A) vertebral column tumors B) spinal cord tumors.

SMN	N (%)	SIR	95% CI
Any site			
Male			
Female			
CNS			
Breast			
Lung			
GI			
Other			

Age-sex-calendar-year-specific cancer incidence rates from the National Cancer Institute's Surveillance, Epidemiology, and End-Results (SEER) registry are used as reference rates in the SIR calculation. See Nagarjan et al., *20 Years Osteosarcoma*

Table 4: Chronic health conditions in spine tumor survivors and siblings. A) vertebral column tumors B) spinal cord tumors.

		Survivors	**Siblings**	**Chi-Square p-value**
Chronic condition		**n (%)**	**n (%)**	
Any Grade 3-4	No			

	Yes			
Cardiovascular	No			
	Yes			
Endocrine	No			
	Yes			
Respiratory	No			
	Yes			
Gastrointestinal	No			
	Yes			
Renal	No			
	Yes			
Neurological	No			
	Yes			
Immunologic	No			
	Yes			
Hematologic	No			
	Yes			

Table 5: Neurologic-specific sequelae in survivors and siblings. A) vertebral column tumors B) spinal cord tumors

		Survivors	**Siblings**	**Chi-Square p-value**
Chronic condition		**n (%)**	**n (%)**	
Scoliosis	No			
	Yes			
Problems with balance or equilibrium	No			
	Yes			
Tremors of movement problems	No			
	Yes			
Numbness in the arms or legs	No			
	Yes			
Abnormal sensation in the arms or legs	No			
	Yes			
Prolonged pain in back, arms, or legs	No			
	Yes			
Weakness in arms	No			
	Yes			
Weakness in legs	No			

	Yes			

Table 6: Multivariable analysis of risk factors associated with a long-term adverse neurologic sequela*

	HR	**CI**	**p-value**
***Gender*^**			
Men			
Women	1		
***Chemotherapy exposure*^**			
Yes			
No	1		
***Radiation exposure*^**			
Yes			
No	1		
***Surgery*^**			
Yes			
No	1		
***Cancer recurrence*^**			
Yes			
No	1		

*Neurologic sequelae as listed in Table 9

^These are just examples of independent variables. The final model will depend on results of the univariate analysis.

Table 7: Mean cumulative count per 100 individuals of late-occurring spine surgery (for scoliosis and for all other spine surgeries) in survivors of spinal tumors and CCSS siblings.^

	Mean Cumulative Count, survivors (95% CI)	Mean Cumulative Count, survivors treated w/ surgery (95% CI)	Mean Cumulative Count, survivors treated w/o surgery (95% CI)	Mean Cumulative Count, siblings (95% CI)	Number of Interventions per 1000 person years, survivors (95% CI)	Number of Interventions per 1000 person years, siblings (95% CI)	Adjusted Rate Ratio (95% CI)*
Vertebral Column Tumors							
Total Late Spine Surgeries							
Scoliosis correction							
All other							
Spinal Cord Tumors							
Total Late Spine Surgeries							
Scoliosis correction							

All other							

*Adjusted for age, race, sex, and insurance status
^See Dieffenbach and Murphy et al., *Late Surgery*

Table 8: Health-related quality of life outcomes based on the Medical Outcomes Survey-Short Form (SF-36) for spine tumor survivors and CCSS siblings, adjusted for age at evaluation stratified by tumor histology.

	Impairment n (%)	**RR (95%CI)**	**p-value**
HR-QOL			
Physical health			
Physical functioning			
All Survivors			
Ewing Sarcoma			
Other Vertebral Column			
Astrocytoma			
Other CNS Malignancy			
Siblings		1	
Physical role			
All Survivors			
Ewing Sarcoma			
Other Vertebral Column			
Astrocytoma			
Other CNS Malignancy			
Siblings		1	
Bodily pain			
All Survivors			
Ewing Sarcoma			
Other Vertebral Column			
Astrocytoma			
Other CNS Malignancy			
Siblings		1	
General health			
All Survivors			
Ewing Sarcoma			
Other Vertebral Column			
Astrocytoma			
Other CNS Malignancy			
Siblings		1	

Mental health			
Vitality			
All Survivors			
Ewing Sarcoma			
Other Vertebral Column			
Astrocytoma			
Other CNS Malignancy			
Siblings		1	
Social functioning			
All Survivors			
Ewing Sarcoma			
Other Vertebral Column			
Astrocytoma			
Other CNS Malignancy			
Siblings		1	
Role-emotional			
All Survivors			
Ewing Sarcoma			
Other Vertebral Column			
Astrocytoma			
Other CNS Malignancy			
Siblings		1	
Mental Health			
All Survivors			
Ewing Sarcoma			
Other Vertebral Column			
Astrocytoma			
Other CNS Malignancy			
Siblings		1	

Table 9: Psychosocial outcomes based on the Brief Symptom Inventory (BSI-18) for spine tumor survivors and CCSS siblings stratified by tumor histology.

	Impairment n (%)	**RR (95%CI)**	**p-value**
BSI-18			
Depression			
All Survivors			
Ewing Sarcoma			

Other Vertebral Column			
Astrocytoma			
Siblings		1	
Anxiety			
All Survivors			
Ewing Sarcoma			
Other Vertebral Column			
Astrocytoma			
Other CNS Malignancy			
Siblings		1	
Somatic			
All Survivors			
Ewing Sarcoma			
Other Vertebral Column			
Astrocytoma			
Other CNS Malignancy			
Siblings		1	

Table 10: Physical and social outcomes for spine tumor survivors and CCSS siblings assessed by CCSS follow up surveys stratified by tumor histology.

	Modified Poisson Regression adjusted for age at physical function		
Outcome	**Yes n (%)**	**RR (95% CI)**	**p-value**
Limited physical performance			
All Survivors			
Ewing Sarcoma			
Other Vertebral Column			
Astrocytoma			
Other CNS Malignancy			
Siblings		1	
Help needed for routine needs			

		1	
Help needed for personal care needs			
All Survivors			
Ewing Sarcoma			
Other Vertebral Column			
Astrocytoma			
Other CNS Malignancy			
Siblings		1	
Cannot work or attend school			
All Survivors			
Ewing Sarcoma			
Other Vertebral Column			
Astrocytoma			
Other CNS Malignancy			
Siblings		1	
Inability to Drive			
All Survivors			
Ewing Sarcoma			
Other Vertebral Column			
Astrocytoma			
Other CNS Malignancy			
Siblings		1	

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Figure 1: Overall survival curves of pediatric spine tumor survivors (all survivors, vertebral column survivors, and spinal cord survivors graphed separately) and siblings (Line graph. % survival on Y-axis, years since diagnosis on X-axis)

Figure 2: Cumulative incidence curves of subsequent malignant neoplasms (SMN) including and excluding tumor recurrence (Line graph. Cumulative incidence % on the Y-axis, years since diagnosis on the X-axis. 1 line for new SMN; 1 line for tumor recurrence)

Figure 3^: Mean cumulative count per 100 individuals of late-occurring spine surgery in all spine tumor survivors, survivors of vertebral column tumors, and also survivors of spinal cord tumors (separately) versus siblings.

^Line graph. Y axis is mean cumulative count per 100 individuals, X axis is time since cancer diagnosis. See Dieffenbach and Murphy et al., *Late Surgery*

Figure 4: Treatment exposures by decade of diagnosis (bar graph. Exposures listed along the x-axis including surgery, XRT, chemo and those combinations. A bar for each exposure within a decade block 1970s, 1980s, 1990s to show percentage of survivors with each exposure in that decade)

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