

Childhood Cancer Survivor Study
Analysis Concept Proposal

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Title: Comparison of Health Status Outcomes between Survivors of Childhood onset Upper and Lower Extremity Sarcomas: A Report from the Childhood Cancer Survivor Study (CCSS).

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1 Background and Rationale:

Survival rates for children with extremity sarcoma were poor before the introduction of multi-agent chemotherapy.¹⁻⁴ The introduction of multi-agent chemotherapy,⁵⁻⁷ including the use of effective local control modalities, dramatically improved outcomes for these patients. Current series report 5 year event-free survival for 60-70% of these children.⁸⁻¹³ Sarcoma survivors, however, remain at high-risk for medical complications as they age because their treatment includes high-doses of chemotherapy and aggressive local control modalities, including surgical resection and/or high-dose radiotherapy.¹⁴

The presence of organ system impairments and associated functional loss among childhood cancer survivors are dose-related and predicted by the agents used for treatment.¹⁵ Among extremity sarcoma survivors, both the multimodal chemotherapy agents, and the necessity for local control, have the potential to contribute to long-term neurosensory and musculoskeletal impairments that may eventually interfere with overall health status domains.

Sensory impairments are particularly problematic for children whose treatment required surgical resection of peripheral nerves or extensive cutaneous tissue. Gonadal disorders may contribute to altered growth in children whose treatment included pelvic

radiation or surgery.¹⁶ Bone mineral density deficits may be prevalent among survivors treated with radiation to the skeleton, and with a history of glucocorticoid or cyclophosphamide administration.^{17,18} Dysplasia and asymmetry,¹⁹⁻²¹ limb shortening,²²⁻²⁴ and spinal growth abnormalities,²⁵ like scoliosis or kyphosis,¹⁶ may result in the loss of the growth plate during surgery or bone damage due to radiation therapy. Weakened bones are susceptible to fracture,²⁶ and structural abnormalities interfere with internal organ system and muscle function. Muscular hypoplasia or atrophy,^{24,27} fibrosis, weakness,^{22,23,28} and limited joint range of motion^{22,24} are possible outcomes. Prosthetic failure among childhood sarcoma survivors who have had limb sparing surgeries often necessitates additional surgical intervention.²⁹

Previous reports from the CCSS have indicated that extremity sarcoma survivors are at increased risk of poor health status,³⁰ and that poor health status is associated with less than optimal participation outcomes, like educational achievement, full-time employment, and a healthy level of physical activity.³⁰ No previous analyses of the CCSS data have compared differences in health status and participation outcomes between upper and lower extremity sarcoma survivors, nor have they evaluated in detail whether or not the mechanisms used for local control in this survivor population influences these health status or participation in life roles. **This proposal aims to compare health status and participation outcomes between upper and lower extremity sarcoma survivors, and to examine the influence of the type of local control on these outcomes. We also aim to look at health status and participation outcomes longitudinally in this population. Specifically; we aim to determine if the trajectory of health status or participation varies as a function of whether or not the original tumor was located in the upper or lower extremity.**

2Study population:

Study participants will include individuals in the original CCSS survivor cohort with either a bone or soft tissue sarcoma located in the upper (including the scapular and clavicular areas) or the lower (including the sacrum and pelvis) extremity. The analyses will be limited to those who were alive and who completed the baseline, 2003, and/or 2007 questionnaires, and who consented to medical record abstraction. Site codes (from ICD-O2) C40.0, C40.1, C40.2, C40.3, C40.8, C40.9, C49.1, C49.2, C49.3, C49.5 from diagnosis categories “soft tissue sarcoma” and “bone tumor” will be used to select participants. The most recent data freeze includes 1094 individuals from the baseline questionnaire, 813 from follow-up 2003, and 712 from follow-up 2007. Of these individuals, 661 completed all three questionnaires and will be included in the longitudinal analysis described below.

3Methods:

3.1This proposal addresses health status outcomes among pediatric sarcoma survivors and will be divided into two sections, each with specific aims, separate hypothesis and statistical approaches.

3.2Analysis 1: Health status outcomes among upper and lower extremity sarcoma survivors. We are interested in: 1) Reporting the prevalence of poor health status and participation among upper extremity and lower extremity pediatric sarcoma survivors as reported on three different questionnaires (baseline, follow-up 2003, follow-up 2007); 2) Comparing the prevalence of poor health status and participation outcomes between upper and lower extremity sarcomas using observations from all time points; and 3) Evaluating the influence of local control status outcomes among upper and lower extremity sarcoma survivors.

3.3Analysis 2: Longitudinal evaluation of health status among pediatric sarcoma survivors. We are interested in evaluating health status and participation outcomes over time among pediatric sarcoma survivors to see if the trajectory varies as a function of whether the tumor is located in the upper or the lower extremity.

4Analysis 1: Overall Health Status Outcomes in Sarcoma Survivors

4.1Aims and Hypotheses

4.1.1Aim 1: Compare the general health, mental health, activity limitations, functional impairments, pain and anxiety between upper extremity and lower extremity sarcoma survivors.

4.1.1.1Hypothesis 1: Upper extremity sarcoma survivors will have different prevalence rates for poor health status outcomes than lower extremity sarcoma survivors.

4.1.2Aim 2: Compare the educational achievement, employment status, income, marital status and physical activity levels between upper extremity and lower extremity sarcoma survivors.

4.1.2.1Hypothesis 2: Upper extremity sarcoma survivors will have different prevalence rates for participation restrictions than lower extremity sarcoma survivors.

4.1.3Aim 3: Evaluate the impact of local control measures on general health, mental health, activity limitations, functional impairments, pain and anxiety among extremity sarcoma survivors.

4.1.3.1Hypothesis 3: Predictors of poor health status outcomes will include local control measures in a dose response fashion. Those with more extreme amputation and higher maximum radiation doses will have a higher prevalence of poor outcomes.

4.1.4 Aim 4: Evaluate the impact of local control measures on achievement, employment status, income, marital status and physical activity levels among extremity sarcoma survivors.

4.1.4.1 Hypothesis 4: Predictors of participation restrictions will include local control measures in a dose response fashion. Those with more extreme amputation and higher maximum radiation doses will have a higher prevalence of poor outcomes.

4.2 Analysis Framework

4.2.1 Outcomes of interest

4.2.1.1 Domains of Health Status

4.2.1.1.1 General Health (J35 BL, E1 FU2003, L19 FU2007)

4.2.1.1.2 Mental Health (J16-J35 BL, G1-G18 FU2003, L1-L18 FU2007)

4.2.1.1.3 Functional Impairment (N10-N12 BL, E12, E15, E16 FU2003, N22-N24 FU2007)

4.2.1.1.4 Activity Limitations (N14 b,c,e BL, E4-E6, E11 FU2003, N26 b,c,e FU2007)

4.2.1.1.5 Pain (J36 BL, G19 FU2003, L21 FU2007)

4.2.1.1.6 Anxiety (J37 BL, G20 FU2003, L20 FU2007)

4.2.1.2 Participation Outcomes

4.2.1.2.1 Educational Attainment (O1 BL, 1 FU2003, A3 FU2007)

4.2.1.2.2 Employment (O5-6 BL, 4 FU2003, A4 FU2007)

4.2.1.2.3 Marital Status (L2 BL, 2 FU2003, M2 FU2007)

4.2.1.2.4 Personal Income (Q9 BL, S3 FU2003, A8 FU2007)

4.2.1.2.5 Physical Activity (N9 BL, D1-7 FU2003, N15-21 FU2007)

4.2.2 Exploratory Variables

4.2.2.1 Tumor location (upper or lower extremity)

4.2.2.2 Local Control Mechanisms

4.2.2.2.1 Radiation (maximum dose to the limb)

4.2.2.2.2 Amputation type

4.2.3 Potential Confounders and effect modifiers

4.2.3.1.1 Tumor type

4.2.3.1.2 Gender

4.2.3.1.3 Race/Ethnicity

4.2.3.1.4 Age at diagnosis

4.2.3.1.5 Current age

4.2.3.1.6 Time from diagnosis to questionnaire completion

4.2.3.1.7 Chemotherapy for primary disease

4.2.3.1.7.1 Anthracycline dose/score

4.2.3.1.7.2 Alkylating agent dose/score

4.2.3.1.7.3 Platinum dose/score

4.2.3.1.7.4 Vincristine (yes/no)

4.2.3.1.8 Chest radiation (yes/no)

4.2.3.1.9 Abdominal radiation (yes/no)

4.2.3.1.10Surgical procedure on lung excluding biopsy

4.2.4**Statistical approach:** Outcomes will be dichotomized to define “adversely” affected individuals as follows:

4.2.4.1Poor general health - answers fair or poor vs. good, very good or excellent

4.2.4.2Poor mental health – score of 63 or higher on the brief symptom inventory on any of the three subscales vs. no score of 63 or higher on any of the three subscales of the Brief symptom Inventory

4.2.4.3Functional impairment – answers yes to any of the three questions vs. answers no to all three questions listed in 4.2.1.1.3 above

4.2.4.4Activity limitation – answers limited for more than three months over the past two years to any of the three questions vs. does not answer limited for more than three months over the past two years to any of the three questions listed in 4.2.1.1.4 above

4.2.4.5Pain – answers a lot of or very bad excruciating pain vs. no, small amount or medium amount of pain

4.2.4.6Anxiety – answers a lot or very many/extreme anxiety/fears vs. no, small or medium amount of anxiety/fears

4.2.4.7High school graduate yes vs. no

4.2.4.8Unmarried vs. married

4.2.4.9Annual household income \leq \$20,000 vs. annual household income $>$ \$20,000

4.2.4.10Participated in physical activity in past month vs. did not participate in physical activity in past month

4.2.5Using observations from all time points, generalized estimating equations with a binomial distribution and a log link will be used to compare prevalence rates of poor health status and participation restrictions between upper and lower extremity sarcoma survivors in the cohort, and to evaluate the impact of local control mechanisms on the outcome. Models will include a repeated statement and exchangeable correlation matrix to account for within participant correlation, utilizing robust variance estimates for inference. Initial models will be adjusted for age, gender, race and time since diagnosis. Models that examine the impact of local control mechanisms will be stratified by tumor site and additionally adjusted for chemotherapy, chest radiation and surgical procedure on the lung.

5Analysis 2: Longitudinal Health Status Outcomes in Sarcoma Survivors

5.1Aims and Hypotheses

5.1.1Aim 1: Compare changes in the general health, mental health, activity limitations, functional impairments, pain and anxiety between upper extremity and lower extremity sarcoma survivors over time.

5.1.1.1 **Hypothesis 1:** Upper extremity sarcoma survivors will have less deterioration in health status over time than will lower extremity sarcoma survivors.

5.1.2 **Aim 2:** Compare changes in employment status, income, marital status and physical activity levels between upper extremity and lower extremity sarcoma survivors over time.

5.1.2.1 **Hypothesis 2:** Upper extremity sarcoma survivors will have smaller declines in participation outcomes than lower extremity sarcoma survivors.

5.2 Analysis Framework

5.2.1 Outcomes of interest

5.2.1.1 Domains of Health Status

5.2.1.1.1 General Health (J35 BL, E1 FU2003, L19 FU2007)

5.2.1.1.2 Mental Health (J16-J35 BL, G1-G18 FU2003, L1-L18 FU2007)

5.2.1.1.3 Functional Impairment (N10-N12 BL, E12, E15, E16 FU2003, N22-N24 FU2007)

5.2.1.1.4 Activity Limitations (N14 b,c,e BL, E4-E6, E11 FU2003, N26 b,c,e FU2007)

5.2.1.1.5 Pain (J36 BL, G19 FU2003, L21 FU2007)

5.2.1.1.6 Anxiety (J37 BL, G20 FU2003, L20 FU2007)

5.2.1.2 Participation Outcomes

5.2.1.2.1 Educational Attainment (O1 BL, 1 FU2003, A3 FU2007)

5.2.1.2.2 Employment (O5-6 BL, 4 FU2003, A4 FU2007)

5.2.1.2.3 Marital Status (L2 BL, 2 FU2003, M2 FU2007)

5.2.1.2.4 Personal Income (Q9 BL, S3 FU2003, A8 FU2007)

5.2.1.2.5 Physical Activity (N9 BL, D1-7 FU2003, N15-21 FU2007)

5.2.2 Exploratory Variables

5.2.2.1 Tumor location (upper or lower extremity)

5.2.3 Potential Confounders and effect modifiers

5.2.3.1.1 Gender

5.2.3.1.2 Race/Ethnicity

5.2.3.1.3 Age at diagnosis

5.2.3.1.4 Current age

5.2.3.1.5 Time from diagnosis to questionnaire completion

5.2.4 **Statistical approach:** Generalized estimating equations will also be used to evaluate the difference between upper and lower extremity sarcoma survivors in change in the prevalence of poor health status and participation outcomes over time. A binomial distribution with a log link will be assumed in order to directly estimate relative risks, or prevalence ratios. Models will include a repeated statement to account for within participant correlation. Initial models will include data from all three time points and will evaluate whether the impact on the

outcome of changing time is different for upper versus lower extremity sarcoma survivors via interaction terms between time since diagnosis and tumor location. Models will be adjusted for age, gender, race. Model diagnostics will be used to evaluate the appropriate functional form required for the time variable in the model (i.e. linear, or more flexible spline or simply categorical factors). Adjusted models will be used to create figures depicting the change in predicted prevalence over time for each group.

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Table 1. Characteristics of the study population

	All sarcoma survivors		Upper Extremity (N=)		Lower Extremity (N=)		p-value *
	N	%	N	%	N	%	
Gender							
Male							
Female							
Race/Ethnicity							
Black							
Hispanic							
White							
Other							
Age at diagnosis (years)							
0-4							
5-9							
10-14							
15-20							
Age at cohort entry (years)							
<20							
20-29							
30-39							
40-49							
Survival time at cohort entry (years)							
5-9							
10-14							
15-19							
20-24							
25-30							
30+							
Age at 2003 questionnaire (years)							
<20							
20-29							
30-39							
40-49							
50+							
Survival time at 2003 questionnaire (years)							
5-9							
10-14							
15-19							
20-24							

25+							
30+							
Age at 2007 questionnaire (years)							
<20							
20-29							
30-39							
40-49							
50+							
Survival time at 2007 questionnaire (years)							
5-9							
10-14							
15-19							
20-24							
25-30							
30+							
Diagnosis							
Ewing sarcoma							
Osteosarcoma							
Soft tissue sarcoma							
Treatment							
Anthracline dose							
Alkylating agent dose							
Platinum dose							
Vincristine							
None							
Any							
Chest radiation							
None							
Any							
Abdominal radiation							
None							
Any							
Thoracotomy							
Yes							
No							
Local control							
Surgery							
Biopsy only							
Tumor resection without reconstruction							
Limb sparing soft tissue only							
Limb sparing including bone							
Amputation							

Forequarter							
Above elbow							
Below elbow							
Hemipelvectomy							
Above knee							
Below knee							
Radiation dose (max)							

* From chi-square statistics

Table 2. Poor Health status among sarcoma survivors by location of primary tumor and time since diagnosis

	Total (N=)	General health		Mental Health		Functional impairment		Activity Limitation		Pain		Anxiety	
		N	%	N	%	N	%	N	%	N	%	N	%
Tumor location													
Upper extremity													
Lower extremity													
Time since diagnosis (years)													
5-9													
10-14													
15-19													
20-24													
25-20													
30+													
Age (years)													
<20													
20-29													
30-39													
40-49													
50+													
Gender													
Female													
Male													
Race/ethnicity													
Black													
Hispanic													
White													
Other													
Tumor type													
Ewing sarcoma													
Osteosarcoma													
Soft tissue sarcoma													

Table 3. Participation restrictions among sarcoma survivors by location of primary tumor and time since diagnosis (limited to those aged 25+ years at evaluation)

	Total (N=)	Did not graduate from high school		Unemployed		Not married or living as married		Personal Income < \$20,000/year		No physical activity in past month	
		N	%	N	%	N	%	N	%	N	%
Tumor location											
Upper extremity											
Lower extremity											
Time since diagnosis (years)											
5-9											
10-14											
15-19											
20-24											
25-20											
30+											
Age (years)											
<20											
20-29											
30-39											
40-49											
50+											
Gender											
Female											
Male											
Race/ethnicity											
Black											
Hispanic											
White											
Other											
Tumor type											
Ewing sarcoma											
Osteosarcoma											
Soft tissue sarcoma											

Table 4. Relative risk of reporting poor health status among sarcoma survivors by location of primary tumor and time since diagnosis

	General health		Mental Health		Functional impairment		Activity Limitation		Pain		Anxiety	
	RR	95% CI	RR	95% CI	RR	95% CI	RR	95% CI	RR	95% CI	RR	95% CI
Tumor location												
Upper extremity												
Lower extremity												
Time since diagnosis (years)												
5-9												
10-14												
15-19												
20-24												
25-20												
30+												
Age (years)												
<20												
20-29												
30-39												
40-49												
50+												
Gender												
Female												
Male												
Race/ethnicity												
Black												
Hispanic												
White												
Other												
Tumor type												
Ewing sarcoma												
Osteosarcoma												
Soft tissue sarcoma												

*Adjusted for within person correlation

Table 5. Relative risk of reporting participation restrictions among sarcoma survivors by location of primary tumor and time since diagnosis (limited to those aged 25+ years at evaluation)

	Did not graduate from high school		Unemployed		Not married or living as married		Personal Income < \$20,000/year		No physical activity in past month	
	RR	95% CI	RR	95% CI	RR	95% CI	RR	95% CI	RR	95% CI
Tumor location										
Upper extremity										
Lower extremity										
Time since diagnosis (years)										
5-9										
10-14										
15-19										
20-24										
25-20										
30+										
Age (years)										
<20										
20-29										
30-39										
40-49										
50+										
Gender										
Female										
Male										
Race/ethnicity										
Black										
Hispanic										
White										
Other										
Tumor type										
Ewing sarcoma										
Osteosarcoma										
Soft tissue sarcoma										

*Adjusted for within person correlation

Table 6. Poor Health status among sarcoma survivors by tumor location, local control and primary cancer therapy

	Total (N=)	General health		Mental Health		Functional impairment		Activity Limitation		Pain		Anxiety	
		N	%	N	%	N	%	N	%	N	%	N	%
Tumor location													
Upper extremity													
Lower extremity													
Local control													
Surgery													
Biopsy only													
Tumor resection													
Limb sparing soft tissue													
Limb sparing including bone													
Amputation													
Forequarter													
Above elbow													
Below elbow													
Hemipelvectomy													
Above knee													
Below knee													
Maximum radiation dose (tertiles)													
Treatment													
Anthracine dose (tertiles)													
Alkylating agent dose (tertiles)													
Platinum dose (tertiles)													
Vincristine													
None													
Any													
Chest radiation													
None													
Any													
Abdominal radiation													
None													
Any													
Thoracotomy													
Yes													
No													

Table 7. Participation restrictions among sarcoma survivors by tumor location, local control and primary cancer therapy (limited to those aged 25+ years at evaluation)

	Total (N=)	Did not graduate from high school		Unemployed		Not married or living as married		Personal Income < \$20,000/year		No physical activity in past month	
		N	%	N	%	N	%	N	%	N	%
Tumor location											
Upper extremity											
Lower extremity											
Local control											
Surgery											
Biopsy only											
Tumor resection											
Limb sparing soft tissue											
Limb sparing including bone											
Amputation											
Forequarter											
Above elbow											
Below elbow											
Hemipelvectomy											
Above knee											
Below knee											
Maximum radiation dose (tertiles)											
Treatment											
Anthracine dose (tertiles)											
Alkylating agent dose (tertiles)											
Platinum dose (tertiles)											
Vincristine											
None											
Any											
Chest radiation											
None											
Any											
Abdominal radiation											
None											
Any											
Thoracotomy											
Yes											
No											

Table 8. Relative risk of reporting poor health status among sarcoma survivors by location, local control and primary cancer therapy

	General health		Mental Health		Functional impairment		Activity Limitation		Pain		Anxiety	
	RR	95% CI	RR	95% CI	RR	95% CI	RR	95% CI	RR	95% CI	RR	95% CI
Tumor location												
Upper extremity												
Lower extremity												
Local control												
Surgery												
Biopsy only												
Tumor resection												
Limb sparing soft tissue												
Limb sparing including bone												
Amputation												
Forequarter												
Above elbow												
Below elbow												
Hemipelvectomy												
Above knee												
Below knee												
Maximum radiation dose (tertiles)												
Treatment												
Anthracine dose (tertiles)												
Alkylating agent dose (tertiles)												
Platinum dose (tertiles)												
Vincristine												
None												
Any												
Chest radiation												
None												
Any												
Abdominal radiation												
None												
Any												
Thoracotomy												
Yes												
No												

*Adjusted for within person correlation, time since diagnosis, age, gender, race/ethnicity

Table 9. Relative risk of reporting participation restrictions among sarcoma survivors by tumor location, local control and primary cancer therapy (limited to those aged 25+ years at evaluation)

	Did not graduate from high school		Unemployed		Not married or living as married		Personal Income < \$20,000/year		No physical activity in past month	
	RR	95% CI	RR	95% CI	RR	95% CI	RR	95% CI	RR	95% CI
Tumor location										
Upper extremity										
Lower extremity										
Local control										
Surgery										
Biopsy only										
Tumor resection										
Limb sparing soft tissue										
Limb sparing including bone										
Amputation										
Forequarter										
Above elbow										
Below elbow										
Hemipelvectomy										
Above knee										
Below knee										
Maximum radiation dose (tertiles)										
Treatment										
Anthracine dose (tertiles)										
Alkylating agent dose (tertiles)										
Platinum dose (tertiles)										
Vincristine										
None										
Any										
Chest radiation										
None										
Any										
Abdominal radiation										
None										
Any										
Thoracotomy										
Yes										
No										

*Adjusted for within person correlation, time since diagnosis, age, gender, race/ethnicity

Figures (will have six panels for health status and five panels for participation outcomes)

Proportion of those with poor health status over time by tumor location – will put relative risk on figure comparing upper extremity to lower extremity at each time point and for trend – will only include those who completed all three questionnaires for this analysis – will adjust these models at least for time since diagnosis and age. A potential alternative figure may be developed illustrating how prevalence changes as a function of time since diagnosis using predicted probabilities from the multivariable model.

