CHILDHOOD CANCER SURVIVOR STUDY
ANALYSIS CONCEPT PROPOSAL

Project Title: Neurocognitive functioning in survivors of osteosarcoma

Working Group: Psychology

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Background and Rationale

Methotrexate is a chemotherapy agent used widely in the treatment of childhood cancers, but much of the research regarding its neuropsychological effects have focused on survivors with acute lymphoblastic leukemia (ALL) [1, 2]. The drug is linked to (1) acute neurotoxicity with associated neuroimaging findings, and (2) significant neurocognitive impairment [3-9]. Long-term functional deficits can occur in the domains of executive function, sustained attention, memory, processing speed, visual-motor integration, and fine motor dexterity [10]. The drug has additionally been associated with learning deficits in math and reading and diminished IQ [11-13]. Osteosarcoma patients are exposed to methotrexate at four- to five-fold higher cumulative doses during treatment compared to ALL patients [14]. While it was previously believed that these survivors were spared these late effects because of their older age of exposure, research demonstrating long-term neurocognitive deficits in adult breast cancer survivors treated with methotrexate suggests this may not be the case [15]. The population of osteosarcoma survivors remains understudied for long-term neurocognitive outcomes [14, 16].

The biological basis for the neurotoxic effects of methotrexate is thought to be multifactorial with contributions from direct toxic effect to astrocytes and neurons, as well as disruption of multiple biochemical pathways leading to metabolic imbalances including elevated homocysteine levels [17]. Methotrexate is associated with cortical atrophy, necrotizing leukoencephalopathy, subacute myeloencephalopathy, mineralizing angiopathy, and cerebellar sclerosis [18]. In osteosarcoma patients specifically, acute neurotoxicity has included seizures, paresis, aphasia, cortical blindness, and behavioral changes [19]. Neuroimaging studies in patients with acute encephalopathy following methotrexate treatment often show altered diffusivity in brain white matter on diffusion-weighted imaging during the acute episode [20].

Moreover, MRI can continue to show residual T2 abnormalities even after neurological findings have resolved [20].

There is also compelling evidence suggesting a possible link between chronic health conditions and neurocognitive impairment in both survivors of Hodgkin's lymphoma and osteosarcoma [14, 21]. Specifically, osteosarcoma survivors with grade 3 or 4 Common Terminology Criteria for Adverse Events chronic health conditions had poorer memory and processing speed compared to survivors with < grade 3 conditions [14]. Osteosarcoma patients are often treated with anthracyclines, bleomycin, and alkylating agents which have been associated with cardiac, pulmonary, and endocrine morbidities [22].

The Childhood Cancer Survivor Study presents a unique opportunity to study neurocognitive late effects in osteosarcoma survivors because there is uniform ascertainment of these measures using standardized instruments for a large sample of survivors. It provides appropriate control groups to study comparison to a typically developing sample (i.e. siblings) as well as to survivors who underwent a similar duration of intensive in-patient therapy but did not receive methotrexate (i.e. Ewing sarcoma survivors).

Proposed Specific Aims

Our specific aims are to:

(1) Determine the prevalence and patterns of neurocognitive impairment in osteosarcoma survivors in the CCSS.

(2) Compare the risk of neurocognitive impairment in osteosarcoma survivors to age- and gender-adjusted siblings and Ewing sarcoma survivors.

(3) Identify patient and treatment factors associated with worse impairment in osteosarcoma survivors.

(4) Identify current chronic health conditions associated with worse impairment in osteosarcoma survivors.

Hypothesis

(1) Osteosarcoma survivors will report increased neurocognitive impairment compared to siblings and to age- and gender-adjusted Ewing sarcoma survivors

(2) More severe impairment will be associated with increased doses of methotrexate, anthracyclines, and chest radiation, as well as the presence of current chronic health conditions (Grade 2+ for cardiac, pulmonary, or endocrine).

Methods

Study population

Osteosarcoma and Ewing sarcoma survivors in the Childhood Cancer Survivor Study diagnosed from 1970 to 1986, along with sibling controls, who completed the CCSS-Neurocognitive Questionnaire (CCSS-NCQ) in Follow Up 2 Survey in 2003.

Outcome Variables

The primary outcome will be the CCSS-NCQ, a 25-item questionnaire developed by the Childhood Cancer Survivor Study to assess cognitive and emotional functioning in areas commonly affected by cancer therapy [23]. For each item, patients were asked to report the frequency with which they experienced the problem over the last 6 months on a Likert scale ranging from 1 ("Never a problem") to 3 ("Often a problem"). This tool examines the four domains of task efficiency, emotional regulation, organization, and memory, and has been previously validated in a CCSS sample [23].

- CCSS-NCQ corresponds to questions J.1 – J.25 on Follow-Up 2 survey in 2003.
- Similar to a previous CCSS paper using this instrument in a larger sample of non-CNS cancer survivors [16], we will examine continuous scores and frequency of impairment in each domain, with impairment defined as scores corresponding to 1.3 standard deviation above the mean for the sibling group's score (approximately the worst 10% of siblings' scores as higher scores indicate worse impairment).

As secondary outcomes, we will analyze the following:

- Education (special education resources and highest level [less than high school vs. high school diploma vs. some college vs. college graduate])
    - Special education (yes vs. no; reason for special education) corresponds to question O.3 on the Baseline survey for the original cohort
    - Highest level of education corresponds to question A.3 on the Follow-up 4 survey in 2007
- Employment (current employment status [working full-time vs. working part-time vs. caring for home or family vs. unemployed and looking for work vs. unable to work due to illness or disability vs. retired vs. student vs. other])
    - Employment corresponds to question A.4 on the Follow-up 4 survey in 2007

Predictor variables

We will use from the Baseline survey date of birth, sex, and race/ethnicity. Cancer treatment information from medical record abstraction for each survivor will be obtained, including date of diagnosis, chemotherapy (yes/no and cumulative dose), radiation therapy (yes/no, dose, and site), surgery (yes/no). For chemotherapy, we will specifically examine whether survivors received methotrexate and/or anthracyclines. For radiation sites, we will specifically examine chest/neck (average dose). For surgery, we will specifically examine whether surgery was limb-sparing vs. amputation. We will also collect information for each survivor on whether or not they have any CTCAE grade 2+ cardiac, endocrine, or pulmonary condition from the CCSS master matrix for chronic conditions.

Data Analysis Plan

We will calculate descriptive statistics for demographic and treatment variables for osteosarcoma survivors, Ewing sarcoma survivors and siblings who have completed the CCSS-NCQ. These statistics will be compared between osteosarcoma survivors vs. Ewing sarcoma survivors, and

osteosarcoma survivors vs. siblings with generalized linear models, using identity or log-binomial link functions, for continuous and binary outcomes, respectively. Generalized estimating equations will be used for the sibling comparison to account for potential within-family correlation [24].

For each domain of the CCSS-NCQ, we will compare osteosarcoma survivors vs. Ewing sarcoma survivors and osteosarcoma survivors vs. siblings both with 1) mean scores and standard deviations, as well as 2) percentages of individuals with scores in a low functioning or impaired range (defined as falling within the worst 10% range of siblings' scores). We will use multivariable log-binomial regression with adjustment for demographic factors that differ between groups. For comparing mean scores on each domain of the CCSS-NCQ between osteosarcoma survivors and siblings, we will use generalized estimating equations to account for potential within-family correlation [24].

Log-binomial models will be used to assess the association of patient and treatment factors on cognitive and behavioral outcomes for the osteosarcoma survivors. Prevalence ratios for impairment in subgroups of survivors compared with the referent group will be reported with corresponding 95% confidence intervals, based on standard large sample inference method for generalized linear models. SAS version 9.4 (SAS Institute, Cary, NC) will be used to conduct all analyses. Within the original cohort, we will use univariate binomial regression to examine the relative risk of poor adult education and employment outcomes using each BPI domain as a predictor.

Appendix. Skeleton Tables and Figures

Table 1. Participant Characteristics

Characteristic	**Osteosarcoma survivors**		**Ewing sarcoma survivors**		**Siblings**	
	# (%)	P	# (%)	p	# (%)	p
Sex Female Male						
Race/ethnicity White Black Hispanic Other						
Age at diagnosis, years	y +/- mean (range)		y +/- mean (range)		N/A	N/A
Age at evaluation	y +/- mean (range)		y +/- mean (range)		y +/- mean (range)	
Highest Education Less than high school High school diploma Some college College degree						
Treatment Chemotherapy without RT RT without chemotherapy Chemotherapy and RT No chemotherapy or RT					N/A	N/A

Table 2. Comparison of self-reported neurocognitive outcomes between osteosarcoma survivors, Ewing sarcoma survivors, and siblings

Group		**Task Efficiency**				**Organization**				**Memory**				**Emotional Regulation**			
	No.	Mean (SD)	p	% impaired*	p	Mean (SD)	p	% impaired	p	Mean (SD)	p	% impaired	p	Mean (SD)	p	% impaired	p
Siblings																	
Osteosarcoma survivors																	
Ewing sarcoma survivors																	

*Impaired is defined as 1.3 standard deviations above the mean for the sibling group's mean score for all domains.

Table 3. Association of patient and treatment factors with self-reported neurocognitive impairment among osteosarcoma survivors: univariate analysis

Patient or Treatment Factor	**Task Efficiency**			**Organization**			**Memory**			**Emotional Regulation**		
	%	PR (95% CI)	p	%	PR (95% CI)	p	%	PR (95% CI)	p	%	PR (95% CI)	p
Sex Male Female												
Ethnicity White Other												
Age at diagnosis (years) 0 – 4.99 5 – 9.99 10 – 14.99 15 - 18												
Surgery None Limb-sparing Amputation												
Chemotherapy Yes No												
Cumulative methotrexate dose*												
Cumulative anthracycline dose (mg/m^2)*												
Maximum radiation dose to chest/neck None 1 – 19.9 Gy^2 20 – 29.9 Gy^2 ≥30 Gy^2												

Any vascular toxic treatment (anthracycline and/or chest/neck radiation) Yes No												
Current chronic health condition (Grade 2 or higher for cardiac, pulmonary, endocrine) Yes No												

*For methotrexate and anthracyclines, we will obtain the distribution of cumulative dose as a continuous variable and then analyze these variables categorically using either tertiles or quartiles (decided after examining the range and distribution of these values).

Table 4. Association of patient and treatment factors with self-reported neurocognitive impairment among osteosarcoma survivors: multivariate analysis

Patient or Treatment Factor	**Task Efficiency**			**Organization**			**Memory**			**Emotional Regulation**		
	%	PR (95% CI)	p	%	PR (95% CI)	p	%	PR (95% CI)	p	%	PR (95% CI)	p

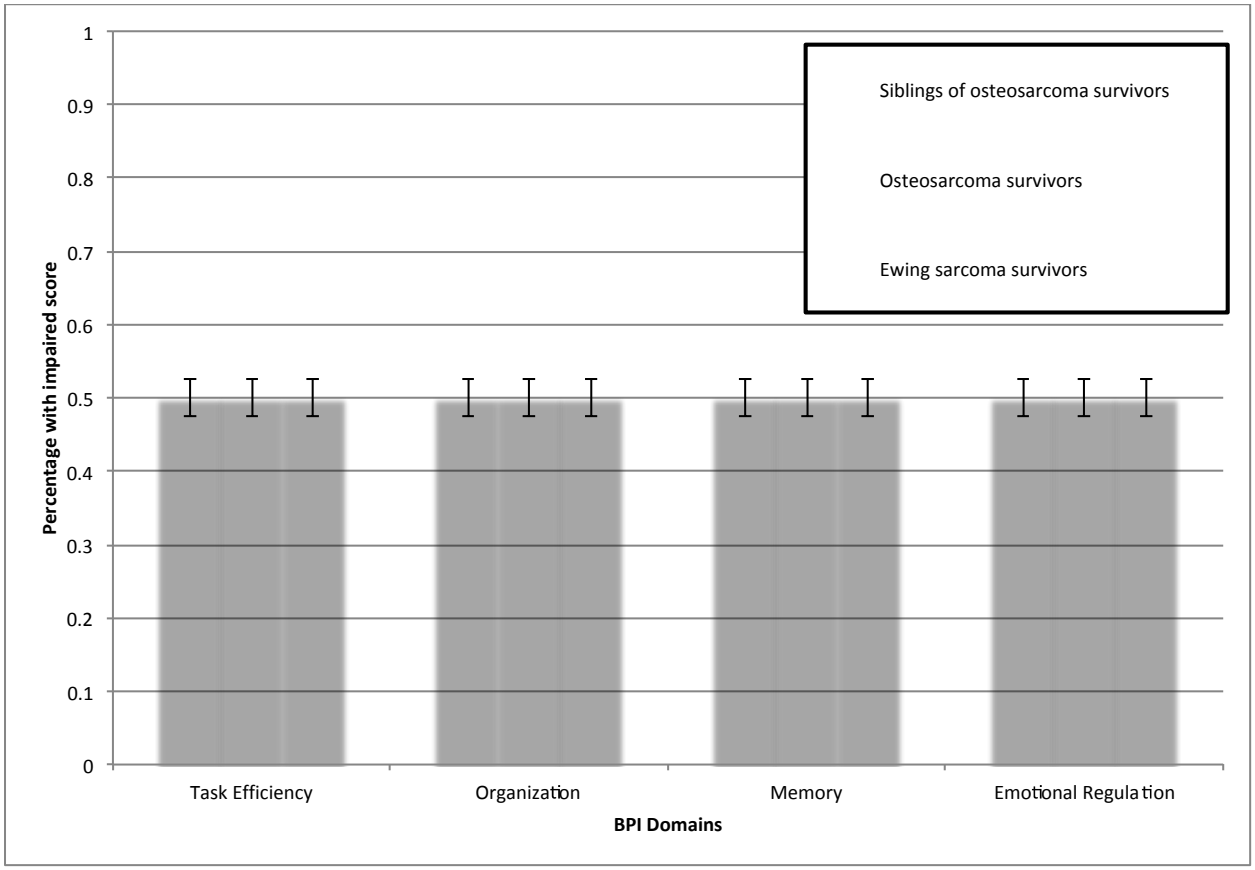
**Please note that this table will be constructed with backwards-stepwise regression, using variables significant at p<0.20 in Table 3.*

Table 5. Relative risk of use of special education services, educational attainment and employment in osteosarcoma survivors, based on impairment* in neurocognitive functioning

Cognitive and Behavioral Functioning as measured by the BPI	**Use of special education services**			**Educational attainment of some college or higher**			**Current Employment**		
	No (%)	**RR**	**p**	**No (%)**	**RR**	**p**	**No (%)**	**RR**	**p**
Task Efficiency Impaired No impairment									
Organization Impaired No impairment									
Memory Impaired No impairment									
Emotional Regulation Impaired No impairment									

*Impaired is defined as 1.3 standard deviations above the mean for the sibling group's mean score for all domains.

Figure 1. Percentages and 95% confidence intervals of impairment in neurocognitive domains in osteosarcoma survivors compared with Ewing sarcoma survivors and siblings. Impaired function is defined as 1.3 standard deviations above the mean for the sibling group's mean score.



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