Childhood Cancer Survivor Study
Analysis Concept Proposal

Title: Cognitive and academic difficulties in rhabdomyosarcoma survivors: A report from the Childhood Cancer Survivor Study

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Background: Rhabdomyosarcoma is the most common malignant soft-tissue tumor in the pediatric population. These tumors can develop anywhere in the body, but the most common primary sites are the head and neck (35%), the pelvis and genitourinary tract (26%), and the extremities (19%) (Crist et al, 1995). Standard treatment includes surgical resection, systemic chemotherapy, and radiation therapy.

Radiation therapy is a key component of treatment for rhabdomyosarcomas that cannot be fully resected, as is the case with many tumors of the head and neck. However, radiation to the brain is known to cause neurocognitive side effects, such as deficits in intelligence, memory, attention, and executive function, especially in young children (e.g., Spiegler et al, 2006; Harila et al., 2009). Importantly, such neurocognitive deficits appear to cause academic difficulties (Mitby et al., 2003).

Although extensive work has been done exploring the impact of radiation on long term cognitive function in diseases such as leukemia and brain tumors, studies examining the effects of radiation on survivors of rhabdomyosarcoma have been limited. However, cognitive late effects have been observed in survivors of childhood rhabdomyosarcoma. Heyn et al. (1986) reported late effects of therapy in 50 survivors of childhood orbital rhabdomyosarcoma who were treated on the Intergroup Rhabdomyosarcoma Study (IRS)-I protocol (1972-1978). Details were limited, but 10% were reported to have school difficulties.

Raney et al. (1999) wrote a descriptive review of 213 relapse-free survivors of localized soft tissue sarcomas of the head and neck treated on the IRS-II (1978-1984) and IRS-III (1984-1987) protocols. All patients were treated with systemic chemotherapy, and patients with signs of meningeal impingement were also given intrathecal chemotherapy. Patients with known residual disease received high doses of radiation therapy (40-50 Gy total) to the primary tumor site. Patients whose tumors showed signs of meningeal impingement received whole-brain radiation of 24-30 Gy. Of the 71 patients whose records provided information about schooling, 35 (49%) were reported to have various learning disabilities. Twenty-two of these patients had received whole-brain radiation and 16 of them had also received intrathecal chemotherapy. These data indicate that survivors of soft tissue sarcoma of the head and neck may be at risk for significant morbidity from their treatment, though the impact of this morbidity on advancement to higher levels of education and employment is unknown.

A study by Paulino et al. (2000) examined the late effects of therapy in 17 survivors of head and neck rhabdomyosarcomas who were treated at a single institution from 1967 through 1994. All patients received systemic chemotherapy and high doses of radiotherapy (41-65 Gy, median 50 Gy) to the primary tumor site, and 15 of them had a portion of the brain within the radiation field. Three of the 15 patients (20%) were noted to have delayed intellectual and academic achievement, one of whom required special education services. All three of these patients had received whole brain radiation and intrathecal chemotherapy.

Thus, there is evidence that survivors of head and neck rhabdomyosarcomas develop adverse neurocognitive effects from their radiation therapy. However, our understanding of the variables that specifically impact this population are lacking. There has been no substantive attempt to examine which clinical variables may influence the cognitive outcome of this population, primarily due to the limited number of patients studied and their limited follow-up. Furthermore, details regarding radiation therapy and its influence on neurocognitive outcome have not been examined in any significant fashion, although dosage and radiation exposure to different regions of the brain would likely affect intellectual outcome and quality of life (QOL) for these survivors. This has particular significance given the recent advances of radiation therapy and the development of techniques of confocal radiation and most recently proton beam radiation. An understanding of the influence of radiation on the outcome of these patients could lead to treatment modifications to limit radiation exposure in critical regions of the brain and potentially impact the outcome of these patients in a substantial way. The goal of this study is to use data from the CCSS to better characterize the cognitive, academic, and QOL late effects of treatment for patients with head and neck rhabdomyosarcomas.

Specific aims:

Primary aim:

1. To describe the neurocognitive, emotional, and health-related quality of life outcomes of survivors with rhabdomyosaroma as compared to siblings.

Secondary aims:

1. To identify diagnostic and treatment variables associated with neurocognitive, emotional, and health-related quality of life outcomes in survivors of rhabdomyosarcoma.
2. To examine whether the primary tumor site influences the long-term impact of neurocognitive, emotional and health-related quality of life outcomes on this population.

Hypotheses:

1. Survivors of rhabdomyosarcoma have higher rates of neurocognitive and psychological impairment and lower reported health-related quality of life compared to siblings.
2. The risk and severity of the neurocognitive and psychologic sequelae and differences in QOL correlate to the dose and location (as coded by the CCSS to specific regions of the brain) of radiation therapy
3. Survivors of rhabdomyosarcoma who were treated for head/neck tumors will have higher rates of neurocognitive and psychological impairment and lower reported health-related quality of life compared to rhabdomyosarcoma survivors with primary tumors located in other parts of the body.

Rationale for the hypotheses: Various studies have demonstrated the adverse effect of radiation on neurocognitive functioning, psychological outcomes and health-related quality of life. Radiation remains a central component of disease control for rhabdomyosaroma. Doses of radiation necessary to treat rhabdomyosaroma exceed doses observed to have an adverse

outcome in these areas. Thus, patients receiving radiation to treat head and neck primary tumors often have radiation exposure to the adjacent brain that may have a significant impact on the long-term outcomes of these patients.

Methods:
This proposal seeks to address the neuropsychological and QOL status of rhabdomyosaroma survivors compared to sibling controls. Significant differences in the disease and sibling control populations will be further analyzed to determine the impact of several variables listed below, including the impact of radiation dosage exposure to the brain.

Subjects: The study population will include all 421 survivors in the CCSS cohort with a confirmed diagnosis of rhabdomyosarcoma (ICD-O codes: 8900/3-rhabodomyosacrcoma; 8901/3-pleomorphic rhabdomyosarcoma; 8902/3-mixed type rhabdomyosarcoma; 8903/0-fetal rhabdomyosarcoma; 8904/0-adult rhabdomyoma (glycogenic rhabdomyoma); 8910/3-embryonal rhabdomyosarcoma (sarcoma botryoides, botryoid sarcoma); 8920/3-alveolar rhabdomyosarcoma) in the years 1970-1986, achieving five-year survival since diagnosis, with informed consent to participate in the CCSS. Sites of the primary disease will be acquired from the database established by Mueller et al (2014) which mapped CCSS cancer site codes (ICD-O-2 site codes to IRS site codes. (Orbit, Other Head and Neck, Parameningeal, GU, Bladder/prostate, Extremity, Retroperitoneum, All others). A sibling comparison group will include all siblings of CCSS who responded to the follow-up 2003 questionnaire.

Outcomes of interest: The primary outcomes of interest include neurocognitive functions as assessed by the Neurocognitive Questionnaire (NCQ) domains, emotional function as assessed by the Brief Symptom Inventory (BSI) scales, and health related quality of life (QOL) as measured by the Medical Outcomes Study SF-36 instrument (all contained within the Follow-up 2003 study). In addition, we wish to examine the impact of the treatment of these patients on educational attainment, employment, marital status, health insurance status, and household income.

Explanatory variables:

1. Primary diagnosis
2. Primary site of diagnosis (head/ neck versus non-head/neck)
3. Age at diagnosis (Baseline A2)
4. Age at Baseline Questionnaire
5. Age at 2003 Questionnaire
6. Length of follow-up
7. Gender (Baseline A2)
8. Race/ethnicity (Baseline A4, 4a)
9. Impairment of vision, hearing or speech (Baseline C1-19; sensory impairment yes/no)
10. Thyroid disease (Baseline E1-4; yes/no)

Treatment obtained from Medical Record Abstraction Form:

11. Chemotherapy (yes/no)
12. Intrathecal chemotherapy (Cytosine Arabinoside –IT, Methotrexate –IT)
13. Alkylator agents (BCNU, Busulfan, Carboplatin, Chlorambucil, Cis-platinum, CCNU, Cyclophosphamide, Ifosfamide, Melphalan, Nitrogen Mustard, Procarbazine, Thiotepa),calculated Alkylator Score derived by summing the tertiles of each drug received, as previously described (Mertens, AC et al., 2001)
14. Radiation dose will be derived from four anatomic regions of the brain which has been established for the CCSS cohort as previously described (Armstrong GT et al., 2010); cumulative doses of radiation will be divided into four distinct categories for analysis

(none, <30Gy, 30-49Gy, >/=50Gy), unless distribution requires collapsing dose into fewer categories

15. Surgery (yes/no) (site specific, particularly for surgical procedures involving the brain)
16. Anti-depressant and anti-anxiety medications (FU 2003, Section Q; yes/no)

Outcome variables:

1) CCSS NCQ: (Follow-Up 2003 section J) Task Efficiency, Emotional Regulation, Organization, Memory. Factor scores will be dichotomized based on whether the performance is considered "impaired" or not (Yes/No), with impairment defined as a performance falling ≤ 10th percentile based on sibling group norms.
2) BSI: 2003 Follow-up [questions G1 to G18]
Anxiety, Depression, Somatization. Factor scores will be dichotomized based on whether the performance is considered "impaired" or not (Yes/No), with impairment defined as a performance falling ≤ 10th percentile based on standardized norms.
3) SF-36:, (item #E1 through #E22 and #F1 through #F14 in both 2003 LTFU and 2003 LTFU Sibling), Physical function, Role limitation due to Physical Function, Bodily Pain, General Health, Vitality, Role limitation due to Emotional Function, Social Function, and the Mental Health scales will be converted into T-scores based on the norms in the standardization manual. These scores will then be dichotomized based such that scores falling below a T-score of 40 will be identified as being impaired.
4) Education (FU 2003, Q1)
5) Employment (FU 2003, Q4)
6) Marital Status (FU 2003, Q2, Q3)
7) Health Insurance Status (FU 2003 Section M)
8) Household Income (FU 2003 Section S)

Statistical methods:

Frequency distributions will be used to categorize relevant outcome variables, predictors and covariates according to reasonable groupings consistent with previous CCSS manuscripts. (table I).

Descriptive statistics (means, standard deviations, percents) will be calculated to describe survivor characteristics, including diagnosis and treatment factors. Descriptive statistics will be calculated for the primary outcome of interest (BSI, NCQ and health related QOL). Outcomes will be classified as impaired based on performance falling below 10%ile of reference norms. Descriptive statistics will also be examined for secondary outcomes (education, employment, marital status, health insurance and household income).

For the primary aim, comparisons of the primary outcome variables will be made between the RMS survivor cohort and the sibling cohort, adjusting for demographic characteristics identified through univariable modelling and which will be included in the adjusted models if their inclusion modifies the survivor versus sibling effect.

Among survivors, univariate logistic regression analyses will be conducted between possible explanatory variables and outcome variables (with separate analyses conducted for each NCQ, BSI and QOL factor). Those variables that are significant at $p<0.10$ will be evaluated in multivariable models. Multivariable logistic regression will then be conducted to identify which variables independently predict primary outcomes.

For the second objective, the multivariable analysis from above will be modified with the addition of a factor allowing comparison of outcomes between the groups of survivors defined by disease site (Orbit, Other Head and Neck, Parameningeal) designated “Head and Neck” (186 of the 421 subjects) with those defined by other locations (GU, Bladder/prostate, Retroperineum, Extremity, Other, Unknown) designated as “Non-Head and Neck”. These logistic regression models will be adjusted for demographic and treatment characteristics identified through the above modelling, which will be included if they are significant or if their inclusion modifies the location effect.

A third analysis will be conducted comparing the socio-demographic outcomes of education (college degree versus no college degree), employment (employed full time versus not), marital status (ever married versus never married) and household income (greater than $40,000 versus less than $40,000) between groups defined by primary predictors of neurocognitive impairment (yes/no; defined as impairment on any one of the four NCQ factors), emotional distress (yes/no; defined as impairment on any three of the BSI scales) and impaired HRQOL (defined as impairment on any one of the four physical scales [yes/no] or any one of the four mental scales [yes/no]). Logistic regression models will be used to evaluate these associations and will *a priori* be adjusted for gender and current age. Due to potential correlations between the emotional and neurocognitive predictors, each will initially be evaluated in age and sex adjusted univariate models. Careful consideration of possible colinearity will be considered in determining whether a full multivariable model makes sense.

Note: If binary outcome rates exceed 10%, direct modeling of relative risk estimates using log binomial models will be pursued instead of logistic regression.

References:

Armstrong, GT et Al. Region-specific radiotherapy and neuropsychological outcomes in adult survivors of childhood CNS malignancies. Neuro-Oncology 12(11): 1173-86.

Crist W, et al. The Third Intergroup Rhabdomyosarcoma Study. J Clin Oncol. 1995 Mar;13(3):610-30.

Harila MJ, et al. Progressive neurocognitive impairment in young adult survivors of childhood acute lymphoblastic leukemia. Pediatr Blood Cancer. 2009 Aug;53(2):156-61.

Heyn R, et al. Late effects of therapy in orbital rhabdomyosarcoma in children. A report from the Intergroup Rhabdomyosarcoma Study. Cancer. 1986 May 1;57(9):1738-43.

Mitby PA, et al. Utilization of special education services and educational attainment among long-term survivors of childhood cancer: a report from the Childhood Cancer Survivor Study. Cancer. 2003 Feb 15;97(4)1115-26.

Mertens, AC et al. Late mortality experience in five-year survivors of childhood and adolescent cancer: the Childhood Cancer Survivor Study. J Clin Oncol 2001 19(13) 3163-72.

Mueller E, et al. 2014.

Paulino AC, et al. Long-term effects in children treated with radiotherapy for head and neck rhabdomyosarcoma. Int J Radiat Oncol Biol Phys. 2000 Dec 1;48(5):1489-95.

Raney RB, et al. Late complications of therapy in 213 children with localized, nonorbital soft-tissue sarcoma of the head and neck: A descriptive report from the Intergroup Rhabdomyosarcoma Studies (IRS)-II and - III. IRS Group of the Children's Cancer Group and the Pediatric Oncology Group. Med Pediatr Oncol. 1999 Oct;33(4):362-71.

Spiegler BJ, et al. Comparison of long-term neurocognitive outcomes in young children with acute lymphoblastic leukemia treated with cranial radiation or high-dose or very high-dose intravenous methotrexate. J Clin Oncol. 2006 Aug 20;24(24):3858-64.

Appendix: Examples of some tables that will be used in the study's data analysis.

Table 1: Descriptive and demographic characteristics of the study population

Characteristic	**All RMS survivors**	**Head/neck RMS survivors**	**Non head/neck RMS survivors**	**Siblings**	**P value (all survivors vs. sibs)**	**P value (head/neck survivors vs. sibs)**	**P value (non head/neck vs. sibs)**	**P value (head/neck vs. non head/neck)**
Sex, No. (%) Male Female								
Age at baseline survey, median yrs ± SD (range)								
Age at 2003 survey, median yrs ± SD (range)								
Race/ethnicity, No. (%) White Black Hispanic Other								
Education, No. (%) Some HS HS graduate Some college College degree								
Marital status, No. (%) Single Married Divorced/separate								
Employment, No. (%) Full time Other								
Household income, No. (%) Less than $20,000 $20,000-39,999 $40,000-59,999 $60,000 and higher								
Heath insurance, No. (%) Private Medicaid Uninsured								
Impairment None Hearing Speech Vision								
Age at diagnosis, median yrs ± SD (range)				N/A	N/A	N/A	N/A	
Length of follow up, median yrs ± SD (range)				N/A	N/A	N/A	N/A	
Primary tumor site, No. (%) All head and neck Orbit Parameningeal Other head/neck All non head and neck GU Bladder/prostate Retroperitoneum Extremity Other Unknown				N/A	N/A	N/A	N/A	N/A
Treatment, No. (%) Surgery Chemotherapy IT chemotherapy				N/A	N/A	N/A	N/A	

Radiation								
Alkylator score, median ± SD (range)				N/A	N/A	N/A	N/A	
Cranial radiation dose, No. (%) None <30 Gy 30-49 Gy ≥50 Gy			N/A	N/A	N/A	N/A	N/A	N/A
Radiation dose to anatomic brain region, Mean Gy ± SD (range) Region 1 Region 2 Region 3 Region 4			N/A	N/A	N/A	N/A	N/A	N/A

Table 2A: Example adjusted models predicting impairment on NCQ for survivors versus siblings

	Task efficiency		Organization		Memory		Emotional regulation	
	No. (%)	OR (95% CI)	No. (%)	OR (95% CI)	No. (%)	OR (95% CI)	No. (%)	OR (95% CI)
Siblings		Ref		Ref		Ref		Ref
RMS Survivors								

*Adjusted for factors identified via multivariable modelling.

Table 2B: Example multivariable models predicting impairment on NCQ* among survivors

	Task efficiency		Organization		Memory		Emotional regulation	
	No. (%)	OR (95% CI)	No. (%)	OR (95% CI)	No. (%)	OR (95% CI)	No. (%)	OR (95% CI)
Gender								
Male		Ref		Ref		Ref		Ref
Female								
Age at diagnosis								
0-3 years								
4-9 years								
10-21 years		Ref		Ref		Ref		Ref
Primary tumor site								
All head and neck								
All non head and Neck		Ref		Ref		Ref		Ref
Surgery								
Yes								
No		Ref		Ref		Ref		Ref
Chemotherapy								
Yes								
No		Ref		Ref		Ref		Ref
Cranial radiation dose								
None		Ref		Ref		Ref		Ref
30-50 Gy								
≥50 Gy								
Anti-depressant or anti-anxiety								
Yes								
No		Ref		Ref		Ref		Ref

Table 3A: Adjusted comparison of percent of survivors versus siblings with impaired outcomes on BSI*

	Depression		Anxiety		Somatization		Global status index	
	No. (%)	**OR (95% CI)**	**No. (%)**	**OR (95% CI)**	**No. (%)**	**OR (95% CI)**	**No. (%)**	**OR (95% CI)**
Siblings RMS Survivors		Ref		Ref		Ref		Ref

* Adjusted for factors identified via multivariable modelling.

Table 3B: Multivariable analysis of risk factors associated with impaired outcomes on BSI among RHS survivors.

	Depression		Anxiety		Somatization		Global status index	
	No. (%)	**OR (95% CI)**	**No. (%)**	**OR (95% CI)**	**No. (%)**	**OR (95% CI)**	**No. (%)**	**OR (95% CI)**
Gender Male Female		Ref		Ref		Ref		Ref
Age at diagnosis 0-3 years 4-9 years 10-21 years		Ref		Ref		Ref		Ref
Primary tumor site All head and neck All non head and Neck		Ref		Ref		Ref		Ref
Surgery Yes No		Ref		Ref		Ref		Ref
Chemotherapy Yes No		Ref		Ref		Ref		Ref
Cranial radiation dose None 30-50 Gy ≥50 Gy		Ref		Ref		Ref		Ref
Anti-depressant or anti-anxiety Yes No		Ref		Ref		Ref		Ref

Table 4A: Comparison of percents ofsurvivors versus siblings with impaired outcomes on SF-36*

	Physical function		Role physical		Bodily pain		General health		Vitality		Role emotional		Social function		Mental health		PCS		MCS	
	No. (%)	OR (95% CI)	No. (%)	OR (95% CI)	No. (%)	OR (95% CI)	No. (%)	OR (95% CI)	No. (%)	OR (95% CI)	No. (%)	OR (95% CI)	No. (%)	OR (95% CI)	No. (%)	OR (95% CI)	No. (%)	OR (95% CI)	No. (%)	OR (95% CI)
Siblings		Ref		Ref		Ref		Ref		Ref		Ref		Ref		Ref		Ref		Ref
RMS Survivors																				

*Adjusted for factors identified via multivariable modelling.

Table 4B: Multivariable analysis of risk factors associated with impaired outcomes on SF-36

	Physical function		Role physical		Bodily pain		General health		Vitality		Role emotional		Social function		Mental health		PCS		MCS	
	No. (%)	OR (95% CI)	No. (%)	OR (95% CI)	No. (%)	OR (95% CI)	No. (%)	OR (95% CI)	No. (%)	OR (95% CI)	No. (%)	OR (95% CI)	No. (%)	OR (95% CI)	No. (%)	OR (95% CI)	No. (%)	OR (95% CI)	No. (%)	OR (95% CI)
Gender																				
Male		Ref		Ref		Ref		Ref		Ref		Ref		Ref		Ref		Ref		Ref
Female																				
Age at diagnosis																				
0-3 years																				
4-9 years																				
10-21 years		Ref		Ref		Ref		Ref		Ref		Ref		Ref		Ref		Ref		Ref
Primary tumor site																				
All head and neck																				
All non head and Neck		Ref		Ref		Ref		Ref		Ref		Ref		Ref		Ref		Ref		Ref
Surgery																				
Yes																				
No		Ref		Ref		Ref		Ref		Ref		Ref		Ref		Ref		Ref		Ref
Chemotherapy																				
Yes																				
No		Ref		Ref		Ref		Ref		Ref		Ref		Ref		Ref		Ref		Ref
Cranial radiation dose																				
None		Ref		Ref		Ref		Ref		Ref		Ref		Ref		Ref		Ref		Ref
30-50 Gy																				
≥50 Gy																				
Anti-depressant or anti-anxiety																				
Yes																				
No		Ref		Ref		Ref		Ref		Ref		Ref		Ref		Ref		Ref		Ref

Table 5: Multivariable analysis of associations between emotional and neurocognitive risk factors with socio-demographic outcomes.

	<College Education		**< FT Employment**		**Not Married**		**<40K HH Income**	
	No. (%)	**OR (95% CI)**	**No. (%)**	**OR (95% CI)**	**No. (%)**	**OR (95% CI)**	**No. (%)**	**OR (95% CI)**
Neurocognitive Impairment								
Yes								
No		Ref		Ref		Ref		Ref
Emotional Distress								
Yes								
No		Ref		Ref		Ref		Ref
HRQOL (SF-36)								
PCS Impairment								
Yes								
No		Ref		Ref		Ref		Ref
MCS Impairment								
Yes								
No		Ref		Ref		Ref		Ref
Gender								
Female								
Male		Ref		Ref		Ref		Ref
Current Age								
<25 yrs								
≥25 yrs		Ref		Ref		Ref		Ref