Childhood Cancer Survivor Study
Concept Proposal and Analytic Plan

Study Title
Temporal changes in therapy and neurocognitive outcomes, social attainment, and quality of life in adult survivors of pediatric brain tumors

Primary Working Group: Psychology
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Background and Rationale:
Survivors of pediatric brain tumors are at risk for neurocognitive impairment.[1] Long-term neurocognitive outcomes are multi-determined and beyond treatment exposures, worse neurocognitive performance has been associated with younger age at diagnosis,[2] hydrocephalus,[3,4] pre-, peri- and post-operative complications,[5,6] tumor location,[7,8] presence of genetic syndromes,[9] neurologic complications including posterior fossa mutism[10] or epilepsy,[11] and larger tumor volume.[12] Female sex is not consistently associated with poorer neurocognitive outcomes in survivors of pediatric brain tumors,[13] but has been associated with more rapid decline in some longitudinal studies.[3,14]

Cranial radiation therapy (CRT) is a well-established risk factor for adverse neurocognitive outcomes. Whole brain radiation therapy (WBRT) and craniospinal radiation (CSI) have been shown to be more detrimental than focal CRT, [8,15,16] and higher doses more detrimental than lower doses.[17] Moreover, the temporal lobes, hypothalami, and hippocampi are more vulnerable to CRT-induced damage.[10,18-20] Several studies have shown focal radiation to the posterior fossa region, in the absence of whole brain radiation, to be associated with stable or better neurocognitive outcomes;[21,22] however, conflicting evidence exists.[23]

Less is known about associations between neurocognitive outcomes and treatment with chemotherapy only in survivors of pediatric brain tumors. When examined, studies have focused on the potential benefit of replacing radiotherapy with chemotherapy in very young children and using radiation only as a second-line treatment in case of recurrence. Those studies reported average IQ, or IQ improving after end of treatment, in survivors treated with chemotherapy only.[24,25] Studies examining the impact of chemotherapy used in combination with CRT have shown an additive negative effect of chemotherapy on cognitive outcomes.[14,26]

Over the past several decades, treatment protocols and methods have been modified to reduce the negative effect of cancer-directed therapies on cognitive development including delaying CRT,[25] reducing radiation field and dose,[17,27] using advanced neurosurgical techniques (e.g. neuro-navigation),[28] reducing doses of chemotherapy or, more recently, treatment with proton beam radiation therapy.[29] It is not known, however, if these changes in treatment protocols yield reduced long-term neurocognitive impairment.

Over the years survival rates have improved dramatically for all types of childhood cancer, including brain tumors,[30] but more efficient treatment protocols have also been associated with more severe late effects. Two previous CCSS studies have found increased prevalence of poor health and chronic conditions among survivors treated more recently as compared to survivors treated in earlier eras,[31,32] however, both studies found improvement in functional status and use of special education services respectively, associated with reduced CRT dose. That is, cognition might improve with specific treatment changes, but might also deteriorate in long-term survivors due to a higher prevalence of severe chronic conditions. Improved survival rates might also cause a survival bias when assessing neurocognitive impairment over time, i.e. sicker children live to long-term survival compared to only relatively healthy children surviving on earlier protocols.

The most common types of brain tumors are astrocytomas, medulloblastomas/PNET and ependymomas, accounting for 31.9%, 15-20% and 5.5% respectively (excluding high grade gliomas for astrocytomas).[33,34] Treatment changes have increased survival rates over the years and survival rates are now 97.1% for pilocytic astrocytoma, 87.3% for other low grade gliomas, 70.1% for medulloblastomas, 56.0% for other types of PNET:s and 72.7% for ependymomas.[33] The following major treatment changes have been observed:

Low grade astrocytoma: Gross total resection (GTR) alone often attains cure for low grade glioma without additional exposure to chemotherapy and radiotherapy. Until the 1980s surgical resection followed by CRT was the most common treatment when total gross resection was not achieved (and in the 1970s, RT was even considered after GTR), with the exception of children younger than 3 years of age at diagnosis for whom delaying of CRT was recommended.[35-37] This changed in the 1990s when CRT as front line therapy following resection was more commonly restricted to children >12, with younger children preferentially receiving front line chemotherapy (most commonly with vincristine and carboplatin). In this latter scenario, RT was recommended primarily for patients with progressive disease after chemotherapy.[38] Treatment has continued to change into the 2000s. with chemotherapy replacing CRT to a larger extent.[39,40]

Medulloblastoma/PNET: The first survivors of medulloblastoma/PNET were reported after the introduction of 30-40Gy CSI in the late 1970s.[41,42] During the 1980s, chemotherapy was incorporated as adjuvant therapy for medulloblastoma and led to improved disease control.[43,44] By the 1990s, medulloblastoma patients were routinely risk-stratified based on age, extent of surgical resection and metastatic status at diagnosis, allowing standard-risk (SR) patients to receive reduced dose CSI (23.4-Gy)[45]. This risk-adapted therapy improved five-year survival for patients with high-risk (HR) disease and allowed for reduced therapeutic exposure (CSI) in patients with SR disease while maintaining or improving overall survival.[46,47]

Ependymoma: Current standard of care for these tumors includes upfront maximal achievable surgical resection.[48] In rare cases, gross total resection may be sufficient for cure in non-metastatic disease,[49] but focal radiation therapy to the tumor bed with a minimum of 45Gy is considered to be standard of care for most children with ependymoma. Children with suspected dissemination often receive craniospinal radiation to manage leptomeningeal disease. Several chemotherapy treatment protocols have been evaluated over the years, both to delay CRT for children young at diagnosis and to treat disease recurrence however no chemotherapy regimen has been established to improve overall survival compared to RT alone. Complete tumor resection and focal RT remain the most successful treatment approaches and standard treatment has not changed much over the years.[50]

The primary aim of this study is to examine neurocognitive impairment in long-term survivors of pediatric brain tumors as a function of temporal changes in therapy and as a function of diagnosis decades.

Specific Aims

Aim 1: To examine associations between neurocognitive impairment and treatment exposures (corresponding to major historical changes in therapeutic approaches) stratified by primary diagnosis (medulloblastoma; astrocytoma; ependymoma).

Hypothesis 1a: Medulloblastoma survivors who were treated with current standard risk therapy will have a lower prevalence of neurocognitive impairment compared to survivors treated with historical and current high-risk therapy.

Hypothesis 1b: Survivors of astrocytoma who were treated with modern therapies and were able to avoid or delay radiation therapy will have a lower prevalence of neurocognitive impairment.

Hypothesis 1c: Survivors of ependymoma who were treated with modern therapies and focal radiation therapy will have a lower prevalence of neurocognitive impairment compared to survivors treated with historical therapy or whole brain radiation.

Aim 2a: To examine social attainment outcomes by treatment exposures (corresponding to major historical changes in therapeutic approaches) stratified by primary diagnosis (medulloblastoma; astrocytoma; ependymoma).

Aim 2b: To examine the potential mediating effects of neurocognitive impairment on the association between treatment exposures and social attainment outcomes.

Aim 3a: To examine quality of life and emotional distress by treatment exposures (corresponding to major historical changes in therapeutic approaches) stratified by primary diagnosis (medulloblastoma; astrocytoma; ependymoma).

Aim 3b: To examine the potential mediating effects of neurocognitive impairment on the association between treatment exposures and quality of life and emotional distress.

Exploratory: To examine associations between treatment era and neurocognitive impairment stratified by primary diagnosis.

Analysis Framework

Study Population: Survivors enrolled in CCSS original and expansion cohorts with a primary diagnosis of CNS astrocytoma (n=2688), medulloblastoma (n=1040), or ependymoma (n=500).

Inclusion criteria:

- ≥18 years of age at the time of NCQ completion at Follow-up 2 OR Follow-up 5. We will use FU2 for the original cohort and FU5 for the expansion cohort.

Exclusion criteria:

- Genetic syndromes associated with cognitive impairment unrelated to primary cancer diagnosis, e.g. Klinefelter or Turner.

Treatment:

- Survivors will be assigned to a treatment era based upon their date of diagnosis (1970s vs. 1980s vs. 1990s)
- Survivors will also be divided into mutually exclusive treatment groups based on changes in therapeutic exposures by diagnostic group.
    - Medulloblastoma (as per Salloum, et al. [31])
        - (1) historical therapy (surgery + CSI ≥30Gy, no chemotherapy)
        - (2) current SR therapy (surgery + CSI <30Gy + chemotherapy)
        - (3) current HR therapy (surgery + CSI ≥30Gy + chemotherapy)
    - Astrocytoma (as per de Blank et al. CCSS concept):
        - (1) No radiation exposure (+/- surgery, chemotherapy)

        - (2) Historical: immediate radiation (<2yrs from diagnosis) (+/- surgery, chemotherapy)
        - (3) Current: delayed radiation (>=2yrs from diagnosis) (+/- surgery, chemotherapy)

    - Ependymoma (as per de Blank et al. CCSS concept):
        - (1) Whole brain RT (>20Gy in each of the 4 brain segments)
        - (2) Focal brain RT (>20Gy in at least 1 but not all 4 brain segments)

Outcomes:

- **Neurocognitive problems** will be assessed using the CCSS Neurocognitive Questionnaire (NCQ), a questionnaire with 25 listed statements to be rated on a 3-point scale as "never a problem", "sometimes a problem" or "often a problem". These questions are combined into four factors:
    - Task efficiency
    - Emotional regulation
    - Organization
    - Memory

  Impairment in each domain will be calculated based on scores derived from the sibling cohort (>90th %ile). However, we also will examine the frequency of impairment to determine if we can establish two levels of impairment (e.g., 90-95th %ile; >95th %ile).

- **Social attainment** will be assessed using the following:
    - **Educational attainment**
        - ≤High school graduate
        - Training/education beyond high school
        - College graduate or higher
    - **Employment**
        - Full-time: working full-time, caring for home or family, student
        - Part-time: working part-time
        - Unemployed, disabled, retired
    - **Marital status**
        - Single, never married
        - Married, living as married, widowed, divorced, separated or no longer married
    - **Independent living**
        - Independent living: live with spouse/partner, live alone, live with children
        - Non-independent: live with parents, roommates, brother/sister or other relative
    - **Driver's license** (yes/no)
    - **Require assistance with routine needs** (yes/no)
    - **Require assistance with personal care needs** (yes/no)

- **Health-related Quality of Life (HRQOL) will be assessed using SF-36**
    - Physical function
    - Role limitations due to physical health problems
    - Bodily pain
    - General health
    - Vitality
    - Social functioning
    - Role limitations due to emotional problems
    - Emotional well-being
    - Physical Component Summary scores (PCS)
    - Mental Component Summary scores (MCS)

  T-scores <40 will be considered significantly reduced HRQOL.

- **Emotional distress**
    - Psychological distress (anxiety, depression and somatization) will be measured with the BSI-18. T-scores ≥63 will be considered to represent significant psychological distress symptoms.

Covariates

- Age at evaluation (years, continuous)
- Sex
- Race/ethnicity (White/non-Hispanic vs. other)
- Age at diagnosis (years, continuous)
- Age at radiation
- Radiation
    - Focal: max dose >20 Gy in 1-3 brain segments
    - Whole brain/CSI: max dose >20 Gy in all 4 brain segments
    - Maximum dose to 4 regions: frontal, temporal, posterior fossa, parieto-occipital regions
- Disease relapse/second malignant neoplasms
- Genetic syndromes related to cancer, e.g. Neurofibromatosis or Tuberous sclerosis
- Epilepsy will be defined as > Grade 2 using CTCAE v. 4.03
- Stroke will be defined as > Grade 2 using CTCAE v 4.03
- Vision and/or hearing impairment will be defined as > Grade 2 using CTCAE v. 4.03
- Chemotherapy – agents & doses to be examined

Analytic Approach

Aim 1: To examine associations between treatment exposures (corresponding to major historical changes in therapeutic approaches) stratified by primary diagnosis (medulloblastoma; astrocytoma; ependymoma) and neurocognitive impairment.

Descriptively we will examine the proportion of CNS survivors with neurocognitive impairment by specific treatment exposure groups as defined above (e.g., historical, average risk, high risk) stratified by diagnostic group. Neurocognitive impairment will be defined as scores >90th percentile using sibling comparison data for each group independently.

We will use multivariable generalized linear modeling (log-binomial or modified Poisson) to examine the impact of treatment exposure group (stratified by diagnosis) on neurocognitive impairment with adjustment for age, sex, race/ethnicity, age at diagnosis [if not included in treatment group], and neurologic late effects (e.g. stroke, seizure). Prevalence ratios and 95% CIs will be reported.

Aim 2a: To examine social attainment outcomes by treatment exposures (corresponding to major historical changes in therapeutic approaches) stratified by primary diagnosis (medulloblastoma; astrocytoma; ependymoma).

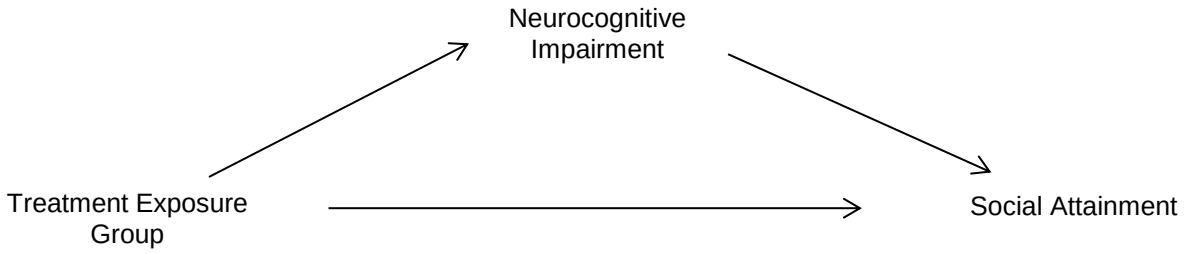
Descriptively we will examine the proportion of CNS survivors with social attainment deficits by specific treatment exposure groups as defined above (e.g., historical, average risk, high risk) stratified by diagnostic group.

We will use similar multivariable modeling as for Aim 1 to examine the impact of treatment exposure group (stratified by diagnosis) on social attainment with adjustment for age, sex, race/ethnicity, age at diagnosis [if not included in treatment group], and neurologic late effects (e.g. stroke, seizure, vision, hearing).

Aim 2b: To examine the potential mediating effects of neurocognitive impairment on the association between treatment exposures and social attainment outcomes.

If the associations in Aim 2a exist, we will complete mediation analyses to examine the impact of neurocognitive impairment on social attainment.

We will use established methods for causal mediation analysis in a potential-outcome framework.[51-54] Briefly, in causal mediation analysis, we are interested in exploring whether the association between an exposure (E) and outcome (Y) is the result of a direct effect or an indirect effect through a mediator (M). The figure below illustrates a reduced-form directed acyclic graph (DAG)[55] of our exposure-mediator-outcome relations, where the exposure of interest is treatment group, the mediator of interest is neurocognitive impairment, and the outcome of interest is social attainment. Causal mediation analysis enables us to decompose the total effect (i.e. the combined direct and indirect effects) into separate direct and indirect effects.[51-54] Given our aim of understanding the mechanism by which neurocognitive impairment effects social attainment, our analyses will focus on estimating natural direct and indirect effects, which uses the observed (naturally varying) values of the mediator, and preserves the observed exposure-outcome association.[52,53]



To strengthen identifiability assumptions for valid interpretation of natural direct and indirect effects, we will adjust for a minimal sufficient set of common causes (i.e. covariates to reduce confounding bias) of the exposure and outcome, exposure and mediator, and mediator and outcome.[54] Given that our outcomes of interest are dichotomous, we will estimate prevalence ratios (PRs) and corresponding 95% confidence limits (CL) for total, direct, and indirect effects using automated methods for causal mediation analysis by Valeri and Vanderweele.[54] Specifically, we will use multivariable polytomous logistic regression to estimate PRs for total, direct, and indirect effects of treatment exposure group on social attainment. The mediator (neurocognitive impairment) will be incorporated in the models as a dichotomous variable. PRs will be adjusted for a minimal sufficient set of covariates to reduce confounding bias.

Aim 3a: To examine quality of life and emotional distress by treatment exposures (corresponding to major historical changes in therapeutic approaches) stratified by primary diagnosis (medulloblastoma; astrocytoma; ependymoma).

Descriptively we will examine the proportion of CNS survivors with reduced quality of life and emotional distress symptoms by specific treatment exposure groups as defined above (e.g., historical, average risk, high risk) stratified by diagnostic group.

We will use multivariable modeling to examine the impact of treatment exposure group (stratified by diagnosis) on quality of life with adjustment for age, sex, race/ethnicity, age at diagnosis [if not included in treatment group], and neurologic late effects (e.g. stroke, seizure, vision, hearing).

Aim 3b: To examine the potential mediating effects of neurocognitive impairment on the association between treatment exposures and quality of life and emotional distress.

If the associations in Aim 3a exist, we will complete mediation analyses to examine the impact of neurocognitive impairment on quality of life and emotional distress. The analytic approach will follow that described in Aim 2b where the exposure of interest is treatment group, the mediator of interest is neurocognitive impairment, and the outcome of interest is quality of life and emotional distress.

Exploratory Aim: To examine associations between treatment era and neurocognitive impairment

stratified by primary diagnosis.

Because not all therapeutic changes (i.e. advances in neurosurgery, neuroimaging, post-operative care, hydrocephalus management) are measured or captured in the proposed treatment exposure groups, we will also examine the prevalence of neurocognitive impairment across era of diagnosis (1970's v 1980's v 1990's) stratified by primary diagnostic group.

Table 1. Characteristics of survivors

	Medulloblastoma		Astrocytoma		Ependymoma	
Age at evaluation						
Age at diagnosis						
Age at CRT treatment						
Time since diagnosis						
Sex						
Female						
Male						
Race/Ethnicity						
White/non-Hispanic						
Other						
Neurosurgery (yes/no)						
Chemotherapy						
None						
Cisplatin, cumulative dose						
Carboplatin, cumulative dose						
Vinca alkaloids						
Corticosteroids						
Epipodophyllotoxin, cumulative dose						
Alkylating agents (cyclophosphamide equivalent dose)						
Radiation (average cGy for treated survivors)						
None						
Max dose to frontal regions						
Max dose to temporal regions						
Max dose to parieto-occipital regions						
Max dose to posterior fossa region						
WBRT dose						
Treatment group	**Treatment group**	**n(%)**	**Treatment group**	**n(%)**	**Treatment group**	**n(%)**
	Historical therapy		Historical therapy		Surgery only	
	Current SR therapy		Surgery only		Surgery + RT	
	Current HR therapy		Surgery + chemo		Surgery + RT + chemo	
			Surgery + chemo + RT		Surgery + CSI + focal RT	
Disease relapse/second malignant neoplasms						
Neurocutaneous syndrome (NF-1 or TS)						
Epilepsy						
Stroke						
Vision or hearing impairment						

Table 2. Treatment groups per decade, medulloblastoma

	1970s		1980s		1990s	
	n	%	n	%	n	%
Historical						
Current SR						
Current HR						

Table 3. Neurocognitive impairment by decade of diagnosis for survivors of medulloblastoma

	1970s		1980s		1990s	
	n	%	n	%	n	%
Task Efficiency						
Emotional Regulation						
Organization						
Memory						

Table 4. Neurocognitive impairment by treatment exposure for survivors of medulloblastoma

	Historical		Average risk		High risk	
	n	%	n	%	n	%
Task Efficiency						
Emotional Regulation						
Organization						
Memory						

Table 5. Social attainment by treatment exposure, medulloblastoma

	Historical		Average Risk		High Risk	
	n	%	n	%	n	%
<College graduate						
Unemployed						
Never married						
Non-independent living						
Driver's license						
Assistance with routine needs						
Assistance with personal care needs						

Table 6. Neurocognitive impairment by treatment exposure, medulloblastoma

	Task Efficiency		Emotional Regulation		Organization		Memory	
	RR	p	RR	p	RR	p	RR	p
Treatment								
Historical								
Current SR								
Current HR								
Sex								
Race								
Age at assessment								
Age at diagnosis								
Relapse/SMN								
Epilepsy								
Stroke								

Note: Neurocutaneous syndromes will be included as a covariate for astrocytoma only

Similar tables will be developed for astrocytoma and ependymoma.

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