1. STUDY TITLE: Location of CNS Directed Radiotherapy to Predict Neurocognitive, Psychological and Health Related Quality of Life Outcomes in Survivors of CNS Tumors

2. WORKING GROUP AND INVESTIGATORS:

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3. BACKGROUND AND RATIONALE:

Survivors of childhood CNS tumors are at increased risk for poor long-term neurocognitive, psychological and health-related quality of life (HRQOL) outcomes.[1] Most early studies of cognitive deficits in such patients focused on global functioning, measured with intelligence tests (e.g. Global IQ). More recent studies have found evidence of abnormalities in specific neurocognitive functions including: processing speed, attention, and executive functions. Time since diagnosis/treatment appears to be an important factor for manifestation of neurocognitive deficits.[2-4] The impact on global cognitive abilities may not fully emerge until at least five years after diagnosis, with a steady decline in function over time[2,4,5]. In fact, the average decrease in IQ in such patients is reported to be 4 to 6 points per year[2,5].

Previous publications associating poor functional outcome with the use of CRT have been limited in their ability to identify associations with specific regions of RT exposure to the CNS. While it can be hypothesized that poor outcome in executive functions and memory formation would be more closely associated with RT exposure to frontal or temporal lobes, respectively, such hypotheses have been difficult to evaluate for several reasons. First, many populations, such as those treated for acute lymphoblastic leukemia were treated with a homogeneous dose to the entire brain, and therefore lack heterogeneity in dose to different regions of the brain necessary for such a evaluation. Secondly, while patients with CNS tumors, as a population, may receive heterogeneous doses to varied brain regions, a sufficiently large population for such an evaluation has not been previously ascertained. Finally, such an evaluation has been

previously limited by the difficulty of obtaining region-specific dosimetry in an aging population of CNS tumor survivors.

The CCSS population of CNS tumor survivors presents a unique opportunity to evaluate region-specific RT dosimetry and its effects on neurocognitive, psychological and HRQOL outcomes. CNS region-specific dosimetry has been quantified with great rigor in this large sample (1,877) of CNS tumor survivors. To quantify radiation exposure, the brain was partitioned into four anatomic segments (frontal cortex, temporal lobes including H-P axis, posterior fossa, parietal and occipital cortex) and maximum radiation doses were estimated for each region. In this quantification it was assumed that any segment received the full-beam dose if at least half of the total segment/region was included in the beam, otherwise this segment was considered to have received scatter dose. Treatment diagrams and photographs taken in the treatment position were reviewed to make the determination of which brain segments were irradiated. If diagrams were not available, a written description of the medical record was used to estimate the regions included and the dose administered. Further details of the dosimetry method have been previously reported.[6,7] It has been previously reported by the CCSS that survivors who received CNS-directed cranial radiotherapy (CRT) are at risk for poor psychological and health-related quality of life (HRQOL) outcomes and a forthcoming report (Ellenberg et. al) will document the risk for poor neurocognitive outcome in this population.[8,9] However, none of these publications have looked for associations with region specific CRT exposure.

The population of CNS tumor survivors in the CCSS population is the ideal target population for such an evaluation. In addition to its large size, sufficient heterogeneity exists in regard to region-specific RT dose to allow a region-specific analysis. This has been demonstrated in a previous publication reporting stroke outcomes by region-specific RT exposure[10]. In addition, we have reported sociodemographic outcomes by region-specific RT exposure in this population of CNS tumor survivors (accepted pending minor revisions, JNCI; See Table 1 for an example of this analysis). In this analysis we identified that lower rates of employment, education and marriage are all associated with frontal and temporal lobe RT doses of >50 Gy with no association with RT exposure to the posterior fossa or the parietal-occipital lobe region.

We hypothesize that deficiencies in neurocognitive function based on a similar RT exposure pattern are the cause of such poor sociodemographic outcomes (Figure 1) but this has not previously been demonstrated in this population. The association between neurocognitive outcome and sociodemographic outcomes and neurocognitive function has recently been demonstrated among survivors of ALL in a forthcoming CCSS report (Kadan-Lottick et al, submitted to JAMA). In this analysis, marriage and educational level was associated with attention and processing speed, while educational level was also associated with memory skills. Given the association

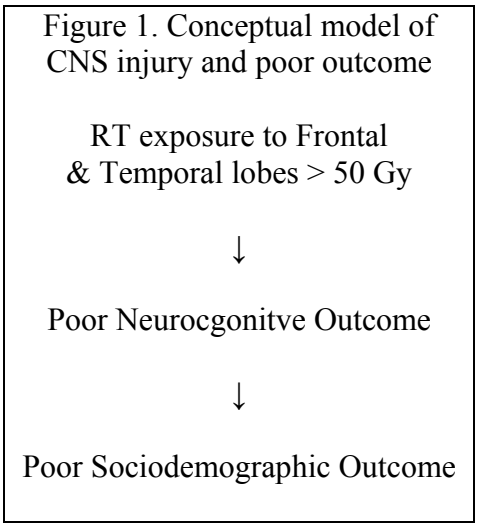

Figure 1. Conceptual model of CNS injury and poor outcome

that we have already demonstrated in the CNS tumor survivors between high dose RT to frontal and temporal regions and marriage and educational outcomes, we expect an association between high dose RT to frontal and temporal lobes and the specific neurocognitive functions of attention, processing speed, and memory.

Psychological distress has been identified as occurring more frequently in survivors of CNS tumors compared to siblings[8]. Psychological distress is also significantly associated with marriage and educational level. In a recent CCSS analysis a significant association between psychological distress and neurocognitive function was demonstrated (Ellenberg et al, submitted to Neuropsychology). As such, we proposed to examine the association between high dose RT exposure to frontal and temporal lobes and psychological outcomes. Specifically, and consistent with existing literature on brain injury,[11,12] we expect an association between frontal and temporal RT exposure and increased emotional symptoms.

HRQOL is also an important factor to consider in this analysis. Previous research in CCSS had demonstrated an association between CRT and poor physical QOL[9]. This same analysis also demonstrated a significant association between sociodemographic outcomes (e.g. educational level, employment) and reduced physical, social, and emotional HRQOL. Given the association between sociodemographic outcomes and specific neurocognitive functions (i.e. processing speed/attention and memory) and the association between these outcomes and HRQOL, we expect high dose RT exposure to areas related to these neurocognitive functions to also impact HRQOL.

4. SPECIFIC AIMS/OBJECTIVES/RESEARCH HYPOTHESES:

4.1. Primary Aim:

4.1.1. To identify associations between segment-specific RT dose and neurocognitive, psychological, and HRQOL outcomes among adult survivors of CNS tumors

4.2. Hypotheses:

4.2.1. RT exposure to segment 2 (temporal/hypothalamic) and segment 3 (frontal lobe) will be associated in a dose-dependant manner with poor outcomes in memory and attention/processing speed as measured by the NCQ, with no association with RT dose to segments one (posterior fossa) and four (occipital lobe).

4.2.2. RT exposure to segment 2 and segment 3 will be associated with higher rates of anxiety and depression as measured by the BSI-18.

4.2.3. RT exposure to segment 2 and segment 3 will be associated with reduced HRQOL.

5. ANALYSIS FRAMEWORK:

5.1. Primary Outcomes Variables:

5.1.1. CCSS NCQ: 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 $\leq 10^{th}$ percentile based on sibling group norms.

5.1.2. BSI: Anxiety, Depression, Somatazation. Factor scores will be dichotomized based on whether the performance is considered "impaired" or not (Yes/No), with impairment defined as a performance falling $\leq 10^{th}$ percentile based on standardized norms.

5.1.3. SF-36: 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.

5.2. Primary predictors:

5.2.1. RT segment-specific dose to 4 CNS segments (dose levels: no RT, 1-29 Gy, 30-49 Gy, 50+ Gy)

5.3. Covariates:

5.3.1. CNS Tumor Diagnosis
5.3.2. Age at diagnosis (include a priori)
5.3.3. Sex (include a priori)
5.3.4. Household Income
5.3.5. Chemotherapy (CNS exposure, yes/no)
5.3.6. Major Medical Condition
5.3.7. Psychotropic medication use: Antidepressants, Anxiolytics

5.4. Related to the specific hypotheses, the following analyses will be conducted:

5.4.1. Frequency distributions will be examined to categorize relevant outcome variables and covariates according to reasonable groupings and consistent with previous CCSS manuscripts.
5.4.2. Descriptive statistics will be reported for all predictors, outcomes, and covariates.
5.4.3. Logistic regression analyses will be conducted for each outcome variable (CCSS-NCQ, BSI and SF-36 as described in 5.1.1, 5.1.2 and 5.1.3) using RT segment-specific dose as the primary predictor controlling for covariates as indicated above to create Odds ratios for impairment at different dose exposure (See Tables 3-6)
5.4.4. Univariate analyses will be conducted first to identify variables contributing to each outcome.
5.4.5. Variables that are significant in univariate analyses will be included in multi-variate analyses for each outcome.

5.5. Subject population:

5.5.1. CCSS Survivor Cohort for Follow-up 2 survey (i.e. Follow-up 2003)

5.5.1.1. Inclusion criteria

- CNS tumor survivors who completed CCSS-NCQ, BSI, and SF-36 questionnaires and have treatment data available

5.5.1.2. Exclusion criteria

- Paralysis
- Mental Retardation

5.5.1.3. Variables

- Cancer Diagnosis
- Radiation Therapy
- Chemotherapy Variables
- Age
- Sex
- BSI (G1-18)
- CCSS-NCQ (J1-25)
- Current Psychopharm (Q8)
- Current Household Income (S2)

5.6. Tables and figures:

Table 1. Sociodemographic Outcomes in CNS Tumor Survivors by Region-specific Cranial RT Dose* (as seen in CNS summary manuscript, currently under review at JNCI.) PLEASE NOTE: THIS TABLE IS ONLY AN EXAMPLE OF OUR METHODS.

RT Exposure	Education < college graduate		Unemployed		Never Married		Income <$20,000		Uninsured	
	OR	95% CL	OR	95% CL	OR	95% CL	OR	95% CL	OR	95% CL
Posterior Fossa										
None	1.0		1.0		1.0		1.0		1.0	
< 30 Gy	0.9	0.6-1.6	1.2	0.6-2.2	1.2	0.7-2.1	1.5	0.7-3.2	1.1	0.5-2.7
30-49 Gy	0.8	0.4-1.6	1.2	0.6-2.5	1.7	0.8-3.3	2.0	0.9-4.6	0.8	0.3-2.4
50+ Gy	0.9	0.5-1.6	1.2	0.6-2.3	1.1	0.6-2.1	2.3	1.0-4.9	0.8	0.3-2.1
Temporal Lobe										
None	1.0		1.0		1.0		1.0		1.0	
< 30 Gy	1.0	0.6-1.6	1.3	0.7-2.3	1.3	0.8-2.2	1.5	0.7-3.2	1.1	0.5-2.6
30-49 Gy	1.4	0.8-2.6	1.5	0.8-2.8	**3.5**	**1.8-6.8**	**2.1**	**1.1-4.6**	**1.8**	0.7-4.4
50+ Gy	**2.1**	**1.2-3.4**	**1.8**	**1.1-3.1**	**2.1**	**1.3-3.6**	**2.8**	**1.5-5.5**	**1.7**	0.8-3.7
Frontal Lobe										
None	1.0		1.0		1.0		1.0		1.0	
< 30 Gy	0.9	0.5-1.5	1.2	0.7-2.2	1.3	0.8-2.3	1.6	0.8-3.3	1.1	0.5-2.7
30-49 Gy	1.1	0.5-2.3	1.6	0.7-3.3	**2.5**	**1.2-5.4**	1.5	0.6-3.6	0.9	0.3-2.9
50+ Gy	**2.2**	**1.0-5.0**[#]	**2.4**	**1.1-5.4**	**3.4**	**1.4-8.0**	1.3	0.5-3.4	0.8	0.2-2.9
Occipital Lobe										
None	1.0		1.0		1.0		1.0		1.0	
< 30 Gy	0.9	0.5-1.5	1.2	0.6-2.1	1.3	0.7-2.2	1.6	0.8-3.2	1.1	0.5-2.7
30-49 Gy	0.6	0.3-1.2	1.0	0.5-2.2	1.2	0.5-2.6	1.6	0.6-4.1	1.1	0.3-3.6
50+ Gy	0.8	0.4-1.5	1.5	0.7-3.2	1.4	0.7-2.9	1.2	0.5-3.2	1.2	0.4-3.8

Table 2. Descriptive Statistics for Publication

	No	**%**
Sex		
Female		
Male		
Age at Diagnosis		
0-4 years		
5-9 years		
10-14 years		
>14 years		
Diagnosis		
Astrocytoma		
Medulloblastoma/PNET		
Ependymoma		
Other CNS		
Radiation Therapy		
Segment 1		
None		
0-29		
30-49		
50+		
Segment 2		
None		
0-29		
30-49		
50+		
Segment 3		
None		
0-29		
30-49		
50+		
Segment 4		

None	
0-29	
30-49	
50+	
Chemotherapy	
Methotrexate (yes/no)	
Corticosteroid (yes/no)	

Table 3. Neurocognitive Outcomes in CNS Tumor Survivors by NCQ Domain and Cranial RT Dose for Publication

	Task Efficiency			Emotional Regulation			Organization			Memory		
	Mean	95%CI	% Impaired	Mean	95%CI	% Impaired	Mean	95%CI	% Impaired	Mean	95%CI	% Impaired
Posterior Fossa												
None												
<30 Gy												
30-49 Gy												
50+ Gy												
Temporal Lobe												
None												
<30 Gy												
30-49 Gy												
50+ Gy												
Frontal Lobe												
None												
<30 Gy												
30-49 Gy												
50+ Gy												
Occipital Lobe												
None												
<30 Gy												
30-49 Gy												
50+ Gy												

* Cognitive domains taken from CCSS-NCQ Task Efficiency, Emotional Regulation, Organization, and Memory Factors, respectively.
# %Impaired = percent of patients falling ≤ 10^{th} percentile based on reference to sibling controls, which is the standard threshold used for clinical impairment

Table 4. Neurocognitive Outcomes in CNS Tumor Survivors by Region-specific Cranial RT Dose adjusted (at minimum) for gender, age at diagnosis and RT dose to other segments (for Publication)

RT Exposure	Task Efficiency		Emotional Regulation		Organization		Memory	
	OR	95% CL	OR	95% CL	OR	95% CL	OR	95% CL
Posterior Fossa								
None								
< 30 Gy								
30-49 Gy								
50+ Gy								
Temporal Lobe								
None								
< 30 Gy								
30-49 Gy								
50+ Gy								
Frontal Lobe								
None								
< 30 Gy								
30-49 Gy								
50+ Gy								
Occipital Lobe								
None								
< 30 Gy								
30-49 Gy								
50+ Gy								

Table 5. BSI-18 Outcomes in CNS Tumor Survivors by Cranial RT Dose for Publication

	Anxiety			Depression			Somatization			Composite Score		
	Mean	95%CI	% Impaired	Mean	95%CI	% Impaired	Mean	95%CI	% Impaired	Mean	95%CI	% Impaired
Posterior Fossa												
None												
<30 Gy												
30-49 Gy												
50+ Gy												
Temporal Lobe												
None												
<30 Gy												
30-49 Gy												
50+ Gy												
Frontal Lobe												
None												
<30 Gy												
30-49 Gy												
50+ Gy												
Occipital Lobe												
None												
<30 Gy												
30-49 Gy												
50+ Gy												

Table 6. BSI-18 Outcomes in CNS Tumor Survivors by Region-specific Cranial RT Dose adjusted (at minimum) for gender, age at diagnosis and RT dose to other segments (for Publication)

RT Exposure	Anxiety		Depression		Somatization		Composite Score	
	OR	95% CL	OR	95% CL	OR	95% CL	OR	95% CL
Posterior Fossa								
None								
< 30 Gy								
30-49 Gy								
50+ Gy								
Temporal Lobe								
None								
< 30 Gy								
30-49 Gy								
50+ Gy								
Frontal Lobe								
None								
< 30 Gy								
30-49 Gy								
50+ Gy								
Occipital Lobe								
None								
< 30 Gy								
30-49 Gy								
50+ Gy								

6. SPECIAL CONSIDERATION:

6.1. Kumar Srivastava has agreed to conduct the statistical analyses at St. Jude Children's Research Hospital, under the supervision of Wendy Leisenring. We believe that we can complete the statistical procedures locally and, thus, not add to the list awaiting the Statistical Centers. Wendy will review all analyses and methods prior to sending the paper to the publications committee for review.

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Initial validation of the Pediatric Automated Neuropsychological Assessment Metrics for childhood-onset systemic lupus erythematosus
The generalizability of neurocognitive test/retest data derived from a nonclinical sample for detecting change among two HIV+ cohorts
The Modified Checklist for Autism in Toddlers: an initial study investigating the early detection of autism and pervasive developmental disorders
The seven minute screen: a neurocognitive screening test highly sensitive to various types of dementia
A 7 minute neurocognitive screening battery highly sensitive to Alzheimer's disease
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Reliable screening for neuropsychological impairment in multiple sclerosis
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