1. **Title**: Updated Epidemiology of Secondary CNS Malignancy Following Radiotherapy Exposure in Childhood Cancer Survivors

2. **Working group and investigators**: This project will be developed through the SMN Working Group. Proposed investigators include:

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3. **Background**: The Childhood Cancer Survivor Study (CCSS) has provided a wealth of information regarding outcomes of those who have survived malignancy during childhood and adolescence. The cohort continues to grow and now includes over 25,000 participants.[1,2] The development of a subsequent neoplasm is one of the well-described, often devastating complications of curative therapy. Prior studies have examined the incidence and risks associated with the development of subsequent malignancies.[3-7]

   Subsequent neoplasms of the central nervous system (CNS) carry with them significant morbidity and mortality. Outcomes are poor if the subsequent neoplasm is malignant with 6-15% overall survival.[8, 9] Neglia et al. examined the incidence of and risks associated with the development of subsequent CNS tumors in the original CCSS cohort.[10] This study, as well as others, have demonstrated the importance of therapeutic radiation exposure to the risk of development of subsequent CNS tumors.[9, 11-18] Thus, radiation exposure, either as the result of environmental cause[19] or treatment for an underlying malignancy,[10,12] is now recognized as a major risk factor for the development of malignant CNS tumors.

   In earlier treatment eras, including the time period many of the initial CCSS cohort members were diagnosed and treated, cranial radiation was used more frequently for acute lymphoblastic leukemias. Recognition of the second neoplasm risk and neurocognitive declines associated with therapeutic radiation exposure has resulted in decreased use in current treatment protocols.[20] Decreased long-term survival has been observed for patients with low-grade glioma (LGG) exposed to radiation, and treatment regimens for LGG now incorporate radiation sparing treatment plans.[21,22] It has also been recognized that the risk for developing a secondary glioma is highest in children <5 years of age at the time of radiation exposure.[23] More modern treatment protocols avoid radiation in the youngest cancer patients where possible. However, the decrease in radiation use has resulted in increased chemotherapy intensity, which may also have an impact on subsequent CNS neoplasm development.[3]

   With the expansion of the CCSS cohort to include survivors diagnosed between 1987 and 1999, we have an opportunity to comprehensively assess subsequent malignancies involving the CNS to evaluate if changes in upfront therapy have resulted in changes in cumulative incidence or risk. The overarching hypothesis of this proposal is that individuals treated in the most recent treatment era will experience lower cumulative incidence and have decreased risk for development of subsequent CNS malignancies because of reduced therapeutic radiation exposure. This hypothesis will be addressed through the following specific aims:

4. Specific Aims

4.1 Estimate the cumulative incidence of subsequent malignant neoplasms of the central nervous system in survivors of childhood cancer across treatment eras within the CCSS cohort (see 5.2.2 for treatment era definitions).

4.1.1 Stratify treatment era cumulative incidence estimates by age at diagnosis of original malignancy, original malignant diagnosis, and therapeutic exposures.

Hypothesis: The cumulative incidence of subsequent CNS malignancy will be influenced by radiation exposure and earlier age of diagnosis and treatment. As radiotherapy use has decreased with time, the incidence of subsequent CNS neoplasms will be lower in more recent treatment decades.

4.2 Construct dose-response curves using radiation dose to four segments of the brain. Brain segment radiation data was previously shown to approximate specific tumor location dose[24], and this simplified dosimetry will permit a cohort approach rather than a nested case control approach as previously performed by Neglia, et al.[10]

Hypothesis: The risk of subsequent malignancies in the CNS will increase with an increasing dose of radiation received.

4.3 Evaluate additional demographic and treatment exposure risk factors for development of secondary CNS malignancies, for those who received CNS-directed radiotherapy (see 5.4.2 for definition) and who were not exposed to CNS radiation for their childhood cancer.

Hypothesis: Younger age at childhood cancer diagnosis is expected to increase risk for secondary CNS malignancy. We do not anticipate identifying a chemotherapy exposure that increases risk, but for the small population with secondary CNS malignancy who did not receive CNS-directed radiation, another treatment exposure may be implicated.

4.4 Evaluate overall survival from the time of diagnosis of a secondary CNS malignancy and determine all-cause specific mortality among childhood cancer survivors with subsequent CNS malignancy.

Hypothesis: Outcomes will remain poor for individuals who develop a secondary CNS malignancy regardless of the treatment era of their primary childhood cancer.

5. Analysis Framework: This analysis will include ≥5 year survivors of childhood cancer enrolled in the CCSS cohort. Individuals with unknown treatment exposure will be excluded.

5.1 Secondary malignant CNS tumors will be identified by the ICD-O-3 primary brain and CNS site/histology listing, utilizing the 5th digit behavior code of 3. This will specifically exclude benign meningiomas from this analysis. ICD-O codes 9530/3, 9538/3, and 9539/3 will also be excluded as subtypes of meningioma. The date of occurrence of the secondary CNS tumor must be over 5 years from the original cancer diagnosis.

5.2 Descriptive characteristics:

5.2.1 Childhood malignancy, age at diagnosis, sex, race.

5.2.2 Year of therapy for childhood malignancy (1970-79, 1980-89, 1990-99).

5.2.3 Time from initial diagnosis to secondary CNS malignancy and age at attainment.

5.2.4 Location of secondary CNS malignancy.

5.3 Environmental/lifestyle exposures: smoking status, alcohol use.

5.4 Ever smoking at least 100 cigarettes, and if yes, number of years smoked.

5.5 Therapeutic exposures

5.5.1 Therapeutic radiation: Dose is reported for 4 brain segments (frontal, parietal, occipital, and midbrain segments).

5.5.2 For patients receiving therapeutic radiation, identify those exposed to CNS radiation via cranioradiotherapy (CRT), craniospinal irradiation (CSI), and/or total body irradiation (TBI). For the purposes of this study, head radiation exposing the CNS will be included, but radiation fields exposing but not targeting the spinal cord (e.g. chest irradiation) will be classified as non-CNS radiotherapy. For individuals with subsequent CNS neoplasm who received non-CNS directed radiotherapy per this definition, exposure fields will be described.

5.5.3 Chemotherapy exposure.

5.5.3.1 Alkylating agents (reported as cyclophosphamide equivalent dose);[26] cumulative exposure

5.5.3.2 Epipodophyllotoxins; cumulative exposure

5.5.3.3 Platinating agents;[27, 28] cumulative exposure
5.5.3.4 Anthracyclines (based on doxorubicin isotoxic equivalent dose);[29] cumulative exposure
5.5.3.5 Intrathecal Methotrexate; cumulative exposure
5.5.3.6 Antimetabolites (6MP and 6TG); yes/no (cumulative exposure not available)[30]

5.5.4 Hematopoietic cell transplant (yes/no and type if available).

5.6 To compare the incidence of CNS cancers in the CCSS cohorts across treatment era, standardized by general population rates, standardized incidence ratios (SIRs) and excess absolute risks (EARs) for secondary CNS malignancy will be calculated. Age, sex, and calendar year-specific rates from the Surveillance, Epidemiology, and End Results Program (SEER) will be used to evaluate expected number of cases. Piecewise multivariable Poisson models for the risk of CNS cancers, with offset terms based on age, sex and calendar-year SEER rates will be used to evaluate SIRS and compare SIRs and EARs between treatment eras.

5.7 The cumulative incidence curves for secondary CNS malignancy will be calculated treating death as a competing risk event, for survivors, treated with and without radiation therapy (categorized as Non-CNS, CRT, CSI, TBI) for the primary cancer. Additional curves presenting relevant subgroups identified in the multivariable analysis below may be generated.

5.8 A multivariate Cox regression analysis of the risk of secondary CNS malignancy as a function of demographics, environmental/lifestyle exposures, and therapeutic exposures will be performed estimating hazard ratios for factors associated with secondary CNS malignancy development. See specific variables to be evaluated in sections 5.2 - 5.4 above. Most SMN risk factor analyses use age as the time scale for modelling, though evaluation of time since cohort entry as the scale will be carried out, using the metric which is most strongly associated with development of the outcome. Survivors will enter the analysis at the age they are 5 years after primary cancer diagnosis (or alternatively, on a time scale, this will be time "zero" for all). Follow-up will end at age (time) of subsequent CNS malignancy, last contact or death. Initial analyses will examine univariate relationships and subsequently, multivariable models including factors significant at the 0.10 level will be examined, eliminating factors that are not statistically significant at 0.05 unless they modify the effect of other factors in the model. A priori, we plan to adjust for sex and age at diagnosis.

5.8.1 An examination of whether inclusion of treatment exposures attenuates the effects of treatment era will be performed.

5.8.2 Since diagnosis of primary childhood cancer and treatment variables are highly correlated, a separate model will be fit for primary childhood cancer diagnosis, adjusting for non-treatment factors.

5.9 Amongst participants exposed to CNS radiation, we will model excess relative risk (ERR) of radiation dose exposure ranges, utilizing the methodology employed by Neglia, et al,[10] where a dose-response model inclusive of effect modification was derived from the general model ERR = $(B_1D + B_2D^2)\exp(B_3D + B_4D^2)$, in which D is dose and $B1$-$B4$ are regression coefficients, and B_1D corresponds to a linear dose-response relationship with B_1 representing ERR/Gy. We will evaluate the need for the quadratic term, as well as other potential curve shapes, to determine the best fit. Possible modification of B_1 under this model by sex, age at original cancer diagnosis, treatment decade, attained age, and time since first cancer will also be evaluated.

5.10 To determine all-cause and CNS-malignancy-specific mortality among childhood cancer survivors with subsequent CNS malignancy. Median follow up of patients diagnosed with any subsequent CNS malignancy will be reported in months. Three, 5 and 10 year survival (OS) from diagnosis of subsequent CNS malignancy will be estimated using Kaplan-Meier methods. Cause-specific mortality will be estimated at the same time points using cumulative incidence, treating death from other causes as competing risk events. Two-sided P values < .05 will be considered statistically significant.

Proposed Tables

Table 1: Descriptive characteristics and therapeutic exposures of long-term survivors (>5 years) with subsequent CNS malignancies per treatment era. [This table provides numbers of patients with secondary CNS malignancy divided into different characteristics and treatment exposures]

	No. (%)				
Characteristic	**1970-1979**	**1980 - 1989**	**1990 - 1999**	Total	**P-value**

	(N =)	(N =)	(N =)		
Age (years) at attainment, mean (SD) 5-9 10-14 15-20 21-25 26-30 31-35 36-40 40+					
Years from primary diagnosis, mean (SD)					
Sex Male Female					
Race White, non-Hispanic Black, non-Hispanic Hispanic/Latino Other					
Environmental factors Ever-smoked at least 100 cigarettes Number of years smoked, mean (SD)					
Primary Diagnosis Type Leukemia ALL AML Other leukemia CNS tumor Astrocytoma Medulloblastoma/PNET Other CNS Lymphoma Hodgkin's lymphoma Non-Hodgkin's lymphoma Sarcoma Soft-tissue sarcoma Ewing's sarcoma Osteosarcoma Kidney Tumor Neuroblastoma Other					
Treatment Category Surgery only Chemotherapy only Non-CNS directed radiation* CNS directed radiation* CRT CSI TBI Chemotherapy + non-CNS radiation Chemotherapy + CNS radiation HSCT					
Chemotherapy Exposures					
Cyclophosphamide equivalent dose, mg/m^2					

Median (IQR) dose None 1-3999 4000-7999 ≥8000					
Epipodophyllotoxins, mg/m^2 Median (IQR) dose None 1-1000 1001-3999 ≥4000					
Platinum agent, mg/m^2 Median (IQR) dose None 1-400 401-749 ≥750					
Anthracycline, mg/m^2 Median (IQR) dose None 0-100 101-299 ≥300					
Antimetabolites					
Intrathecal Methotrexate, mg/m^2 Median (IQR) dose None 1-39 40-69 ≥70					
Intrathecal Methotrexate + CNS radiation					
CNS Radiation dose exposures, Gy					
0.1-10					
10.1-20					
20.1-30					
30.1-40					
40.1-50					
>50					

*CNS directed radiation defined as those receiving cranio-radiotherapy (CRT), craniospinal irradiation (CSI), and total-body irradiation (TBI)

Table 2: Categorizing incidence of CNS malignancy by histologic diagnosis and treatment era. [This table lists the types of secondary malignant CNS diagnoses that develop in long-term survivors]

	Number			
Histologic Diagnosis of secondary CNS malignancy	**1970-1979 (N =)**	**1980 - 1989 (N =)**	**1990 - 1999 (N =)**	Total
Glioblastoma				
Anaplastic Astrocytoma				
etc				

Table 3: Number of long-term survivors (>5 years) in CNS and non-CNS irradiated cohorts exposed to chemotherapy classes by treatment decade. Included are the median dose exposed for each class (where available) per treatment decade.
[This table provides the number of survivors per treatment decade exposed to chemotherapy agents at various cumulative doses.

I have this table included in case an association between exposure and secondary CNS malignancy is demonstrated. If overall number of CNS tumors is decreasing with each treatment decade, then it may be nice to show a correlative increase/decrease in whatever exposure too for the whole cohort]

	No. (%)			
Cohort exposed to CNS-directed radiation				
Chemotherapy Class	**1970-1979 (N =)**	**1980 - 1989 (N =)**	**1990 - 1999 (N =)**	**P-value**
Cyclophosphamide equivalent dose, mg/m^2 Median (IQR) dose None 1-3999 4000-7999 ≥8000				
Epipodophyllotoxins, mg/m^2 Median (IQR) dose None 1-1000 1001-3999 ≥4000				
Platinum agent, mg/m^2 Median (IQR) dose None 1-400 401-749 ≥750				
Anthracycline, mg/m^2 Median (IQR) dose None 0-100 101-299 ≥300				
Antimetabolites				
Intrathecal Methotrexate, mg/m^2 Median (IQR) dose None 1-39 40-69 ≥70				
Cohort not exposed to CNS-directed radiation				
Chemotherapy Class	**1970-1979 (N =)**	**1980 - 1989 (N =)**	**1990 - 1999 (N =)**	**P-value**
Cyclophosphamide equivalent dose, mg/m^2 Median (IQR) dose None 1-3999 4000-7999 ≥8000				
Epipodophyllotoxins, mg/m^2 Median (IQR) dose				

None 1-1000 1001-3999 ≥4000				
Platinum agent, mg/m^2 Median (IQR) dose None 1-400 401-749 ≥750				
Anthracycline, mg/m^2 Median (IQR) dose None 0-100 101-299 ≥300				
Antimetabolites				
Intrathecal Methotrexate, mg/m^2 Median (IQR) dose None 1-39 40-69 ≥70				

Table 4: Radiation dose exposures per treatment decade for all long-term CCSS survivors (>5 years) treated with CNS-directed radiotherapy.
[This table provides the total number of survivors exposed to various radiation doses. I have this table included in case an association between exposure and secondary CNS tumor is demonstrated. If overall number of CNS tumors is decreasing with each treatment decade, then it may be nice to show a correlative increase/decrease in whatever exposure too for the whole cohort]

	No. (%)			
CNS Radiation Dose Exposure, Gy	**1970-1979 (N =)**	**1980 - 1989 (N =)**	**1990 - 1999 (N =)**	**P-value**
0.1-10				
10.1-20				
20.1-30				
30.1-40				
40.1-50				
>50				

Table 5: Hazard ratio of subsequent malignant CNS neoplasm for demographic and treatment variables, including treatment era.
[In those with subsequent CNS malignancy, this table will provide the hazard ratio of chosen demographic and treatment variables. Variables with a p-value cutoff of 0.1 will be used in the multivariate model as described above.]]

Risk Factors	**Hazard Ratio (95% CI), p-value**
Treatment Decade 1970 – 1979 1980 – 1989 1990 - 1999	
Age (yr) at primary cancer diagnosis 0-4 5-9 10-14 15-20	
Sex Male Female	

Race White, non-Hispanic Black, non-Hispanic Hispanic/Latino Other	
Environmental factors Ever-smoked at least 100 cigarettes Smoked >5 years	
Primary Diagnosis Type Leukemia ALL AML Other leukemia CNS tumor Astrocytoma Medulloblastoma/PNET Other CNS Lymphoma Hodgkin's lymphoma Non-Hodgkin's lymphoma Sarcoma Soft-tissue sarcoma Ewing's sarcoma Osteosarcoma Kidney Tumor Neuroblastoma Other	
CNS Radiation dose exposure, Gy	
0.1-10	
10.1-20	
20.1-30	
30.1-40	
40.1-50	
>50	
Chemotherapy Class	
Cyclophosphamide equivalent dose, mg/m^2 None 1-3999 4000-7999 ≥8000	
Epipodophyllotoxins, mg/m^2 None 1-1000 1001-3999 ≥4000	
Platinum agent, mg/m^2 None 1-400 401-749 ≥750	
Anthracycline, mg/m^2 None 0-100 101-299 ≥300	
Antimetabolites	

Intrathecal Methotrexate, mg/m^2 Median (IQR) dose None 1-39 40-69 ≥70	

Table 6: Hazard ratio of demographic and treatment variables for the subset of patients with secondary CNS malignancy who did not *receive CNS-directed radiotherapy.*

[In those with subsequent CNS malignancy who were not exposed to CNS radiation, this table will provide the HR of chosen demographic and treatment variables. Variables with a p-value cutoff of 0.1 will be used in the multivariate model as described above.]

Risk Factors	**Hazard Ratio (95% CI), p-value**
Treatment Decade 1970 – 1979 1980 – 1989 1990 - 1999	
Age (yr) at primary cancer diagnosis 0-4 5-9 10-14 15-20	
Sex Male Female	
Race White, non-Hispanic Black, non-Hispanic Hispanic/Latino Other	
Environmental factors Ever-smoked at least 100 cigarettes Smoked >5 years Persistent heavy drinking	
Primary Diagnosis Type Leukemia ALL AML Other leukemia CNS tumor Astrocytoma Medulloblastoma/PNET Other CNS Lymphoma Hodgkin's lymphoma Non-Hodgkin's lymphoma Sarcoma Soft-tissue sarcoma Ewing's sarcoma Osteosarcoma Kidney Tumor Neuroblastoma Other	
Chemotherapy Class	
Cyclophosphamide equivalent dose, mg/m^2 None 1-3999	

4000-7999 ≥8000	
Epipodophyllotoxins, mg/m^2 None 1-1000 1001-3999 ≥4000	
Platinum agent, mg/m^2 None 1-400 401-749 ≥750	
Anthracycline, mg/m^2 None 0-100 101-299 ≥300	
Antimetabolites	
Intrathecal Methotrexate, mg/m^2 Median (IQR) dose None 1-39 40-69 ≥70	

Table 7: Standardized incidence ratio (SIR) and excess absolute risk (EAR) of subsequent CNS malignancy by treatment decade of primary childhood cancer. [Standardized incidence ratio and excess absolute risk by treatment decade (hypothesis being that it will decrease each decade)]

Treatment Decade	Observed	Expected	SIR (95% CI)	EAR (95% CI)	Median time to Occurrence, yr
1970-1979					
1980-1989					
1990-1999					

Proposed Figures

- Standardized incidence ratios of subsequent CNS malignancy by treatment decade for primary childhood cancer
- Cumulative incidence curves for secondary CNS malignancies by treatment decade.
- Dose response curve of brain radiation exposure and development of secondary CNS malignancy
- Survival curves following diagnosis of secondary CNS malignancy, with separate lines for treatment decade of the primary childhood cancer

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