Childhood Cancer Survivor Study

Analysis Concept Proposal

Study Title: Evaluation of Subsequent Meningiomas in Childhood Cancer Survivors

Working groups: This project will be developed through the SMN Working Group with secondary oversight by the Epidemiology and Biostatistics Working Group. Proposed investigators include:

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Background and Rationale:

Meningiomas are the most common subsequent CNS tumor among aging adult survivors of childhood cancer (1-3). Multiple meningiomas have been described in childhood cancer survivors, with 10-14% of survivors with meningioma experiencing multiple meningiomas, (1, 4) but multiple occurrences have never been distinguished by recurrent or new subsequent events. Neglia et al. examined the incidence of, and risks associated with, the development of meningiomas in the original Childhood Cancer Survivor Study (CCSS) cohort, examining 66 cases (5).

Radiation exposure, either from environmental cause or necessary treatment, has long been recognized as a major risk factor for the development of benign meningiomas (1, 5-12). In earlier treatment eras, including the period evaluated in the initial CCSS cohort, cranial radiation was frequently used for primary CNS malignancies and acute lymphoblastic leukemias. With time and increased recognition of radiation associated morbidities, treatment evolved to reduce radiation exposure. The effects of modern therapy on risk mitigation for subsequent meningiomas have not been examined quantitatively.

Since Neglia et al.'s seminal paper, the magnitude of meningioma risk, the details of the dose – response relationship, the longitudinal risk of meningioma over time, and the impact of host and treatment factors for meningioma have been examined, but limited to childhood cancer survivor cohorts of approximately 100-170 cases (2, 4, 5, 13, 14). We intend to expand our initial CCSS analysis of meningioma to better understand its occurrence as the survivor population has aged and radiation use has declined. Indeed, as of September 2020, there were 730 cases of subsequent meningioma identified through CCSS initial and expanded cohorts (Armstrong G, email correspondence). Our overarching hypothesis is individuals treated in the most recent treatment era will have experienced lower cumulative incidence and decreased risk for development of subsequent meningiomas due to reduced therapeutic radiation exposure.

Specific Aims and Hypotheses

1) To estimate the cumulative incidence of subsequent meningiomas in survivors of childhood cancer including the original and expanded cohorts.
    a. Sub Aim1: To stratify cumulative incidence estimates by age at diagnosis of original malignancy, original cancer diagnosis, therapeutic exposures and decade of diagnosis.

   Hypotheses: The incidence of meningioma increases with time from radiation exposure and does not plateau. As radiation use has decreased with time, more recent treatment decades will have a lower incidence of subsequent meningioma.

2) To describe the incidence of meningiomatosis, recurrent meningiomas, and metachronous meningiomas among childhood cancer survivors with subsequent meningioma.
   Hypotheses: Given the extended length of time of follow up, the portion of survivors with subsequent meningioma that have more than one meningioma event, recurrent and/or metachronous, will be higher than prior estimates. Of those with more than one meningioma event, a portion will be recurrent meningioma.

3) To identify treatment, disease, and sociodemographic characteristics that predict the risk of subsequent meningioma.
   Hypotheses: Increasing cranial radiation dose, younger age at diagnosis, and female gender will be identified as independent risk factors for meningioma. Intrathecal methotrexate will not be identified.

4) To construct the radiation dose response relationship using brain 4 segment radiation data.
   Hypothesis: A statistically significant radiation dose-response relationship will be observed for first meningioma consistent with prior CCSS reports and reports from other similar cohort studies.

5) To determine all-cause and meningioma-specific mortality among childhood cancer survivors with subsequent meningioma.
   Hypotheses: Three- and five-year overall survival will be consistent with prior CCSS report, and cause of death will vary and include meningioma, progression of primary cancer, and secondary cancer.

<u>Analysis Framework</u>

Study Population

Our analysis will include childhood cancer survivors enrolled in the CCSS cohort (1970-1999) who have completed a baseline questionnaire. Individuals with unknown treatment exposure will be excluded from analysis.

Outcome of Interest

Anatomic location of meningioma will be included in analyses when available in the existing SMN data set. When not available, SMN files will be reviewed to determine if a location can be assigned.

Subsequent meningiomas will only be included if date of occurrence is 5 or more years past date of original cancer diagnosis.

- Any meningioma: Diagnosis with subsequent meningioma ≥ 5 years from childhood cancer diagnosis (include the following ICD-O codes: 9530/0, 9530/1, 9530/3, 9531/0, 9532/0, 9533/0, 9534/0, 9537/0, 9538/1, 9538/3, 9539/1, 9539/3).
- Meningiomatosis: Diagnosis with subsequent meningioma ≥ 5 years from childhood cancer diagnosis with ICD-O code 9530/1.

Subjects with more than one temporal meningioma event will be included in the analysis. Second or more events will undergo detailed re-review by study investigators of available records including radiology reports and any inpatient or outpatient clinical notes, and will be identified as recurrent or metachronous.

- Recurrent meningioma: a meningioma event that has occurred at the same anatomic location as any of the previous meningioma events. Meningiomatosis events will be considered recurrent if at least one lesion is in the same anatomic location as a previous event.
- Metachronous meningioma: a meningioma event that has occurred in a new location from any of the previous meningioma events.

Variables of Interest

- Sociodemographics:
    - original cancer diagnosis
    - age at childhood cancer diagnosis
    - date of original cancer diagnosis
    - decade of original cancer diagnosis (1970-1979, 1980-1989, 1990-1999)
    - age at meningioma diagnosis
    - date of meningioma diagnosis
    - age at last follow up
    - race/ethnicity
    - sex
- Lifestyle exposures:
    - Smoking status (yes [ever smoked at least 100 cigarettes]/no), if yes, number of years smoked
    - BMI from last follow-up survey prior to meningioma diagnosis
- Treatment exposures:
    - Surgery (yes/no; body site)
    - Chemotherapy (yes/no)
        - Alkylating agent (yes/no/cumulative dose)
        - Anthracycline (yes/no/cumulative dose)
        - Epipodophyllotoxin (yes/no/cumulative dose)
        - Platinating agents (yes/no/cumulative dose)
        - Methotrexate IT (yes/no/cumulative dose)
        - Antimetabolites (6MP and 6TG) (yes/no)
    - Hematopoietic cell transplantation (yes/no)
    - Radiation (yes/no; body site)
        - CNS radiation: CNS radiation will be identified as those exposed to cranial radiotherapy, craniospinal irradiation, and/or total body irradiation. Radiation fields exposing but not targeting the spinal cord will be classified as non-CNS

radiotherapy. Exposure will be classified into 4 brain segments (frontal, parietal, occipital, midbrain, and maximum dose segment). Dose will be reported by brain segment.

- Non-CNS radiation: Maximum dose to non-CNS body regions will be reported. Radiation fields exposing but not targeting the spinal cord (e.g. chest irradiation) will be classified as non-CNS radiotherapy.

Statistical Analysis Plan

Survivors of childhood cancer will be considered at risk of meningiomas beginning at entry into the CCSS cohort, 5 years after their childhood cancer diagnosis, until a confirmed diagnosis of meningioma, death, or date of most recent contact.

Aim 1: To estimate the cumulative incidence of subsequent meningiomas in survivors of childhood cancer across the original and expanded cohorts. Sub Aim1: To stratify cumulative incidence estimates by age at diagnosis of original malignancy, original cancer diagnosis, therapeutic exposures and decade of diagnosis. Cumulative incidence of meningioma overall and by sex, age at original cancer diagnosis, treatment decade, and dose of cranial RT will be calculated with a nonparametric estimate using time since diagnosis as the time scale and treating death as a competing risk.

Aim 2: To describe the incidence of meningiomatosis, recurrent meningiomas, and metachronous meningiomas among childhood cancer survivors with subsequent meningioma. Frequency distributions of those with any meningioma, those with recurrent, those with metachronous, those with meningiomatosis, and those without meningioma will be characterized by demographic, lifestyle, clinical, and treatment variables. Distributions will not be mutually exclusive. We will also consider presenting mean cumulative count curves if the numbers with individuals with multiple events are sufficient (16).

Aim 3: To identify treatment, disease, and sociodemographic characteristics that predict the risk of subsequent meningioma. Multivariable Cox regression will be used to estimate the hazards of a first meningioma diagnosis, using time since CCSS study entry as the time scale to assess variables that modify the risk of a first meningioma diagnosis. 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. We may fit a separate model with primary cancer diagnosis, adjusting for non-treatment factors.

Aim 4: To construct the radiation dose response relationship using brain 4 segment radiation data. 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,[5] 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.

Aim 5: To determine all-cause and meningioma-specific mortality among childhood cancer survivors with subsequent meningioma. Median follow up of patients diagnosed with any subsequent and multiple subsequent meningioma will be reported in months. Three, 5 and 10 year survival (OS) from diagnosis of meningioma 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.

Tables and Figures

Table 1. Characteristics of patients in the CCSS cohort

	No (%)				
Characteristic	Any Meningioma	Recurrent Meningioma	Metachronous Meningioma	Meningiomatosis	No Meningioma
Age at diagnosis, years Mean SD Median Range					
Age at initial diagnosis, years 0-4 5-9 10-14 15-20					
Age at last follow-up, years 20-29 30-39 40-49 50+					
Median duration of follow-up, years					
Female sex					
Race/Ethnicity White non-Hispanic Black non-Hispanic Hispanic Other Missing					
Smoking status Never Ever Number of years smoked, mean (SD) Missing					
BMI prior to meningioma					x
Original cancer diagnosis Acute lymphoblastic leukemia					

Acute myeloid leukemia Other leukemia Astrocytoma Medulloblastoma, PNET Other CNS tumor Hodgkin disease NHL Kidney tumor Neuroblastoma Ewing sarcoma Osteosarcoma Soft tissue sarcoma					
Decade of diagnosis of original cancer 1970-1979 1980-1989 1990-1999					
Treatment for original childhood cancer Surgery only Radiation therapy only Chemotherapy only Surgery + radiation Surgery + chemotherapy Radiation + chemotherapy Surgery + radiation + chemo					
RT None CNS Cranial Frontal Parietal Occipital Midbrain Craniospinal TBI Non-CNS Chest Abdomen Other (other specific categories?)					
CrRT dose					

No head/cranium or TBI dose 1-19 Gy 20-39 Gy 40+ Gy					
Hematopoietic cell transplantation No Yes					
Total no of meningiomas/subject 1 2 3 4+					x
WHO grade of meningioma I II III					x
Median age at meningioma diagnosis, years					x
Age at diagnosis of meningioma 5-9 10-19 20-29 30-39 40-49 50+					x
Median interval from original cancer to meningioma diagnosis, years					x
Cause of death for meningioma cases Meningioma Original cancer Accident, homicide, or suicide Secondary glioma Other SMN Cerebrovascular disease Unknown or other					x

Table 2. Risk factors for any subsequent meningiomas among childhood cancer survivors (variables selected *to be determined*)

	Univariable			Multivariable		
Characteristic	HR	95% CI	*P*	HR	95% CI	*P*
Age at diagnosis, y						
Sex						
Ethnicity						
Smoking						
RT						
Treatment era						

Figure 1. Survivors with multiple meningiomas after first subsequent meningioma.

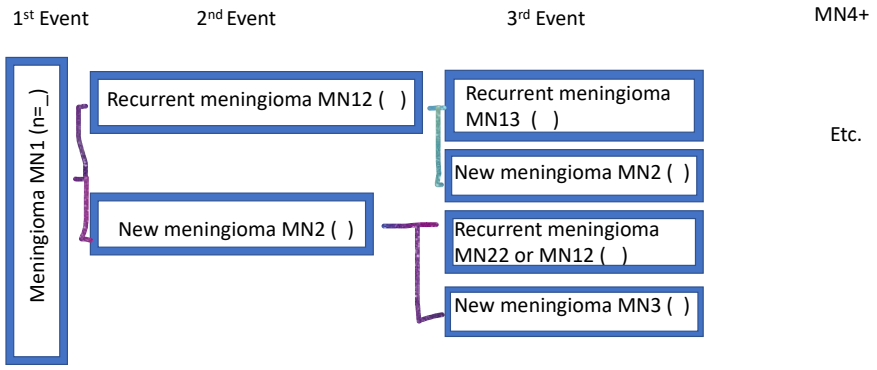

Figure 2. Dose response curve of brain radiation exposure and development of subsequent meningioma, x axis (Dose in Gy), y axis (relative risk)

Figure 3. Cumulative incidence of subsequent meningioma by (A) sex (B) age at original cancer diagnosis (C) treatment decade (D) dose of cranial RT

Figure 4. Time to occurrence of subsequent meningioma in the CCSS cohort from original cancer diagnosis, x axis time since first cancer (years), y axis no of case patients, categories years 5-9, 10-14, 15-19, 20-24, 25-29, 30-34, 35-39, 40+

Figure 5. Cumulative survival after the diagnosis of a subsequent meningioma

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