Childhood Cancer Survivor Study
Analysis Concept Proposal

Date: October 14, 2013

Study Title: Morbidity and Mortality Associated with Meningiomas following Cranial Radiation Exposure for Childhood Cancer

Working groups: Cancer Control and Subsequent Malignancy

Investigators:

Daniel C. Bowers, MD	daniel.bowers@utsouthwestern.edu	214-648-8594
Claire M. Mazewski, MD	claire.mazewski@choa.org	404-785-3515
Kevin C. Oeffinger, MD	oeffingk@mskcc.org	646-888-4730
Joseph C. Hodges, MD, MBA	joseph.hodges@utsouthwestern.edu	214-645-7668
Joseph Neglia, MD	jnegila@umn.edu	612-624-3113
Greg Armstrong, MD, MSCE	greg.armstrong@stjude.org	901-595-5892
Chaya Moskowitz, PhD	moskowic1@mskcc.org	646-735-8117
Wendy Leisenring, ScD	wleisenr@fhcrc.org	206-667-4374
Leslie L Robison, PhD	les.robison@stjude.org	901-595-5817

1. Background and rationale:

1.1 Background: Adult survivors of childhood cancer who have been exposed to cranial radiation therapy have increased rates of subsequent central nervous system (CNS) tumors, including high-grade gliomas and meningiomas.[1-10] The literature reports standardized incidence ratios for a subsequent CNS tumor (including both high-grade gliomas and meningiomas) of 8.1 – 52.3, and an absolute excess risk of a subsequent CNS tumor among childhood cancer survivors of 1.9 – 72.8 per 10,000 person years when compared with the general population.[1,3,11-13] Furthermore, a study by Cardous-Ubbink reported a standardized incidence ratio of subsequent meningioma among childhood cancer survivors of 41.2 (21.3-71.9)[14]

After the first decade following diagnosis of childhood cancer, meningiomas are the most common subsequent CNS tumor.[5,10,15] Armstrong and colleagues report a 3.3% cumulative incidence of meningiomas at 25 years following a CNS tumor.[15] Importantly, their study and others demonstrate that the rate of subsequent meningiomas does not plateau over time.[2,15-17] For example, CNS tumor survivors from the CCSS cohort who were meningioma-free at 25 years have a 3.5% cumulative incidence (95% CI = 0.9 – 6.1%) of being diagnosed with a meningioma by 30 years after primary cancer diagnosis. In addition, the cumulative dose of radiation exposure correlates with rates of subsequent meningiomas.[5,8] Taylor and colleagues' report from the British Childhood Cancer Survivor Study demonstrated a linear correlation between dose of radiation therapy and relative risk of subsequent meningiomas.[8] In their report, the increased relative risk of subsequent meningiomas first appears at exposure doses of 20 Gy and increases to a relative risk of 479.1 (95% confidence intervals: 25.0 – < 657.2; p = < 0.001) at exposure doses of at least 40 Gy.

In contrast to subsequent high-grade gliomas, which are almost universally fatal, cancer survivors with subsequent meningiomas often have a good overall survival. Four studies of childhood cancer survivors have reported survival rates ranging from 65.9 to 100% following diagnosis of a secondary meningioma,[10,17-19] which is comparable with the survival of primary meningiomas in young adults.[20] Note, however, that the study by Taylor and colleagues, which has the largest sample and longest duration of follow-up, reported the lowest survival rate (65.9%).[19] Furthermore, 25 of 42 reported patient deaths were due to the secondary meningioma.

Little is known about the morbidity that is associated with the occurrence of a subsequent meningioma, but it would be expected to be substantial because of the tumor's location and need for an intracranial surgery and/or radiation therapy to achieve tumor control. Based upon the study of the CCSS cohort by Packer and colleagues, rates of late-onset (> 5 years post-diagnosis) neurological deficits among childhood brain tumor survivors ranged from 1.9 – 11.8%.[4] Furthermore, radiation exposure was associated with at least some increased risk of late-onset neurological sequelae. Survivors exposed to ≥ 50 Gy to the frontal region of the brain had a modestly elevated risk for a motor problem (relative risk (RR) = 2.0; $p < .05$) compared with those who received a radiation exposure of < 30 Gy. Furthermore, exposure to ≥ 30 Gy to any segment of the brain, with the exception of the posterior fossa, was associated with more than a two-fold elevated risk for a late-effect seizure disorder.

1.2 Screening Practices for Secondary Meningiomas: Given the high rates of subsequent meningiomas, experts have discussed the potential benefits of screening for meningiomas among childhood cancer survivors who have been exposed to cranial radiation. Three single institution case series have examined screening neuro-imaging among childhood cancer survivors exposed to cranial radiation therapy and reported high rates of subsequent meningiomas (Table A).[21-23] These studies screened a total of 152 patients and found a rate of subsequent meningiomas of 18%. As a result, these studies' authors have recommended routine screening of childhood cancer survivors exposed to radiation therapy for meningiomas in order to facilitate easier resection and reduce mortality and morbidity among survivors with small tumors. Despite these recommendations, a recent survey by Bowers and colleagues of COG member institutions examining imaging practices of survivors of malignant brain tumors treated with cranial radiation therapy reported that only 42% (56/133) of institutions reported performing MRIs beyond 10 years after diagnosis.[24] A better understanding of tumor-related mortality and morbidity due to subsequent meningiomas would be important to make more informed recommendations for screening.

Table A: Studies Describing Asymptomatic Meningiomas Detected by Screening MRI of Childhood Cancer Survivors

Study	Initial Diagnosis	Total Number of Survivors	Number of Survivors Screened	Number of Meningiomas Identified	Interval from Initial Cancer Diagnosis to Meningioma Diagnosis
Banerjee J[21]	ALL	60	49	11 (22%)	25 years (mean)
Goshen Y[22]	ALL	88	76	16* (21%)	21 years (median)
Pääkkö E[23]	Non-CNS tumor survivors	44	27	2 (7%)	16 years (median)
Total		**192**	**152**	**28 (18%)**	

*Included 1 symptomatic meningioma.

Screening recommendations for subsequent meningiomas may be justified because the incidence of subsequent meningiomas is sufficiently high, there is a sensitive screening instrument for detection, MRI and there is an effective intervention, surgical resection that can safely and possibly reduce meningioma-related morbidity and mortality. However, at present, tumor-related morbidity and mortality among childhood cancer survivors with subsequent meningiomas is poorly understood. The three studies examining screening MRI reported above make no mention of tumor-related morbidity and mortality of study subjects.[21-23]

The primary aims of this study will be to examine the neoplasm-related morbidity and mortality among childhood cancer survivors who develop subsequent meningiomas and characterize risk factors for morbidity and mortality in this population.

2. Scientific aims/objectives/research hypotheses:

Hypothesis: High rates of meningioma-related morbidity and mortality exist among childhood cancer survivors exposed to cranial radiation (CRT).

Specific Aims:

1. Report the incidence of meningiomas more than 5 years after primary cancer and characterize these meningiomas among childhood cancer survivors who are exposed to cranial radiation and explore associated risk factors. (Tables 1, 2 and 3).
2. Estimate the frequency of neurologic sequelae among survivors of childhood cancer who develop subsequent meningiomas and explore differences by primary cancer and treatment related factors. (Table 4).
3. Describe mortality among childhood cancer survivors with subsequent meningiomas (Table 2).

3. Study Population:

The study population will consist of childhood cancer survivors from the original CCSS cohort who have been exposed to cranial radiation therapy within 5 years of their primary cancer diagnosis, including those with and without a diagnosis of a subsequent meningioma. Survivors will include those who completed at least one LTFU questionnaire (including the baseline, 2003, or 2007 questionnaires).

As of February of 2012, there were 162 CCSS participants who had been diagnosed with 186 meningiomas that have been confirmed by pathology reports (CCSS Investigator's Meeting Report, 2012). We expect that nearly all of these were in people treated with CRT.

4. Analysis framework: This is a study of childhood cancer survivors from the CCSS cohort who are exposed to cranial radiation to examine subsequent meningioma-related morbidity and mortality.

Outcomes: The outcomes of interest include meningiomas identified as subsequent neoplasms, both benign and malignant meningiomas (ICDO-2 codes 9530-9539) and meningioma-related morbidity and mortality. Although frequency of meningiomas experienced within five years of primary diagnosis will be summarized, formal analyses will be restricted to those occurring more than five years after primary cancer.

Tumor-related morbidity will be assessed by the occurrence of neurological sequelae from the current chronic conditions data set with onset within 12 months of a diagnosis of meningioma (pre- or post-diagnosis), including auditory vestibular-visual sensory deficits, focal neurologic dysfunction, seizures, headaches and surgery (e.g., craniectomy) as listed in Table B below. Mortality will be assessed by patient death, interval from diagnosis of meningioma to patient death, and cause of death.

Table B: Specific questions, including grades of severity, to be examined:

Outcomes:	Survey Questions: Baseline Survey	Follow-up 2000	Follow-up 2007	Relevant diagnoses codes found in textboxes
Auditory-Vestibular-Visual Sensory Deficits:				
Hearing loss requiring a hearing aid and/or deafness in one or both ears	C.1=Yes or C.2=Yes or C.3=Yes or ICD9 code found in C.7 or C.17	12.a=Yes or 12.b=Yes or 12.c=Yes	D.1=Yes or D.2=Yes or D.3=Yes or ICD9 code found in D.7 or D.20	• 389.7 Deaf nonspeaking, not elsewhere classifiable
Tinnitus	C.4=Yes or ICD9 code found in C.7	not asked	D.4=Yes or ICD9 code found in D.7	• 388.1 Noise effects on inner ear • 388.3 Tinnitus • 388.30 Tinnitus, unspecified
Vertigo/persistent dizziness	C.5=Yes	not asked	D.5=Yes	
Legal blindness in one or both eyes	C.8=Yes or relevant ICD9 dx code found in textbox for C.15	12.d=Yes	D.8=Yes or D.9=Yes or ICD9 code found in textbox for D.18	• 369.0, 369.00 Profound impairment of both eyes • 369.1 Moderate or severe impairment, better eye, profound impairment lesser eye • 369.4 Legal blindness, as defined in U.S.A. • 369.6 Profound impairment, one eye • 369.61 One eye: total impairment; other eye: not specified
Double vision	C.11=Yes or ICD9 code found in C.15	not asked	D.12=Yes or ICD9 code found in D.18	• 368.2 Diplopia
Focal Neurological Dysfunction:				
Coordination problems (problems with balance, equilibrium, reaching for/manipulating objects, movements and/or tremors)	J.8=Yes or J.9=Yes	not asked	K.5=Yes or K.6=Yes	
Motor problems: weakness or inability to move arms or legs	J.10=Yes or J.11=Yes	not asked	K.11=Yes or K.12=Yes	
Decreased touch or feeling	J.12=Yes	not asked	K.8=Yes	
Other Neurological Complications:				
Pain or abnormal sensation	J.13=Yes J.36=Yes		K.9=Yes K.10=Yes	
Epilepsy, repeated seizures, convulsions or blackouts	J.4=Yes or J.5=Yes or ICD9 code found in J5 textbox	12.g=Yes or 12.h=Yes or ICD9 code found in 12.h textbox	K.2=Yes or ICD9 code found in K.2 textbox	• 345.0, 345.00 Generalized nonconvulsive epilepsy • 345.1, 345.10 Generalized convulsive epilepsy • 345.3 Grand mal status • 345.4 Localization-related (focal) (partial) epilepsy and epileptic syndromes with complex partial seizures • 345.5, 345.50 Localization-related (focal) (partial) epilepsy and epileptic syndromes with simple partial seizures • 345.7 Epilepsia partialis continua • 345.8, 345.80 Other forms of epilepsy and recurrent seizures • 345.9, 345.90, 345.91 Epilepsy, unspecified • 780.3 Convulsions • 780.39 Other convulsions Convulsive disorder NOS, Fits NOS, Recurrent convulsions NOS, Seizure NOS, Seizures NOS
Seizure Medications	B.8.11=Yes, what medication?	6.k=Yes, what medication?	K.2=yes, what medication?	
Migraine or other frequent/severe headaches	J.6=Yes or J.7=Yes	not asked	K.3=Yes or K.4=Yes	
Surgery (e.g., craniectomy)	I.31=Yes, what surgery?	21.a=Yes or 21b=Yes or 21c=Yes, what surgery?	J.37=Yes, what surgery?	

Explanatory variables to be studied:

Explanatory variables to be studied will include demographic variables, including: age at diagnosis of primary cancer (years), age at diagnosis of meningioma (years), interval from diagnosis of primary cancer to diagnosis of meningioma (years), interval of follow-up

(years), sex, race/ethnicity, primary cancer diagnosis (leukemia, CNS tumor, other), exposure to cranial radiation therapy (dose), history of other subsequent neoplasms, family history of cancer, vital status, cyclophosphamide equivalent dose[25] (CED, mg/m^2), pathology (benign versus malignant), and causes of death.

Data summarizing the results from the study will be presented in the following tables: Tables 1 and 2 will describe demographic and clinical features of childhood cancer survivors who are exposed to cranial radiation and are/are not diagnosed with subsequent meningiomas. Table 3 will calculate standard incidence ratios (SIRs) and excess absolute risk for subsequent meningiomas among childhood cancer survivors exposed to cranial radiation, including an examination of risk factors for elevated excess absolute risk for subsequent meningiomas. Table 4 will calculate the incidence, magnitude of severity, and risk factors for late-onset neurologic sequelae that coincide with the diagnosis of a subsequent meningioma among survivors of childhood cancer. Finally, Table 2 will describe meningioma-related mortality among childhood cancer survivors with subsequent meningiomas.

Analytic plan

Aim 1: We will estimate the cumulative incidence of subsequent meningiomas from 5 years post childhood cancer diagnosis to the first occurrence of meningioma, treating death as a competing risk. Standardized incidence ratios will be estimated using gender-, age-, and calendar year-specific from SEER. The absolute excess risk will be calculated as the observed number of meningiomas minus the expected number, divided by the number of person years at risk and multiplied by 10,000. The association between a meningioma diagnosis and primary cancer treatment-related factors and baseline demographic factors will be evaluated using Cox proportional hazards regression.

Aim 2: We will estimate the frequency of each of the neurological sequelae together with 95% confidence intervals. Only neurological deficits that are reported to have occurred within 12 months of a meningioma diagnosis will be included in this analysis. If the timing of the onset of the neurological outcome is missing, we will impute it using multiple imputation for event-time imputations.[26,27] The frequencies will be reported separately and by treatment-related factors.

Aim 3: Among CCSS participants with meningioma, we will evaluate overall survival using the Kaplan-Meier product limit estimator from the time of diagnosis with meningioma. Cox proportional hazards models will be used to assess if survivors treated with cranial radiation who are diagnosed with a subsequent meningioma differ with respect to their overall survival compared with survivors treated with cranial radiation who have not been diagnosed with a meningioma after adjusting for radiation dose (either by average dose, maximal dose, or quadrant). Meningioma will be treated as a time-dependent covariate in this model. Neurologic-specific mortality excluding strokes (using a combined outcome of a neurologic sequelae excluding stroke) will also be described. Depending upon the number of deaths observed in this category, we may estimate the neurologic-specific cumulative incidence treating death from other causes as a competing risk.[28]

Figures:

1. Cumulative Incidence of Subsequent Meningioma
2. Overall Survival from Meningioma Diagnosis
3. Neurologic-specific Cumulative Incidence (Optional - pending evaluation of available numbers of events)

Table 1: Characteristics of Childhood Cancer Survivors who were Exposed to Cranial Radiation Therapy who Did and Did Not Develop Subsequent Meningiomas

Characteristic	**Meningioma (n = ____)**	**No Meningioma (n = ____)**
Median age at diagnosis of primary cancer, years (range)		
Age at original diagnosis, years, *n (%)*		
< 5		
5 – 10		
11 – 15		
>15		
Median age at last follow-up, years (range)		
Current age, years, *n (%)*		
< 20		
20 – 29		
30 – 39		
> 40		
Median duration of follow-up, years (range)		
Sex, *n (%)*		
Males		
Females		
Race/ethnicity, *n (%)*		
White, non-Hispanic		
Black, non-Hispanic		
Hispanic, non-Hispanic		
Other		
Primary cancer diagnosis, *n (%)*		
Leukemia		
CNS tumor		
Other		
Exposure to cranial radiation therapy, *n (%)*		
0.1 – 19 Gy		
20 – 39 Gy		
> 40 Gy		
Cyclophosphamide Equivalent Dose[25] (CED, mg/m^2)		
0		
>0 - <4,000		
≥4,000 - < 8,000		
≥8,000		
History of other subsequent neoplasms (%)		
Family history of cancer (%)		
Vital status, number alive, *(%)*		

Table 2: Clinical Characteristics of Patients with Subsequent Meningiomas

Characteristic:	**Result:**
Median age at diagnosis of meningioma, years (range)	
Age at meningioma diagnosis, *n (%)*	
< 15 years	
15 – 19 years	
20 – 24 years	
25 – 29 years	
30 – 34 years	
> 35 years	
Median interval from original cancer diagnosis to meningioma diagnosis (range), years	
Interval between primary cancer and meningioma diagnosis, *n (%)*	
5 – 9 years	
10 – 14 years	
15 – 19 years	
20 – 24 years	
> 25 years	
Pathology, *n (%)*	
Benign meningioma	
Malignant meningioma	
Cause of death among participants exposed to radiation and who develop subsequent meningiomas (%)	
Original cancer	
Subsequent meningiomas	
Other	

Table 3: Standardized Incidence Ratios of Subsequent Meningiomas after cranial RT

Variable	Observed, *n*	Expected, *n*	Standardized Incidence Ratio (95% CI)	Excess Absolute Risk (95% CI)	p value
All patients with subsequent meningiomas after CRT					
Primary cancer					
Leukemia					
CNS Tumors					
Other cancers					
Sex					
Male					
Female					
Age at primary cancer diagnosis (years)					
< 5					
6 – 10					
11 – 15					
>15					
Interval from primary cancer diagnosis to subsequent meningioma (years)					
5 – 19					
20 – 29					
> 30					
First-degree relative with cancer					
Yes					
No					

Table 4: Overall Frequency of Neurological Sequelae within ± 12 months of diagnosis of a Subsequent Meningiomas among Childhood Cancer Survivors.

Risk Factors	Number of Patients	Neurological Sequelae				Any Neurologic Sequelae No. (%) [95% CI]
		Auditory-Vestibular-Visual Sensory Deficits No. (%) [95% CI]	Focal Neurological Dysfunction No. (%) [95% CI]	Any Seizure Disorder No. (%) [95% CI]	Any Headache No. (%) [95% CI]	
Primary Cancer Diagnosis						
Leukemia						
CNS tumor						
Other						
Age at Diagnosis of Primary Cancer (years)						
0 – 4.9						
5 - 9.9						
10 – 14.9						
15+						
Interval Since Diagnosis (years)						
5 – 9						
10 – 19						
20 – 29						
30+						
Interval from Primary Cancer Diagnosis to Meningioma Diagnosis (years)						
5 – 9						
10 – 19						
20 – 29						
30+						
Age at Diagnosis of Subsequent Meningioma Diagnosis (years)						
<19.9						
20 – 29.9 years						
30 – 39.9 years						
>40 years						
Radiation Exposure						
No exposure						
0.1 – 20 Gy						
20 – 40 Gy						
> 40 Gy						
Number of Meningiomas/Patient						
1						
≥ 2						

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