Childhood Cancer Survivor Study
Analysis Concept Proposal

Title:

Neurologic and Neurosensory Adverse Sequelae in Long-term Survivors of Childhood Brain Tumors: An Update and Expanded Risk Factor Analysis Using the CCSS 2007 Follow-up Survey

Working Group and Investigators:

This proposed publication will be within the Chronic Disease Working Group with secondary oversight from the Second Malignancy and Psychology Working Groups.

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Background and Rationale:

Survivors of pediatric brain tumors are at a significant risk for long term sequelae from the tumor and its treatment. The Childhood Cancer Survivor Study follows approximately 14,000 5+ year survivors of childhood cancer treated from 1970-1986, and data collected on the survivors has been extensively used to characterize late effects. Reports from the CCSS have raised awareness of the need for close follow-up in multi-disciplinary clinics and spurred attempts to reduce late morbidity and mortality from childhood brain tumors and their treatment.

As the CCSS cohort has aged, investigators are finding an increased incidence of second malignancies, late mortality and chronic health conditions among survivors of CNS tumors (Neglia 2006; Armstrong 2009). In 2003, Packer and colleagues evaluated 1607 patients in the CCSS diagnosed between 1970 and 1986 with a primary CNS tumor and found that children surviving brain tumors are at a significant risk for both early and late neurologic and neurosensory sequelae. Recent CCSS studies have demonstrated adverse neuropsychological and neurocognitive sequelae in survivors of childhood brain tumors, particularly for patients treated with higher radiation doses. (Armstrong 2010, Ellenberg 2010) Two recent CCSS studies have shown that ocular and auditory late

effects are associated with radiation in a dose-dependent manner and that cumulative incidence of ocular and auditory late effects continued to increase 15-20 years after diagnosis for high-risk survivors. (Whelan 2010, Whelan 2011) The Whelan studies examined the baseline questionnaire only for survivors of all types of childhood cancer; we seek to expand on these findings by evaluating data through FU2007 and by focusing on multiple neurologic and neurosensory adverse sequelae specifically in patients with brain tumors.

The specific aims of the proposed study are intended to build on previous articles describing neurologic and neurosensory deficits reported on the CCSS Baseline questionnaire. The recently completed 2007 follow-up study (FU2007) provides the opportunity to extend the observation window on the CCSS cohort over an additional 10 year period. The additional years of follow up now available from the FU2007 questionnaire will provide substantial new information about late-onset neurologic sequelae among 5+ year survivors of pediatric brain tumors and enhance our understanding of the risk profile over time. The proposed investigation will help define the time frame in which neurologic late effects occur, dose response relationships for radiation and chemotherapy and the impact of covariates on the risk of developing late neurologic effects as patients age. The analysis will also answer the important question of whether extended cumulative incidence curves in this population demonstrate continuing risk of new onset neurologic deficits or a plateau. Results will have implications for long term follow-up guidelines and may help better inform newly diagnosed patients about risks associated with alkylator-based chemotherapy and radiation therapy, which remain important components of treatment regimens for many CNS tumors, although new research protocols are limiting or delaying radiation exposure in young children.

Specific Aims:

1. Describe the neurologic and neurosensory adverse sequelae occurring in long-term (5+ year) survivors of childhood brain tumors and evaluate the relative risk of these deficits compared to sibling controls.
2. Examine the temporal pattern of onset from 5 years post cancer diagnosis through FU2007 for each different type of neurologic and neurosensory deficit using cumulative incidence curves in order to determine if risks continue to increase or plateau.
3. Assess factors associated with development of neurologic and neurosensory adverse sequelae including tumor type, gender, age at initial cancer diagnosis, present age, cancer therapy (surgery, radiation therapy with dosimetry, chemotherapy), habits (physical activity, alcohol, smoking), cancer status, and secondary malignant neoplasms (SMN).
4. Summarize mortality, recurrence of original cancer and incidence of SMN through FU2007 in order to provide an appropriate context with which to integrate the information on neurosensory deficits.

Hypotheses:

1. Survivors of childhood CNS malignancies will have an increased risk of late onset adverse neurologic conditions compared to sibling controls.
2. Age at diagnosis and cancer treatment will impact the risk of developing late neurosensory or neurologic impairment.
    a. Worse neurologic and neurosensory outcomes will occur in children diagnosed with cancer at earlier ages.
3. The incidence of (new onset) seizures, strokes will continue to rise with increasing age, but the incidence of new motor and coordination problems in patients without the above will plateau with increasing age.
4. Visual impairment will be more frequent in patients who received radiation therapy to the whole brain, posterior fossa or temporal lobe and the incidence will initially increase with age (as was seen by Whelan et al 2010) and then plateau.
5. Auditory late effects will be more frequent in patient who received radiation therapy to the temporal lobe and/or posterior fossa (in a dose-response manger) or who received cis-platin chemotherapy. These effects will be more common in patients treated <5 years and the incidence will initially increase with age (as was seen by Whelan et al 2011) and then plateau.

Analysis Framework:

Subject population

Inclusion Criteria: Survivor of CNS tumors and all siblings

Outcomes

Outcomes will be determined from all available data (Baseline through FU2007 survey). .

1. Mortality (National Death Index data, updated for the 2007 NDI search)
2. Recurrence and secondary tumors (Baseline through FU2007 surveys)
    a. Original Baseline K1-K8
    b. Original Baseline <18 K1-K8
    c. 2000 Follow up and Sibling 17, 17a
    d. 2003 Follow up and Sibling R1
    e. 2005 Follow up
    f. 2007 Follow up and Sibling P1
3. Hearing /Vision/Speech
    a. Survivor and Sibling Baseline C1-C19
    b. 2000 Follow up and Sibling 12a-12e
    c. 2007 Follow-up and Sibling D1-D22
4. Brain and Nervous System
    a. Survivor and Sibling Baseline J1-J15
    b. 2000 Follow up and Sibling 12f-12h
    c. 2007 Follow-up and Sibling K1-K15

Covariates

1. Age

2. Race
3. Sex
4. Tumor location/histology
5. Chemotherapy (methotrexate, vincristine, cis-platin, ccnu) – cumulative doses
6. Radiation therapy
    a. Location of maximum radiation dose (none, frontal lobe, temporal lobe, parietal/occipital lobe, posterior fossa, spine)
    b. Cumulative doses of radiation (none, <30Gy, 30-49Gy, >/=50Gy) calculated from the time of diagnosis to five years from the time of the original diagnosis
7. Surgery
    a. Yes/no
    b. Total or partial resection
8. Tobacco
    a. Survivor and Sibling Baseline N1-N2
    b. Survivor and Sibling Follow-up 2003 L1-L6
    c. 2007 Follow-up and Sibling N7-N14
9. Alcohol
    a. Survivor and Sibling Baseline N3-N8 (N3-N4 on "Under 18" form)
    b. 2007 Follow-up and Sibling N1-N6
10. Physical activity
    a. Survivor and Sibling Baseline N9-14 (N5-N10 on "Under 18 form)
    b. Survivor and Sibling Follow-up 2003 D1-D7
    c. 2007 Follow-up and Sibling N15-N26

<u>Planned Analyses</u>

1. Descriptive/summary statistics for all outcomes and covariates
    a. Characteristics of CNS tumor survivors and siblings will be described using absolute numbers, means (SD) and/or medians (range) (Table 1)
2. Analysis of recurrence and secondary CNS neoplasms
    a. Cumulative incidence and standardized incidence ratios will be calculated as was done by Armstrong et al (2009) with baseline, follow-up 1 and 2. This analysis will add data from follow-up 3 (2005) and follow-up 4 (2007) and the 2007 NDI search.
    b. As was done with the earlier study, events will be further analyzed by major CNS tumors (Astrocytoma, PNET, Ependymoma) and by major treatment type (surgery alone, surgery + radiation, surgery + radiation + chemotherapy) and radiation dose (none, <30Gy, 30-49Gy, >/= 50 Gy).
3. Cumulative incidence of late onset adverse neurosensory and neurologic conditions will be calculated overall and by brain tumor type (Table 2).
4. Cumulative incidence curves will be used to illustrate the pattern of onset for each type of neurosensory and neurologic condition from 5 years post cancer diagnosis onward.
5. Case-sibling comparisons: we will calculate relative risks and 95% confidence intervals for each type of adverse neurosensory and neurologic condition using

Cox regression analysis with adjustment for sex and race and utilizing age as the time scale.

6. Within the cohort of CNS tumor survivors, Cox regression will be used to evaluate what factors are associated with the onset of adverse neurosensory and neurologic outcomes from 5 years post cancer diagnosis through the 2007 follow-up.
    a. Effects of radiation dose and platinum-based chemotherapy on the risk of late-onset hearing impairments, tinnitus and persistent dizziness (Table 3)
    b. Effects of radiation site and dose on the risk of visual impairment, motor impairment, seizure disorders, SMN and stroke (Table 4)
    c. Univariate and multivariate analysis of cofactors (age, race, sex, tumor location, cancer treatments (Surgery, RT, Chemo, Surgery +RT, Surgery +Chemo, RT+Chemo, or Surgery + RT +chemo), habits (physical activity, alcohol, smoking), cancer status and SMN on neurologic and neurosensory sequelae. Univariate analyses will be conducted first. Factors with a p-value <=0.10 in Univariate analysis will be further examined in multiple variable models.

TABLES

Table 1. Patient characteristics

	Patients		Siblings	
Characteristic	No.	%	No.	%
Age at interview, years				
20-29				
30-39				
40-49				
>/=50				
Sex				
Males				
Females				
Age at diagnosis, years			--	
</=4			--	
5-9			--	
>/=10			--	
Histology			--	
Astroglial			--	
Primitive neuroectodermal tumor			--	
Ependymoma			--	
Other CNS			--	
Treatment			--	
Surgery			--	
Surgery + radiation			--	
Surgery+ chemotherapy			--	
Surgery + radiation + chemotherapy			--	
Radiation			--	

Chemotherapy		--
Radiation + Chemotherapy		--
No treatment		--
Unknown		--

Table 2. Cumulative Incidence and Relative Risk vs. Sibling Cohort of Late Onset Neurologic Outcomes by Brain Tumor Histology

	Astroglial	PNET	Ependymoma	Other	Total
	CI RR	CI RR	CI RR	CI RR	CI RR
Tumor recurrence					
SMN					
Hearing impairment					
Tinnitus/Vertigo					
Seizure disorder					
Coordination problems					
Motor problems					
Sensory problems					
Severe or disabling Learning or Memory problems					
Migraine or other severe headaches					
Stroke					

Table 3. Effects of Radiation Dose to the Whole Brain and/or the Posterior Fossa and Platinum-Based Chemotherapy on the Risk of Late-Onset Hearing Impairments, Tinnitus and Persistent Dizziness

	Whole Brain Radiation Dose (RR and 95% CI)		Posterior Fossa Radiation Dose (RR and 95% CI)		Platinum-Based Chemotherapy (RR and 95% CI)
Condition (RR and 95% CI)	30-49 v <30 Gy	50+ v <30Gy	30-49 v <30 Gy	50+ v <30Gy	Yes v No
Any hearing impairment					
Tinnitus					
Vertigo					

Table 4. Effects of Radiation Site and Dose on the Risk of Late Onset Neurologic Adverse Sequelae

Disorders (RR and 95% CI)	30-49 v <30 Gy	50+ v <30 Gy
Secondary Malignant Neoplasm (SMN)		
Posterior fossa		
Temporal lobe		
Frontal cortex		

Parietal or occipital		
Legal blindness in one or both eyes		
Posterior fossa		
Temporal lobe		
Frontal cortex		
Parietal or occipital		
Any motor disorder		
Posterior fossa		
Temporal lobe		
Frontal cortex		
Parietal or occipital		
Any seizure disorder		
Posterior fossa		
Temporal lobe		
Frontal cortex		
Parietal or occipital		
Severe or Disabling Learning or Memory Problems		
Posterior fossa		
Temporal lobe		
Frontal cortex		
Parietal or occipital		
Stroke		
Posterior fossa		
Temporal lobe		
Frontal cortex		
Parietal or occipital		

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