

Proposal No: 00-02
Topic: Neurologic Outcomes of Brain Cancer Survivors

Lead CCSS Investigator: Roger Packer

Collaborators: Donaldson, Neglia, P. Inskip, Gurney, Robison

Submitted to Publications Committee: 2/15/01

Approved by Publications Committee: 3/1/01

Priority Rating: 2.8

01-02

2-15-01

CCSS Concept Proposal

Neurological Outcomes of Brain Cancer Survivors

Roger Packer	RPACKER@cnmc.org	(Principal Investigator)
Sarah Donaldson	sarah@reyes.stanford.edu	
Joseph Neglia	jneglia@tc.umn.edu	
Peter Inskip	inskippe@mail.nih.gov	
James Gurney	gurney@epi.umn.edu	
Les Robison	robison@epi.umn.edu	

This proposal was developed as part of the CNS data task force. It is one of three analysis projects identified by the task force (neurological outcomes, non-neurological medical outcomes, psychosocial outcomes). The three groups are working in concert with each other to assure that a comprehensive analysis of late effects among brain tumor survivors will be conducted, while avoiding redundancy in the information presented.

Hypothesis 1 – Neurocognitive Outcomes

Background

Neurocognitive damage is common in children surviving brain tumors. In the Childhood Cancer Survivor Study, self-reporting of mental retardation is substantial, occurring in approximately 10% of the cohort. School difficulties, however, are a great deal more frequent. 53% of the cohort required special help in school, including 52% of those with glial tumors, 68% of those with medulloblastoma, and 55% of those with ependymomas. Although 87% of the children surviving brain tumors completed high school, less than one-quarter went on to higher education following high school. 70% of those younger than 3 years of age at diagnosis and 62.8% of those between 3 and 9 years of age required extra educational support. Many factors may play a role in explaining the sequelae seen including tumor histology, age at time of diagnosis, and treatment received.

Primary Hypothesis: Neurocognitive sequelae of children surviving brain tumors, as manifest by school difficulties (placement in a learning disabled or special education program; lack of ability to complete high school; or inability to pursue further training after high school) will be significantly different than sibling controls or other cancer survivors.

Secondary Hypotheses:

- Younger age at therapy will be associated with more severe outcomes
- Children receiving radiotherapy will have an increased number or severity of neurocognitive sequelae, in proportion to the dose/volume of radiotherapy given
- Concomitant use of chemotherapy, in particular methotrexate, will increase late neurocognitive sequelae
- Female gender will be associated with increase neurocognitive sequelae

Methods of Analysis

Determining school performance and mental retardation will quantitate the neurocognitive sequelae of the patients. Question O.1 asks the highest educational level attained. Questions O.3 and O.4 address learning disabled or special education programs. The frequency of positive responses to these questions will be compared within and outside of the CNS tumors subgroup. Using these variables in a multivariate analysis, we will determine to what extent school history differs by age at diagnosis (<5, 5-9, 10-14, 15-21), by tumor histology (astrocytoma, PNET/Medullo, ependymoma, other CNS) and by use of radiotherapy/chemotherapy after adjusting for age at interview. We will compare school-based outcomes to those reported by sibling controls who are appropriately matched on sex and age at interview. Prevalence of mental retardation, as asked in question J.3, will be compared by tumor histology (as above) and other factors such as age at diagnosis and use of radiotherapy and chemotherapy.

Hypothesis 2 – Chronic Headaches

Background

The prevalence of chronic headaches in children surviving brain tumors is poorly characterized. In the initial analysis of the Childhood Cancer Survivor Study, 38% of survivors who completed the questionnaire complained of headaches. Migraines were reported by over 15% of children with medulloblastoma/PNETs and ependymomas. The prevalence of chronic headaches is believed higher than that of the normal population, but population-based data are not available from either the NHIS or the BRFSS studies. Several pathophysiologic pathways could be considered as a source for chronic headaches. The initial neurosurgical procedure may lead to headaches, although it is likely that almost all patients in the cohort will have had surgery. Radiotherapy could produce small vessel vascular damage that may manifest as headache. Children with VP shunts in place may be more likely to have headache as a result of chronic, unrecognized over- or under-shunting.

Primary Hypothesis: Children surviving brain tumors will more often report frequent headaches and migraines than sibling controls of the same age and sex.

Secondary Hypotheses:

- Radiotherapy exposure will increase the frequency of chronic headaches
- Children with VP shunts will have more frequent headaches than children without shunts

Method of Analysis

Questions J.6 (migraine) and J.7 (other frequent headaches) will be used to compare headache frequency in survivors versus sibling controls. Survivors will be stratified in the analysis by treatment (radiation versus no radiation), tumor histology, previous VP shunt placement, and age at diagnosis (as above). Information under B.9 (prescribed pain medications) will be evaluated to determine if prescribed pain medications are more frequently reported among those reporting headaches or migraines than either survivors without headaches or sibling controls. If radiotherapy is found to be significantly associated with a higher likelihood of headaches,

especially migraine, a correlative analysis of radiotherapy dose/volume will be undertaken.

Hypothesis 3 – Neurosensory Deficits

Background

Although poorly documented, children with brain tumors often have significant neurosensory deficits. In the initial analysis of the Cancer Survivor Study, 14% of patients were noted to be blind in one or both eyes, hearing problems were noted in over 30% of patients, 10% of patients had dizziness or vertigo, and 11% of patients had tinnitus. The factors associated with these sequelae are not well known.

Primary Hypothesis: Neurosensory deficits will be increased in brain tumor survivors as compared to sibling controls.

Secondary Hypotheses:

- Neurosensory sequelae among the brain cancer survivors will be increase among children diagnosed at earlier ages
- Neurosensory sequelae will be more common in children with glial tumors
- Children receiving platinum chemotherapies will have an increased frequency of neurosensory sequelae
- Children receiving radiotherapy will have an increased frequency of neurosensory sequelae which will be potentiated by platinum exposure

Methods of Analysis

Hearing and visual problems will be analyzed separately. Any hearing loss will be characterized by combining C.1 (hearing aid), C.2 (deafness in one or both ears) and C.3 (complete deafness) and will be compared with data from the sibling controls. For survivors, differences in hearing loss frequency will be determined according to tumor histology, and, to the extent possible, tumor site (ICD-O site). A secondary analysis will be undertaken to determine the association between hearing loss and radiotherapy or platinum chemotherapy. Similarly, separate analyses will be undertaken to evaluate reported dizziness or vertigo (C.5) or tinnitus (C.4) stratified by tumor histology, tumor site, use of radiotherapy, and chemotherapy. Visual difficulties will be

determined as noted in C.8 (legally blind in one or both eyes). Legal blindness in one or both eyes will be evaluated by tumor histology, site, and radiotherapy.

Hypothesis 4 – Focal Neurologic Dysfunction

Background

Focal neurologic dysfunctions were found to be quite common in the initial analysis of the Childhood Cancer Survivor Study. Problems included balance difficulties in 47%, tremors in 26%, weakness of the arms in 28%, and weakness of the legs in 33%. Although a variety of factors may be responsible for these deficits, it may be that the most likely is the tumor location rather than therapy.

Primary Hypothesis: Focal neurologic dysfunction in long-term survivors of childhood brain tumors will be more common than in siblings or other cancer survivors and related predominantly to tumor site (rather than tumor histology).

Method of Analysis

Focal neurologic deficits will be described and compared to sibling controls from answers provided in the J section of the CCSS follow-up questionnaire. The analysis will include cerebellar deficits J.8 (balance) and J.9 (tremors), individually and in combination, and weakness of the arms (J.10) and legs (J.11). Problems in balance and weakness will be evaluated according to tumor site, tumor histology, use of radiotherapy, and age at diagnosis.

Please note that information on tumor site will be limited, because a majority of cases include only a site code of c71 (brain), without a more specific location. If we find during the analysis that tumor site is not recorded often enough to be reasonably reliable, we will abandon that part of the analysis. Our determination of the viability of site code will include an evaluation that compares those with a specific site code to those with only the general brain site, by sex, respondent (parent or self), age at diagnosis, age at interview, tumor histology, and treatment, to test whether or not differences exist between the groups.

Hypothesis 5 - Seizures

Background

Although children with cortical tumors will frequently present with seizures as one of their earliest manifestations of a brain tumor, the prevalence of chronic seizures in these patients is poorly characterized. In the preliminary analysis of the Childhood Cancer Survivor Study, 28% of CNS patients were found to have seizures, including 32% of those with glial tumors, 21% with medulloblastomas, and 22% with ependymomas. 24.5% were said to be on chronic antiepileptic medication, including 18% of those children with medulloblastomas. It has been believed, although not well documented, that seizures predominantly occur in those children with cortical lesions. This preliminary analysis raises questions about this assumption.

Primary Hypothesis: The risk of having a chronic seizure disorder will be increased in children with hemispheric tumors as compared to children with infratentorial tumors.

Method of Analysis

The prevalence of seizures will be determined by J.4 (epilepsy) and J.5 (repeated seizures) and J.38 (epilepsy or repeated seizures in the past 12 months). Information from question B.8 under the subset of antiepileptic medications will be compared with answers to J.4 and J.5 and J.38. Any patient who reported epilepsy or repeated seizures and who reported being on chronic antiepileptic medications will be considered to have epilepsy. The prevalence of epilepsy will be compared by tumor histology, treatment, and to the extent possible, tumor site (from ICD-O site codes). Limits of this analysis are similar to that of Hypothesis 4, specifically limited data exists on primary tumor site (see above).

We propose that the analysis be conducted at the University of Minnesota under the auspices of Dr. James Gurney with consultation by Dr. Peter Inskip (National Cancer Institute) and Dr. Yutaka Yasui.