Proposal No: 00-07
Topic: Post-Treatment Stroke

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00 - 07

CHILDHOOD CANCER SURVIVOR STUDY
DESCRIPTIVE ANALYSIS

1. **Title**: Descriptive analysis of post-treatment stroke among survivors of childhood and adolescent cancer

2. **Working Group and investigators (name/e-mail/fax)**:
**Working Groups**: Chronic Disease and/or Neurological/Psychosocial


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3. **Specific Aims/Objectives/Research Hypotheses**:
**Aims/Objectives**
   1. To determine the prevalence of stroke in survivors of childhood cancer. 1996 NHIS data will be used to provide comparison population standards for prevalence of stroke characterized by age, sex, ethnicity .
   2. Using a case-case analysis, assess risk factors for stroke after cancer treatment
      A. Compare demographic factors of cancer survivors between with stroke versus without stroke.
         1) Age at cancer diagnosis
         2) Age at first stroke
         3) Sex
         4) Ethnicity
      B. Cancer diagnosis (primary) by specific tumor site
      C. Treatment related and other medical risk factors
         1) Radiation therapy
         2) Chemotherapeutic drug use
      D. Personal history of diabetes, hypertension, coagulopathy

**Hypotheses**:
   1. Brain tumor survivors will have a substantially higher prevalence of stroke than will the general age-matched population and the age matched persons within the CCSS cohort without brain cancer.
   2. Persons with childhood tumors of the head (excluding brain) and neck will have a higher prevalence of stroke than the general age matched population and the age matched sibling controls within the CCSS cohort.
   3. Persons with childhood leukemia, due to craniospinal radiation, will have a higher prevalence of stroke than the general age matched population and the age matched sibling controls within the CCSS cohort.
   4. Persons with childhood solid tumors of the abdomen or extremities will have no increase in stroke prevalence over the general age matched population or the sibling age matched CCSS cohort.

4. **Background and rationale:**
In the past three decades, the prognosis for childhood cancer has markedly improved. Childhood cancer survivors are, in increasing numbers, going on to complete their education and become members of the workforce. The sequelae of the ionizing radiation and chemotherapeutic drugs that these survivors received as part of the therapy for their disease have become more important. It

becomes clinically essential to consider what preventive measures can be taken to lessen if not prevent late effects of therapy.

Patients who, for treatment of various cancers, received radiation to the head and neck would logically be the persons whom one might look for cardiovascular disease with neurologic sequelae as a potential adverse treatment result due to vascular injury. However, we should also remain aware of arterial occlusive disease in areas other than the head: subclavian, axillary and aorta complications have been reported and are the subject of research in surgical management for relief of extremity ischemia, and vascular hypotension (1).

Stroke (cerebrovascular accident) is known to be a late, though perhaps uncommon, sequelae of radiation therapy for childhood brain tumors (2). Mitchell et al. in a report of eleven children seen at the Children's Hospital of Los Angeles, reported strokes occurring six to forty-eight months after completion of treatment. The authors postulated that the stokes and transient ischemic attacks seen in these children were due to damage to medium and large intracranial vessels which the children suffered in addition to variable amounts of mineralizing microangiopathy. Omura et al. retrospectively evaluated thirty-two patients, after excluding patients who had tumor progression, treated for brain tumors at their institution. The children had neurologic followup and serial magnetic resonance imaging for 1.3 to 14 years after therapy. Cerebral vasculopathy developed in six children two to thirteen years after radiation therapy. They found a difference in the mean radiation exposure dose when the six children with subsequent stroke (n=3) or transient ischemic attack (n=3)were compared to those who did not have these neurologic sequelae. They also found that the occlusive changes in the major cerebral arteries were present and detectable on serial MRI. In the three patients with transient ischemic attacks the changes lead to encephaloduroarteriosynangiosis. These patients have had no further neurologic sequelae reported (3).

If survivors of childhood cancer are shown to have a higher incidence of stroke than would be expected for age, their preventative care should include a focus on minimizing stroke risk factors to the extent possible. If they are found to have a significant component of extracranial carotid disease, they may be considered for carotid endarterectomy. The North American Symptomatic Carotid Endarterectomy Trial (NASCET) affirmed the efficacy of carotid endarterectomy as prophylactic therapy for persons with transient ischemic attacks or non-disabling strokes and 70-99% stenosis of the ipsilateral carotid artery (4). If they have intracranial disease that would be amenable to encephaloduroarteriosynangiosis, they may be considered for that procedure instead.

The phenomenon of delayed radiation necrosis with its accompanying stroke like episodes and seizure activity in the setting of gradual onset dementia is a known complication of cranial irradiation. However, the prevalence of stroke in this cohort, without clinical or radiographic evidence of radiation necrosis injury would be of interest and of possible clinical importance. The cognitive difficulties that can be associated with subcortical infarction as well as the physical difficulties that can be associated with cortical injury represent possible detractors from the quality of life of the survivors.

5. **Study design:**

1. Outcome of interest: stroke after completion of cancer treatment
2. Study population: For the case-case analyses, our study population is the entire CCSS cohort. We will compare rates of stoke among those in different treatment groups and different cancer types, while controlling for factors such as age at diagnosis and gender. For the studies that use sibling controls, our study population is that CCSS cohort and the sibling controls. We will compare stroke rates among the siblings to those of any number of subgroups of the survivors (subgroups based on treatment and cancer type), while controlling for age, gender, and anything else relevant. Similarly, we will compare age and gender specific NHIS prevelences to that of several subgroups of the CCSS survivors.
3. Explanatory variables: age at diagnosis, age at interview, ethnicity, gender, type of treatment: surgery only, radiation only, chemotherapy only and treatment -with limitation of detailed analysis to those patients who received radiation to the head (interest in the circle of Willis and internal carotids) and/or neck (carotid region).

## 6 Analysis:

The statistical coordinating center, under the supervision of Dr. Yasui, will conduct the analysis. The tables shown below illustrate the descriptive comparisons of interest. We will evaluate risk of stroke by tumor type, tumor site and treatment while controlling for potentially confounding factors using multivariate regression analysis.

Comparison data will be obtained from the NHIS 1996 public use data set, which is also self reported information and corresponds in time to when a large propotion of the CCSS cohort completed their followup questionnaires. SUDAAN software will be used to adjust for oversampling and intracluster correlations resulting from the complex, multistage sampling design used for NHIS.

## 7 Methods and procedures:

1. Use answers to questions F7-9 in the CCSS questionnaire, selecting all "yes" or "not sure" for further review
   F7-Hypertension not requiring medication
   F8-Hypertension requiring medication
   F9-A stroke or cerebrovascular accident
2. Correlate above with responses to J 8-12 in the CCSS questionnaire to charaacterize severity of residual effects and provide an internal control for F9.
   J8-Problems with balance, equilibrium….
   J9-Tremors or problems with movements
   J10-Weakness or an inability to move arm
   J11-Weakness or inability to move leg
   J12-Decreased sense of touch or feeling…
3. Tables:
   a) #of patients with stroke by diagnosis categories (compared with age at interview matched controls)

| | Age 0-10 years | Age 11-20 years | Age 21-30 years | Age 31-40 years | Number of persons with stroke | Percentage of total # of persons with stroke |
|---|---|---|---|---|---|---|
| NHIS Population | | | | | | |
| Brain tumor pts | | | | | | |
| Head and neck other than brain | | | | | | |
| Hodgkins' disease | | | | | | |
| Non-Hodgkins disease | | | | | | |
| Leukemic pts | | | | | | |
| Kidney tumor patients | | | | | | |
| Neuroblastoma | | | | | | |
| Soft Tissue Sarcoma pts | | | | | | |
| Bone cancers | | | | | | |

b) stroke patients divided into groups by type of treatment

| | Surgery only | | Chemotherapy only | | Radiation only | | Surgery and chemotherapy | | Surgery and radiation only | | Chemotherapy and radiation only | |
|---|---|---|---|---|---|---|---|---|---|---|---|---|
| | # | % | # | % | # | % | # | % | # | % | # | % |
| Brain tumor pts | | | | | | | | | | | | |
| Head and neck other than brain | | | | | | | | | | | | |

| | | | | | | |
|---|---|---|---|---|---|---|
| Hodgkins' disease | | | | | | |
| Non-Hodgkins disease | | | | | | |
| Leukemic pts | | | | | | |
| Kidney tumor patients | | | | | | |
| Neuroblastoma | | | | | | |
| Soft Tissue Sarcoma pts | | | | | | |
| Bone cancers | | | | | | |

c) stroke patients stratified by outcomes that may be related to stroke

| | Diabetes (E5,6,7) | Hypertension (F8) | Clotting disorder (F16) |
|---|---|---|---|
| Brain tumor pts | | | |
| Head and neck other than brain | | | |
| Hodgkins' disease | | | |
| Non-Hodgkins disease | | | |
| Leukemic pts | | | |
| Kidney tumor patients | | | |
| Neuroblastoma | | | |
| Soft Tissue Sarcoma pts | | | |
| Bone cancers | | | |

**Bibliography:**


1. Andros G, Schneider PA, Harris RW, Dulawa LB, Oblath RW, Salles-Cunha SX. Management of arterial occlusive disease following radiation therapy. Cardiovascular Surgery 1996; 4(2): 135-142
2. Mitchell WG, Fishman LS, Miller JH, Nelson M, Zelter PM, Soni D, Siegel SM. Stroke as a late sequela of cranial irradiation for childhood brain tumors. J Child Neurology 1991; 6: 128-133
3. Omura M, Aida N, Sekido K, Kakehi M, Matsubara S. Large intracranial vessel occlusive vasculopathy after radiation therapy in children: clinical features and usefulness of magnetic resonance imaging. Int J. Radiation Oncology, Biol, Phys 1997; 38 (2): 241-249
4. North American Symptomatic Carotid Endarterectomy Trial Collaborators. Beneficial effect of carotid endarterectomy in symptomatic patients with high grade carotid stenosis New England Journal of Medicine 1991;325: 445-453