

Proposal No: 98-22

Topic: Second Primary Neoplasms of the Central Nervous System

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98-22

CHILDHOOD CANCER SURVIVOR STUDY
Analysis Concept Proposal

Submitted: September 14, 1998

1. **Title:** Second Primary Neoplasms (SPNs) of the Central Nervous System among long-term Survivors of Childhood Cancer.
2. **Working Group and Investigators:** the Second Cancers Study Group will oversee This publication. Proposed investigators include:

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3. **Background and Rationale:** Second cancers of the CNS are a recognized complication of primary cancer therapy. A significant excess of CNS tumors (compared to population expected) has been observed among long-term survivors of childhood ALL and childhood brain tumors. In the initial analysis of the CCSS cohort, second tumors of the CNS have been the most second primary neoplasms, reported in 77 instances. The occurrence of a secondary CNS tumor is often devastating. Essentially all of these occurrences will mandate a major neurosurgical procedure, and in many instances the tumors which occur are very aggressive and poorly responsive to therapy. Radiation of a second primary CNS tumor is complicated by the frequent use radiation in the treatment of the initial tumor, and may not be able to be given at usual therapeutic doses.

Prior therapeutic radiation is the only recognized treatment factor that contributes to SPNs of the CNS. Little data is available regarding other potential etiologic or clinical associations. An increased risk appeared to be associated with young age in ALL patients, but has not been consistent in other analyses. Agents used to treat primary CNS tumors, in particular the *n-nitroso* compounds, have been speculated to be etiologic agents for primary CNS tumors in children. Their role in secondary primary CNS tumors has never been investigated.

4. **Specific Aims:**
 - a) Describe the occurrence of second primary CNS tumors by histology, site, and host characteristics including age, sex, and initial cancer.
 - b) Determine the risk of histology specific CNS SPNs and their association with the original cancer diagnosis.

- c) Determine the contribution of initial cancer therapy, overall, and in a dose/response fashion to the etiology of CNS SPNs. Covariates to be considered will include:
 - i) Radiation therapy
 - ii) Alkylating agents
 - iii) Nitroso ureas
- d) Assess the impact of the occurrence of a CNS SPN on mortality and morbidity
- e) Review family histories of children with CNS SPNs for apparent associations and recognized cancer family pedigrees.

Hypotheses:

- a) Children who undergo therapy at a young age are at greater risk for the development of a second CNS primary.
- b) A dose/response radiation effect will be documented which will show an increased likelihood of higher-grade CNS tumors (i.e. glioblastoma, PNET) with higher doses of primary XRT.
- c) Children whose initial CNS therapy includes *n-nitroso* compounds or alkylating agents will be at greater risk of a CNS SPN.
- d) Children with CNS SPNs will have a greater number of first degree relatives with cancer than children without CNS SPNs.

5. Analysis Framework:

- a) outcome of interest: CNS Second Primary Neoplasms
- b) subject population: all CCSS cases with identified CNS SPNs
- c) explanatory variables:
 - i) tumor histology (Astrocytic / PNET / Meningioma / Other)
 - ii) age at primary neoplasm diagnosis, sex
 - iii) primary diagnosis
 - iv) radiation dose / interval
 - v) chemotherapy dose (nitroso-ureas, alkylating agents)
- d) specific tables / figures
 - i) patient characteristics:
 - CNS SPNs / nonCNS SPNs / No SPN
 - Diagnosis, sex, age, race, life status
 - tumor characteristics
 - location by histology
 - latency by histology
 - mean radiation dose
 - ii) population observed / expected ratios for tumor types
 - iii) actuarial curve for distinct tumor types
 - iv) risk of CNS SPN by:
 - radiation (dose categories)
 - chemotherapies (dose categories)
 - v) morbid status of patients with CNS SPNs
 - vi) outcomes of SPNs by therapy information
 - vii) numbers of 1st degree relatives with CNS SPNs (vs entire cohort)

6. **Special Considerations:** A major concern will be assurance that the SPN of the CNS does not represent a recurrence of the primary (for CNS primary tumors). We will have to discuss the need for pathologic review of all specimens as opposed to relying on pathology reports. Analysis of pedigrees may be exceptionally complicated and could be difficult to include depending on the analysis of clinical and pathological endpoints. Radiation therapy dose effects may be critical and could require the inclusion of specific dosimetry.