revised
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**Childhood Cancer Survivor Study**

Analysis Concept Proposal

1. **Title:** Second Primary Sarcomas in Survivors of Pediatric Malignancy

2. **Working Group and Investigators:** Second Malignancy Committee

   Proposed investigators:

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3. **Background and Rationale:**

Treatment of childhood malignancies has become increasingly successful with a current overall cure rate of greater than 80 percent.[1-2] With cure, comes the long term toxic "late effects" of aggressive chemotherapy and radiation therapy. Second malignant neoplasms (SMN) are a well-known late effect of concern for long-term survivors of childhood cancer and their physicians, with a fifteen year cumulative incidence of three to five percent.[3] SMNs are the second leading cause of death in survivors, after the recurrence of the primary cancer.[4] Sarcomas, including osteosarcoma, rhabdomyosarcoma and other soft tissue sarcomas, account for a significant number of these SMN.

To date, there have been no large studies describing second primary sarcomas and their risk factors. There have been large cohort studies describing bone tumors/sarcomas as second malignant neoplasms following childhood cancer.[5-10] The Late Effects Study Group, a 13 institution consortium of pediatric centers from western Europe, Canada and the United States reported in a cohort of 9170 patients who had survived 2 or more years from a childhood cancer diagnosis, 64 patients who developed a second primary bone sarcoma.[5] There was a dose-response gradient with radiotherapy that was associated with increased incidence of bone sarcoma, reaching a 40-fold risk after doses to the bone of more than 6000 rad. In addition, after adjusting for radiotherapy, treatment was alkylators increased the subsequent risk of bone cancer. This group later reported a series of 91 second bone sarcomas. In this series, it was again found that radiation therapy and alkylating agents contributed to the incidence of second bone sarcomas in this series. A shorter interval to the development of SMN was associated with the use of anthracyclines and alkylating agents, though only the anthracycline effect was statistically significant.[6] Hawkins *et al* [7]

described 55 second bone tumors in a cohort study of 13,175 3-year survivors of childhood cancer diagnosed between 1940 and 1983. There was a 26-fold increase in developing second bone cancers in all childhood cancer survivors, except retinoblastoma. Similar to the Late Effects Study Group, there was an increased risk of bone cancer with increased cumulative dose of radiation to the bone. The risk of bone cancer in this study increased linearly, in a statistically significant fashion, with increased cumulative dose of alkylating agents.

The Childhood Cancer Survivor Study (CCSS) is an ongoing cohort of over 14,000 childhood cancer survivors treated between 1970-1986 and surviving at least 5 years. Neglia *et al* reported the occurrences of SMN and their risk factors in the CCSS Cohort. At the time of this publication, 314 SMNs were reported. There were 28 bone cancers and 32 soft tissue sarcomas. Since this publication the CCSS has updated the current numbers of SMN. Currently, there are 1039 patients with SMN and a total of 70 are sarcomas. Analyzing the clinical characteristics of these sarcomas in relation to previous therapies and family history would invaluable for physicians following childhood cancer survivors. Understanding second sarcomas as they relate to chemotherapy or radiation dose, age at diagnosis of primary malignancy, family history would enable physicians to better project long term prognosis, follow up and appropriate screening.

## 4. Specific Aims/Research Hypotheses:

**Aims:**

a) Describe the occurrence of second primary sarcomas by histology, site, and host characteristics including age, sex and initial cancer
b) Determine the risk of histology-specific sarcomas 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 second primary sarcomas. Covariates to be considered will include:
    i) Radiation therapy, dose at site of sarcoma
    ii) Alkylating agents
    iii) Anthracyclines

d) Assess the impact of the occurrence of a second primary sarcoma on morbidity and mortality
    i) Survival time after diagnosis of second sarcoma
    ii) Treatment and resectability of second sarcoma

e) Review family histories of children with second primary sarcomas for apparent associations and recognized cancer family pedigrees.

**Hypotheses:**

**I. Hypotheses to be Tested Using Case-Cohort Analysis**

a) Children who undergo therapy at a young age are at a greater risk for the development of a second primary sarcoma.
b) Children whose initial cancer therapy includes alkylating agents will be at higher risk of a second primary sarcoma
c) Children whose initial cancer therapy includes anthracyclines will be at higher risk of a second primary sarcoma
d) Children with second primary sarcomas will have a greater number of first degree relatives with cancer than children without second primary sarcomas.

**II. Hypothesis to be Tested Using Case-Control Analysis**

**a)** A dose/response radiation effect will be documented which will show an increased likelihood of a second primary sarcoma with higher doses of primary XRT.

**5. Analysis Framework**

**I. Analysis for Case-Cohort Study**

**a)** Outcome of interest: Sarcoma Second Primary Neoplasms
**b)** Subject population: all CCSS cases with identified Sarcoma Second Primary Neoplasms (osseous/bone sarcomas/ other, soft tissue sarcoma/malignant fibrous histiocytoma/schwannoma/MPNST)
**c)** Study Design: Case-cohort
**d)** Explanatory variables:

i) tumor histology (i.e., Osteosarcoma/Rhabdosarcoma/Soft tissue sarcoma NOS)
ii) age at primary neoplasm diagnosis, sex
**iii)** Primary diagnosis
**iv)** Radiation exposure
- Yes/No
- Site
- Dose categories
- Time since radiation

**v)** Chemotherapy
- Exposure
- Alkylators – Yes/No
- Anthracyclines – Yes/No
- Dose effect by quintile

e) Specific Tables / figures

i) Patient characteristics (overall cohort/patients with second sarcomas/patients without second sarcomas)
Sarcoma Second primary neoplasms / Other SMNs
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. Expected ratios will be calculated with use of age-and sex- specific incidence rates from the NCI's SEER program

iii) risk of sarcoma second primary neoplasms by:
radiation (dose categories)
chemotherapies (dose categories)

iv) morbid status of patients with sarcoma second primaries

v) outcomes of SMN by therapy information

vi) numbers of 1st degree relatives with cancer vs. entire cohort

## II. Analysis of Case-Control Study

a) Outcome of interest: Sarcoma Second Primary Neoplasms

b) Subject population: all CCSS cases with identified Sarcoma Second Primary Neoplasms

c) Study Design: Case-control

- Locate sarcoma anatomically in case; estimate dose to this point and to same point in control
- 3 controls per case
- Controls matched to case by:
    1) Age of primary cancer diagnosis
    2) Length of follow-up
    3) Sex

d) Specific Table

- Curves of odds ratio of SMN by doses of radiation in both cases and controls

## Examples of Tables

## Table 1: Descriptive characteristics of patients with second sarcomas

| CHARACTERISTICS | Overall cohort | Cases with a second sarcoma (# / %) | Cases without a second sarcoma (# / %) |
|---|---|---|---|
| Sex<br>- Male #/%<br>- Female #/% | | | |
| Race<br>- Caucasian<br>- Black<br>- Hispanic<br>- Other | | | |
| Age at 1st Cancer<br>- Less than 1 year<br>- 1-3 years<br>- 4-7 years<br>- 8-10 years<br>- 11-14 years<br>- 15-20 years | | | |
| Age at Entry Into CCSS<br>- <20 years<br>- 20-29 years<br>- 30-39 years<br>- >40 years | | | |
| Primary Diagnosis<br>- leukemia<br>- brain/CNS tumor<br>- Hodgkin's<br>- Non-Hodgkin's lymphoma<br>- Kidney tumor<br>- Neuroblastoma<br>- Soft tissue sarcoma<br>- Bone tumor | | | |
| Received Chemotherapy for Primary Malignancy | | | |
| Received Radiation Therapy for Primary Malignancy<br>- chest<br>- abdomen<br>- head and neck<br>- extremities<br>- TBI | | | |
| Received Surgery for Primary Malignancy | | | |
| Received Alkylator Therapy for Primary Malignancy | | | |
| Received Stem Cell Transplant for Primary Malignancy | | | |
| History of Smoking<br>- Former Smoker<br>- Current Smoker<br>< 1 ppd<br>1-2 ppd<br>>2 ppd | | | |
| History of EtOH Use<br>- Never<br>- Light (<1 drink per day)<br>- Moderate (1 drink per day)<br>- Heavy (2-3 drinks per day)<br>- Very Heavy (>3 drinks per day) | | | |
| History of Other SMN<br>- Yes<br>- No | | | |

## Table 2: Descriptive Characteristics of Second Sarcomas

| Tumor Characteristics | #/% |
|---|---|
| Time from diagnosis of second sarcoma from primary malignancy diagnosis<br>- 0-5 years<br>- 5-10 years<br>- 10-15 years<br>- 15-20 years<br>- >20 years | |
| Location of Second Sarcoma<br>- Brain<br>- Head and Neck<br>- Chest<br>- Abdomen<br>- Extremities<br>- Genito-urinary | |
| Histology<br>- Osteosarcoma<br>- Rhabdomyosarcoma<br>- Non Rhabdo STS<br>- Subtypes of NonRMS STS<br>- Ewing's/PNET<br>- | |
| In a Site of Previous Radiation<br>- Yes<br>- No | |

## Table 3: Observed/Expected Ratios by Sarcoma Types

| Tumor Type | Observed Rate | Expected Rate* | O/E Ratio |
|---|---|---|---|
| Osteosarcoma | | | |
| Rhabdomyosarcoma | | | |
| Ewings/PNET | | | |
| Other | | | |

* Expected rates calculated with the use of age- and sex-specific incidence rates (SEER program)

## Table 4: Second Sarcoma Risk by Radiation Dose, Stratified by Age at Primary Diagnosis

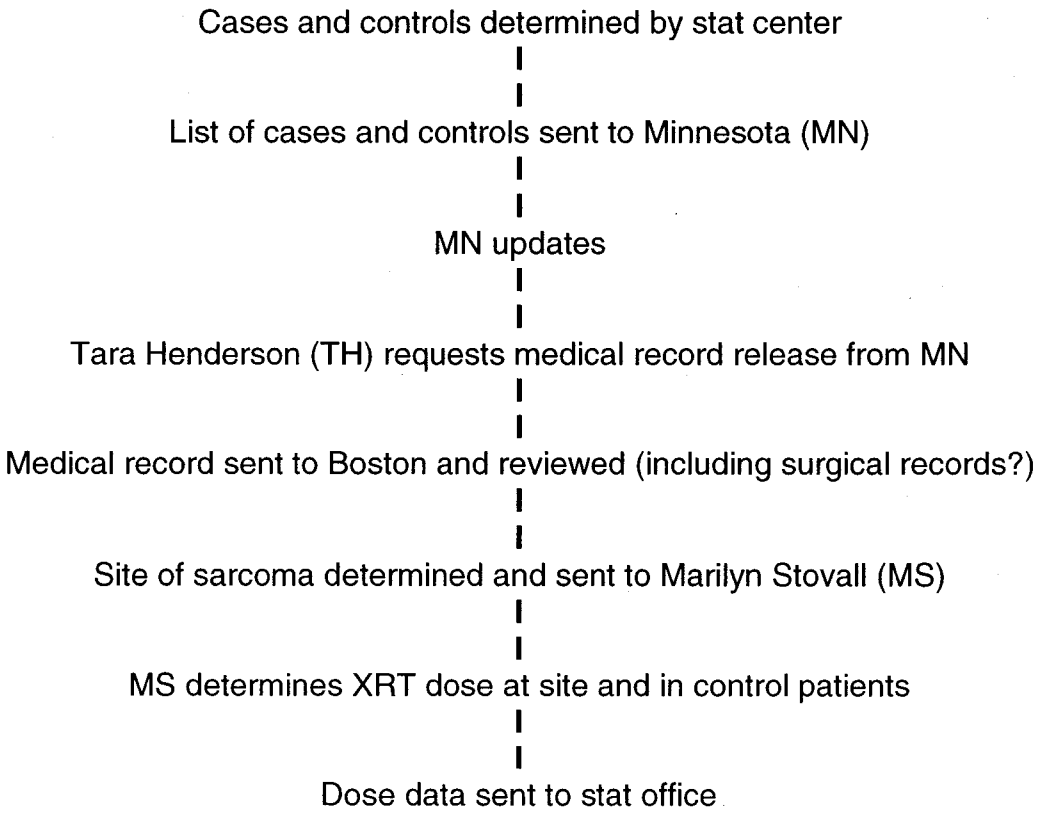
| Age | Radiation Dose (cGy) | | | | |
|---|---|---|---|---|---|
| | None | 1-999 | 1000-2499 | 2500-4000 | 4000+ |
| Less Than 5 years | | | | | |
| Greater Than 5 Years | | | | | |
| Total | | | | | |

## Table 5: Second Sarcoma Risk by Alkylator Dose, Stratified by Age at Primary Diagnosis

| Age | Alkylator Dose (g/m2) | | | | |
|---|---|---|---|---|---|
| | None | <1 | 1-5 | 5-10 | >10 |
| Less Than 5 years | | | | | |
| Greater Than 5 Years | | | | | |
| Total | | | | | |

## Figure 5: Change in Mortality Rates After the Development of a Secondary Sarcoma (Curves)

**Flow of Data for Dosimetry Analysis:**



## References


[1] Blatt *et al.* Late effects of childhood cancer and its treatment, in Pizzo, Poplack, eds.: **Principles and practice of pediatric oncology, 4th Ed**. Philadelphia 2002.

[2]Greenlee *et al.* Cancer statistics, 2000. **CA Cancer J Clin.** 50: 7-33, 2000.

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[5]Tucker *et al.* Bone sarcomas linked to radiotherapy and chemotherapy in children. **NEJM**. 1987; 317 (10): 588-593.

[6]Newton *et al.* Bone sarcomas as second malignant neoplasms following childhood cancer. **Cancer.** 1991; 67(1): 193-201.

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[8] Le Vu *et al.* Radiation dose, chemotherapy and risk of osteosarcoma after solid tumours during childhood. **Int J Cancer.** 1998; 77: 370-377.

[9] Bielack *et al.* Osteosarcoma after allogeneic bone marrow transplantation. A report of four cases from the cooperative osteosarcoma study group. **Bone Marrow Transplantation.** 2003; 31: 353-359.

[10] Ferrari *et al.* Secondary Tumors in Bone Sarcomas After Treatment with Chemotherapy. **Cancer Detection and Prevention.** 1999; 23: 368-374.