Study Title:
Lung Cancer as a Subsequent Malignant Neoplasm in Survivors of Childhood Cancer: A Report from the Childhood Cancer Survivor Study

Working Group:
Second Malignancy

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Background and Rationale:

With 5-year survival rates exceeding 80% and over 420,000 pediatric cancer survivors now alive in the United States,[1] recognition of significant late effects after cancer therapy including subsequent malignant neoplasms (SMN)[2] and multiple chronic medical conditions[3] is now crucial to provide continued care to long-term survivors. The most significant cause of premature mortality (after cancer recurrence) reported from the Childhood Cancer Survivor Study (CCSS) comes from SMN occurrence, with a standardized mortality ratio (SMR) greater than 15.[5,6] While the most frequent SMN (after non-melanoma skin cancer) is breast cancer,[7] other less common SMNs including gastrointestinal cancer,[8,9] renal cancer,[10] late leukemia,[11] and melanoma,[12] also have important health consequences for survivors.

Lung cancer is the most common cancer seen in adults with an estimated 234,030 new cases in 2018. Lung cancer is the leading cause of cancer mortality in both adult men and women.[13] Lung cancer as an SMN has previously been seen in the CCSS with a 30 year cumulative incidence of 0.1%, and an elevated standardized incidence ratio (SIR) of 3.4 (95% C.I. of 1.9 to 6.1).[7] The highest risk patients are those originally diagnosed with Hodgkin lymphoma,[14-16] and much of what we know about lung cancer as an SMN comes from adolescents and adults with Hodgkin lymphoma.[17-19] The Dutch recently reported in the New England Journal of Medicine on a national cohort of Hodgkin lymphoma patients aged 15 to 50 years old at diagnosis. Breast cancer was again the most common SMN with lung cancer second (absolute excess risk of 24.6 per 10,000 person years, SIR of 6.4 (95% C.I. of 5.5 to 7.4), and 30-year cumulative incidence of 6.4%). Risk factor analysis showed supradiaphragmatic radiation with a hazard ratio (HR) of 3, smoking with a HR of 4.86, and the combination with a HR of 14.38.[17] While previously reported as a risk factor,[18,19] chemotherapy did not significantly affect risk in this large multivariable model.

Lung cancer screening has been debated in other high-risk populations and the use of low-dose helical computed tomography (LDCT) has been shown to reduce mortality in selected populations.[20,21] The current recommendations from the American Cancer Society have specific guidelines for lung cancer screening that have been adopted by some and recommended by others to guide screening in pediatric cancer survivors, though the benefit of LDCT is still debated.[13, 22] This study seeks to provide additional information about the risk, characteristics, and outcomes of lung cancer as an SMN, specifically in the pediatric survivor population to serve as a first step in better understanding the potential utility of screening strategies in the future for lung cancer as an SMN.

Specific Aims:

1) Describe cumulative incidence, standardized incidence ratio, and absolute excess risk of lung cancer as a subsequent neoplasm in survivors of childhood cancer.
   Hypothesis: Survivors of childhood cancer will have higher rates of and be at increased risk for development of lung cancer compared to the general population.
2) Describe characteristics of lung cancer cases including time to diagnosis, age at diagnosis, and histology.
   Hypothesis: Survivors of childhood cancer will have distinct characteristics of lung cancer diagnosis compared to the general population, such as presenting at a younger age and having different histological distributions of cancers (small cell vs non-small cell cancers)
3) Identify risk factors associated with the development of lung cancer.
   Hypothesis: Treatment factors such as radiation therapy will increase the risk of secondary lung cancer in a dose-dependent manner. Patient characteristics such as smoking status will increase risk of secondary lung cancer.
4) Describe survival outcomes for patients with lung cancer as a subsequent neoplasm.
   Hypothesis: Survival will be poor for childhood cancer survivors diagnosed with lung cancer as a subsequent malignant neoplasm.

Analysis Framework:

Subject Population

All CCSS study participants from the full cohort who completed the baseline questionnaire will be eligible for these analyses.

Outcome of Interest

The outcome of interest will be lung cancers occurring greater than 5 years from the childhood cancer diagnosis and ascertained through self-report questionnaires and pathologically confirmed by the CCSS Pathology Center. Selected cases identified through self-report and/or death certificate will also be included. Cancers to be considered eligible for inclusion in these analyses will have International Classification of Diseases of Oncology (ICD-O-3) site codes of C34 and C38. The total number of cases that have been identified in the original and expanded cohort is 45 secondary lung cancers along with 9 mesothelioma cases.

Variables

1. age at childhood initial diagnosis

2. age at last follow-up
3. duration of follow-up
4. age at lung cancer diagnosis
5. gender
6. race
7. vital status
8. family cancer history
9. childhood malignancy diagnosis
10. treatment era for childhood malignancy treatment
11. smoking status (ever (including age when started), never)
12. report of emphysema or lung fibrosis (with age of onset)
13. pathology of lung cancer (ICD-0-3 code)
14. prior chemotherapy exposure (with cumulative dose)
    a. Anthracycline cumulative dose (mg/m2)
    b. Cyclophosphamide equivalent dose (mg/m2)
    c. Platinum cumulative dose (mg/m2)
    d. Epipodophyllotoxin cumulative dose (mg/m2)
    e. Methotrexate cumulative dose (mg/m2)
    f. Bleomycin
    g. CCNU

14. Maximum chest radiation exposure as estimate of lung radiation exposure (yes/no and total dose). Radiation exposure data will be taken from previous work done for Dr. Moscowitz' study. MD Anderson has already abstracted substantial amount of data that will allow determination of chest exposure and field size (within categories outlined below) without a "new" abstraction of radiotherapy exposure or the creation of new phantoms. Please see the attached document "CCSS Expanded: Summary of Fields Contributing to Chest Doses" that is attached to this document. Location of the lung tumor within the chest will be categorized using existing data, however lung anatomy is such that a tumor in the "left lower lobe" could be anywhere from the diaphragm to the axilla. This precludes more specific location data. (Note: this plan was reviewed on a January 30, 2019 conference call with Drs. Howell, Armstrong, Ghosh, and Neglia)
    a. none
    b. 0.1-10 Gy
    c. 10.1-20 Gy
    d. 20.1-30 Gy
    e. 30.1-40 Gy
    f. 40.1-50 Gy
    g. >50 Gy
15. Estimated chest field volume exposure (based off chest dose field summary dataset)
    a. small
    b. medium
    c. large
16. Bone Marrow Transplant Exposure (yes/no)

Statistical Analysis Plan:

The distribution of participant characteristics and treatment therapies in survivors with and without secondary lung cancer will be summarized and compared with Pearson chi-squared tests. For Aim 1, cumulative incidence estimates with corresponding 95% confidence intervals (CI), based on patients at risk at a given time point, will be calculated from 5 years after childhood cancer diagnosis to first occurrence of lung cancer, treating death as a competing risk factor and censoring at date of last contact. The standardized incidence ratio (SIR) and absolute excess risk (AER) with corresponding 95% CI will be derived using age, sex, and calendar year specific rates from the Surveillance Epidemiology and End Results (SEER) database. For Aim 2, simple descriptive statistics will be performed regarding distribution of age at diagnosis, distribution of stage at diagnosis, and distribution of histology. For Aim 3, Cox proportional hazards models will be used to assess associations between patient and treatment characteristics and the risk of subsequent lung cancer. Multivariable analysis will be limited to participant characteristics and treatment variables with univariate association at p-value less than or equal to 0.2. Chemotherapy exposures will be collapsed to total anthracyclines, total platinums (Carbo / 4 + Cis), [23,24] and alkylating agents (using the cyclophosphamide equivalent dose). For Aim 4, Cox regression models for mortality with development of lung cancer as a time dependent covariate will be fit. For all Cox models, age will be used as the time scale with entry to analysis at the age at cohort entry and censoring at age of last follow-up or death. All statistical tests will be two-sided with p-value less than or equal to 0.05 as statistically significant.

References:

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Sample Figure/Tables:

Figure 1a: Cumulative incidence curve of lung cancer starting at 5 years after diagnosis
Figure 1b: Cumulative incidence curve of lung cancer by lung radiation exposure
Figure 2: Kaplan-Meier overall survival curve starting from diagnosis of lung cancer

Table 1: Characteristics of survivors who developed lung cancer versus those who did not

Characteristic	**CCSS Cohort Members with Lung Cancer (%)**	**CCSS Cohort Members without Lung Cancer (%)**
Age at initial diagnosis 0-4 yrs 5-9 yrs 10-14 yrs 15+ yrs		
Mean Age at Last Follow-Up		
Mean Duration of Follow-Up		
Gender Male Female		
Race Non-Hispanic White Non-Hispanic Black Hispanic Asian/Pacific Islander Other		
Primary malignancy diagnosis Leukemia Hodgkins Lymphoma Non Hodgkins Lymphoma Primary CNS disease Ewing Sarcoma Osteosarcoma Soft Tissue Sarcoma		
Family history of cancer		
Smoking status Ever (age at start) Never		
Other reported pulmonary outcomes		

None Pulmonary Fibrosis Emphysema Other		
Treatment era 1970-1979 1980-1989 1990-1999		
Anthracycline Cumulative Dose (mg/m2) None 1-100 101-300 >300		
Bleomycin Exposure No Yes		
CCNU Exposure No Yes		
Cyclophosphamide Equivalent Dose (mg/m2) None 1-3999 4000-7999 >8000		
Epipodophyllotoxin Cumulative Dose (mg/m2) None 1-1000 1001-4000 >4000		
Methotrexate Cumulative Dose (mg/m2) None 1-11999 >12000		
Platinum Cumulative Dose (mg/m2) None		

1-400 401-750 >750		
Maximum Chest Radiation Exposure None 0.1-10 Gy 10.1-20 Gy 20.1-30 Gy 30.1-40 Gy 40.1-50 Gy >50 Gy		
Estimation of Radiation Field Volume Small Medium Large		
Bone marrow transplant		
Vital status Alive Deceased		

Table 2: Clinical and pathologic characteristics of secondary lung cancer case

Characteristic	**Lung Cancer Cases**
Age at lung cancer diagnosis	
Time from primary diagnosis to lung cancer (latency)	
Pathologic subtype of lung cancer (ICD-O-3 code)	

Table 3: Unadjusted SIRs and AERs and associated 95% CIs of subsequent lung carcinomas stratified by patient characteristics

Characteristic	Number observed	Number expected	SIR (95% CI)	AER (95% CI)	Cumulative Incidence % (95% CI)
All cases					
Gender					

Male Female					
Age at diagnosis 0-4 y 5-9 y 10-14 y 15+ y					
Current age <30 years 30-39.99 years 40-49.99 years 50-59.99 years >/= 60 years					
Treatment era 1970-1979 1980-1989 1990-1999					
Elapsed Time after Primary Diagnosis 0-9 years 10-19 years >/= 20 years					

Table 4: Unadjusted SIRs and AERs and associated 95% CIs of subsequent lung carcinomas stratified by treatment characteristics

Characteristic	Number observed	Number expected	SIR (95% CI)	AER (95% CI)	Cumulative Incidence % (95% CI)
Anthracycline Cumulative Dose (mg/m2) None 1-100 101-300 >300					
Bleomycin Exposure No Yes					
CCNU Exposure					

No Yes					
Cyclophosphamide Equivalent Dose (mg/m2) None 1-3999 4000-7999 >8000					
Epipodophyllotoxin Cumulative Dose (mg/m2) None 1-1000 1001-4000 >4000					
Methotrexate Cumulative Dose (mg/m2) None 1-11999 >12000					
Platinum Cumulative Dose (mg/m2) None 1-400 401-750 >750					
Maximum Chest Radiation Exposure None 0.1-10 Gy 10.1-20 Gy 20.1-30 Gy 30.1-40 Gy 40.1-50 Gy >50 Gy					
Estimation of Radiation Field					

Volume Small Medium Large					

Table 5: Multivariate analyses of subsequent lung cancers

Characteristic	Hazard Ratios (95% CI)	p-value
Gender Male Female		
Age at initial diagnosis 0-4 y 5-9 y 10-14 y 15+ y		
Anthracycline Cumulative Dose (mg/m2) None 1-100 101-300 >300		
Bleomycin Exposure No Yes		
CCNU Exposure No Yes		
Cyclophosphamide Equivalent Dose (mg/m2) None 1-3999 4000-7999 >8000		
Epipodophyllotoxin Cumulative Dose (mg/m2) None 1-1000 1001-4000		

>4000		
Platinum Cumulative Dose (mg/m2) None 1-400 401-750 >750		
Maximum Chest Radiation Exposure None 0.1-10 Gy 10.1-20 Gy 20.1-30 Gy 30.1-40 Gy 40.1-50 Gy >50 Gy		
Estimation of Radiation Field Volume Small Medium Large		
Smoking Status Ever (age at start) Never		