

Childhood Cancer Survivor Study Analysis Concept Proposal

Title: Late Hospitalizations in Five-Year Survivors of Childhood and Adolescent Cancer

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Background

The probability of 5-year survival from childhood cancer has increased from under 30% in 1960 to almost 80% for those children diagnosed between 1996 and 2002(1). This success has brought with it the need to assess the long-term morbidity and mortality associated with cancer and its treatment. Long-term survivors are at risk for developing a broad spectrum of adverse outcomes including early death, second neoplasms, organ dysfunction, disturbances in growth and development, decreasing fertility, impaired intellectual function, difficulties in obtaining employment and insurance, and overall reduced quality of life(2-4). In addition, a large number of cancer survivors may have unrecognized toxicities and complications requiring hospitalizations for workup and management. This study aims to evaluate “late” hospitalizations (defined as hospitalizations occurring following completion of primary cancer therapy) in individuals who have survived at least 5 years from their childhood or adolescent cancer.

Primary Aim

1) To compare rates of hospitalization among the CCSS cohort and the general United States population, taking into account age and gender. (*Note: We considered using the sibling cohort as a control population; however, comparable outcomes in this cohort were not available since the siblings only completed hospitalization data for FU 1.*)

- Hypothesis: Survivors of childhood cancer have higher rates of hospitalization following cancer therapy compared with age and gender matched population-based controls.
- Outcome of interest: Hx of hospitalization (Q21a, b and c on FU 1, Q A1 on FU 3).
- Plan for analysis: This study is a cross-sectional review of all hospitalizations among CCSS participants since completion of the baseline questionnaire. The follow-up questionnaires pertaining to hospitalization data will be reviewed for all CCSS cases during the time periods from completion of baseline questionnaire to completion of the 2000 (FU 1) follow-up questionnaire, and from the 2000 follow-up to the 2004 (FU 3) follow-up questionnaire. Completion of both questionnaires by the participant is not required for inclusion; participants may contribute different person-years to the analysis. The specific plan for analysis for the primary aim is as follows:

- Hospitalization rate (number of hospitalizations from any cause divided by the person-years at risk) among CCSS cohort cases over the period from 1995 to 2004, according to gender and age decade
- Standardized morbidity ratio for hospitalization, calculated as the observed number of hospitalizations among CCSS cases per year, divided by the expected number of hospitalizations among gender and age matched controls from the U.S. population

Secondary Aims

2) To describe major causes for hospitalization among childhood cancer survivors in the CCSS cohort.

- Hypothesis: Higher incidence rates of hospitalization among cancer survivors are associated with the presence of late effects of cancer diagnosis and therapy. Specific patterns of hospitalization will be identified in the survivor cohort, based on treatment exposures and primary diagnosis.
- Outcomes of interest:
 - Reason for hospitalization, classified according to ICD 9 system: cardiovascular causes (ICD 390-459), respiratory causes (ICD 460-519),

nervous system causes (ICD 320-389), neoplasm (ICD 140-239), gastrointestinal causes (520-579), obstetrical causes (ICD 630-677), external causes (accidents, poisonings, and so on) (ICD 800-999) and other causes (all other ICD codes).

- Plan for analysis: (*Analyses will be performed with and without pregnancy as reason for hospitalization.*)
 - For CCSS cases, frequency distribution for any hospitalization by primary cancer diagnosis and gender
 - For CCSS cases, frequency distribution for any hospitalization by cancer treatment category (no treatment, chemotherapy only, radiation therapy only, surgery only, chemotherapy + radiation therapy, chemotherapy + surgery, radiation therapy + surgery, chemotherapy + radiation therapy + surgery)
 - Frequency distribution of causes for hospitalization among CCSS cases by system (cardiovascular, respiratory, gastrointestinal, neoplasm etc.) and gender
 - Standardized morbidity ratios for hospitalization by body system, calculated as the observed number of hospitalizations for specific causes (e.g. cardiovascular causes) among CCSS cases per year, divided by the expected number of hospitalizations for specific causes among gender and age matched controls from the U.S. population

3) To investigate explanatory factors for hospitalization over time among cancer survivors, including demographic characteristics, and diagnostic and treatment variables.

- Hypothesis: The hazard for first hospitalization is dependent upon diagnosis type, age at diagnosis, time elapsed since diagnosis, relapse of disease, and specific treatments received (including radiation therapy, chemotherapy, and surgery). Survivors who are further from diagnosis, who have had disease relapse, and those who have received more intensive cancer therapy (i.e. chemotherapy and radiation) are more likely to have been hospitalized.

- Outcomes of interest: Time to first hospitalization

- Plan for analysis: Cox proportional hazards modeling of time to first hospitalization will be applied. The outcome to be modeled is first hospitalization from any cause. The start time for the cohort will be 5 years post diagnosis. Thus, hospitalizations prior to

year 5 will not be included in the analysis. For all analyses, death prior to hospitalization will be treated as a competing event and last contact as a censoring time; subjects' follow-up time will be censored at the first of these events. At the latest, follow-up will be censored at the time of completion of the 2004 Follow-up survey (FU 3). In the event that the assumptions of the Cox proportional hazards model are violated, multivariable logistic regression will be performed instead.

Univariate analysis: (Note that the variables below will all be modeled in a categorical fashion. Reference groups will be determined from frequency data prior to analysis.)

- Hazard ratio of hospitalization by primary cancer diagnosis
- Hazard ratio of hospitalization by treatment category (no treatment, chemotherapy only, radiation therapy only, surgery only, chemotherapy + radiation therapy, chemotherapy + surgery, radiation therapy + surgery, chemotherapy + radiation therapy + surgery)
- Hazard ratio of hospitalization by age at diagnosis
- Hazard ratio of hospitalization by time elapsed since diagnosis (*time dependent variable*)
- Hazard ratio of hospitalization by occurrence of second malignancy (yes/no)
- Hazard ratio of hospitalization by gender, ethnicity, insurance, income, and education
- * Relapse status (yes/no) will be evaluated as a potential confounder with a sensitivity analysis

Multivariable analysis: Independent variables which are found to be significant with univariate analysis will be included in the larger model.

Further comments on statistical analysis: We are seeking a dataset including the variables outlined below. Dr. Kurt is an oncology fellow at St. Jude Children's Research Hospital and is expected to complete her own analysis as part of the requirements for her masters degree in Epidemiology. Dr. Kiri Ness will assist her with these analyses at St.

Jude. All analyses will be reviewed and approved by Wendy Leisenring at the Statistical Coordinating Center.

Subject Population:

Cases: Five-year survivors of childhood cancer who have completed the baseline and the 2000 (FU 1) & 2004 (FU 3) follow-up questionnaires.

Controls: National data for hospital utilization will be used to compare hospitalization rates with CCSS cases. The source for national hospitalization data will be the National Center for Health Statistics (NCHS) National Hospital Discharge Survey (NHDS).

Variables:

Exposure variables:

- Age at diagnosis (calculated from date of birth and date of diagnosis abstracted from medical record)
- Diagnosis (eight level diagnosis)
- Time elapsed since diagnosis (calculated from date of diagnosis abstracted from medical record and date of completion of FU1 and FU 3).
- Second malignancy (Q 17 on FU1, Q B1 on FU 3)
- Time since diagnosis of second malignancy (calculated from date of SMN (Q 17 on FU1, Q B1 on FU 3) and date of completion of FU1 and FU 3)
- Radiation therapy including site from MRAF summary (cranium, other head and neck, chest, spine and TBI)
- Chemotherapy drugs, including dose from MRAF summary (Anthracycline (not exposed, 1 -100 mg/m²; 101 - 400mg/m²; 401 + mg/m²; Alkylating agent score (not exposed, 1-2, 3-4, 5+); Epipodophyllotoxin (not exposed, 1 - 982 mg/m²; 983 - 4108mg/m²; 4109 + mg/m²); Bleomycin dose (not exposed; 1 - 59mg/m²; 60 - 118 mg/m²; 119 + mg/m²)
- Surgery including splenectomy (ICD9 41.5) from MRAF summary

-Combination chemotherapy+radiation therapy, chemotherapy+surgery, radiation therapy+surgery, or chemotherapy+radiation therapy+surgery from MRAF summary

Potential confounders:

- Relapse (Q 17 on FU1, Q B1 on FU 3)
- Gender (taken from baseline questionnaire QA2)
- Ethnicity (from baseline questionnaire QA4 and QA4a), categorized as Black, White, Hispanic, Asian/Pacific Islander and Other
- Insurance (taken from most recently completed FU questionnaire—Q 16 FU1 or Baseline Q 2)
- Income (taken from Baseline Q 9)
- Education (taken from most recent FU questionnaire—Q 1 FU1 or Baseline Q O1)

Specific tables:

Table 1: Characteristics of CCSS cases

Characteristic	Survivors (n=)	Percent
Age at diagnosis		
0-4		
5-9		
10-14		
15-20		
Median (range)		
Age at follow-up		
Median (range)		
Time elapsed since diagnosis		
Median (range)		
Diagnosis (8+ level diagnosis)		
Treatment Exposure		

No treatment		
Chemotherapy only		
Radiation therapy only		
Surgery only		
Chemotherapy + radiation therapy		
Chemotherapy + surgery		
Radiation therapy + surgery		
Chemotherapy + radiation + surgery		
Anthracyclines		
Not exposed		
1-100 mg/m2		
101-400 mg/m2		
> 400 mg/m2		
Alkylating agent score		
Not exposed		
1-2		
3-4		
5 +		
Epipodophyllotoxin		
Not exposed		
1-982 mg/m2		
983-4108 mg/m2		
> 4108 mg/m2		
Bleomycin		
Not exposed		
1-59 mg/m2		
60-118 mg/m2		
> 119 mg/m2		
Site of radiation therapy		
Head and neck		
Chest		
Spine		
Total body		
Splenectomy		
Relapse		
Time since relapse		

Median (range)		
Second malignancy		
Time since diagnosis of second malignancy		
Median (range)		

Table 2: Hospitalizations among CCSS Cases

	Number of Hospitalizations	Rate of hospitalization (person-years)	95% CI
Sex			
Male			
Female			
Age at diagnosis			
0-4 years			
5-9 years			
10-14 years			
15-20 years			
Age at last follow-up survey			
18-30 years			
31-40 years			
41-50 years			
> 50 years			
Diagnosis			
Leukemia			
CNS tumors			
Hodgkin's diseases			
Non-Hodgkin's lymphoma			
Kidney (Wilms)			
Neuroblastoma			
Soft tissue sarcoma			
Bone tumors			

Table 3: Cause-specific SM_bRs and 95% Confidence Intervals by Sex and Cancer Diagnosis in CCSS

	Cardiovascular		Pulmonary		Nervous System		Gastrointestinal		Neoplasm		Obstetric		External Causes		Other Causes	
	SM _b R	95% CI	SM _b R	95% CI	SM _b R	95% CI	SM _b R	95% CI	SM _b R	95% CI	SM _b R	95% CI	SM _b R	95% CI	SM _b R	95% CI
All Cases																
Sex																
Male											--	--				
Female																
Diagnosis																
Leukemia																
CNS																
Hodgkin's disease																
Non-Hodgkin's lymphoma																
Kidney (Wilms)																
Neuroblastoma																
Soft tissue sarcoma																
Bone																

Table 4: Explanatory variables for hospitalization among CCSS cases

Covariate	HR	95% CI	P-value
Age at diagnosis			
Time elapsed since diagnosis			
Primary cancer diagnosis			
Leukemia			
CNS tumors			
Hodgkin's diseases			
Non-Hodgkin's lymphoma			
Kidney (Wilms)			
Neuroblastoma			
Soft tissue sarcoma			
Bone tumors			
Treatment category [†]			
No treatment			
Chemotherapy only			
Radiation therapy only			
Surgery only			
Chemotherapy + radiation therapy			
Chemotherapy + surgery			
Radiation therapy + surgery			
Chemotherapy + radiation + surgery			
Occurrence of relapse			
Yes			
No			
Gender			
Male			
Female			
Race/ethnicity			
White			
Black			
Hispanic			
Other			
Insurance			
Yes (United States)			
No (United States)			

Canadian resident			
Income			
< \$40,000			
\$40,000-79,000			
\$80,000 +			
Unknown			
Education			
<High school			
High school graduate			
College graduate			

Figure 1: Cumulative incidence of first hospitalization (including/excluding external causes and obstetrics) overall and by gender.

Figure 2: Cumulative incidence of first hospitalization by primary cancer diagnosis.

Figure 3: Cumulative incidence of first hospitalization by treatment category.

References:

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3. Oeffinger KC, Mertens AC, Sklar CA, Kawashima T, Hudson MM, Meadows AT, et al. Chronic health conditions in adult survivors of childhood cancer. *N Engl J Med.* 2006 Oct 12;355(15):1572-82.
4. Mertens AC. Late Mortality Experience in Five-Year Survivors of Childhood and Adolescent Cancer: The Childhood Cancer Survivor Study. *Journal of Clinical Oncology.* 2001 July 1;19(13):3163-72.