05-19

Childhood Cancer Survivor Study
Analysis Concept Proposal

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Title: Late Recurrence in Survivors of Childhood and Adolescent Cancer: A Report from the Childhood Cancer Survivor Study

Working Group and Investigators:

Proposed working group:
Epidemiology/Biostatistics

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Background and Rationale:

An increasing percentage of childhood and adolescent cancer patients are surviving for at least five years from their initial diagnosis. Five-year survival is often misinterpreted to mean cure, however relapses more than five years from diagnosis do occur. In 2001 Mertens et al reported on late mortality in five-year survivors of childhood cancer from the Childhood Cancer Survivor Study (CCSS) and found the leading cause of death for 5-year survivors to be recurrence of the original cancer (1). Further analysis of these late relapses is warranted. While most patients relapse within the first few years of completing therapy, late relapses, though rare, have been reported for most pediatric cancers.

The literature on late relapses has been limited to case reports, case series and long-term analyses of specific cancers treated through individual study groups or institutions (2-7). These reports, though limited by sample size, have led to recommendations for routine follow-up evaluations and treatment. Continued annual imaging over 5 years from diagnosis is routine for sarcomas for early detection and intervention of late pulmonary relapse (3). For other diseases such as acute lymphoblastic leukemia and Hodgkin's disease, improved survival has been associated with late relapse as opposed to early relapse (4-7). This difference in survival can affect treatment decisions. As more pediatric cancer patients enter long-term follow-up as survivors of their cancer, it is important for both patients and physicians to appreciate the risk of relapse in long-

term follow-up. By understanding diagnosis-specific risks and the implications for survival and treatment, evidence-based recommendations on long-term follow-up can be made.

The CCSS provides a unique opportunity to study late recurrence due to the unparalleled sample size of childhood cancer survivors in this cohort. Prior reports have been limited to analysis of double-digit late recurrences, at most. On a preliminary review of the data, 887 total recurrences were reported five years or more from the original diagnosis with 539 of these being first recurrences. This translates to approximately one in twenty-five pediatric cancer survivors relapsing for the first time 5-years of more after their primary diagnosis. This is a time when many survivors no longer have formal oncology follow-up and is especially true in the young adult population where access to care is a particular problem.

The goal of this analysis is to describe the incidence of late relapse in the overall CCSS cohort and for specific diagnoses within the cohort. The focus of this analysis will be on late recurrence, but we will take into consideration reports of early recurrence.

For this analysis, the event of a recurrence will be defined as self-reported on one of the three CCSS surveys (Baseline: Section K; Follow-up 1: Question 17; follow-up 2: Section R). Early recurrence will be defined as a self-reported occurrence from diagnosis to 5 years post diagnosis. Late recurrence will be defined as recurrence 5+ years post diagnosis. When looking at late recurrence events, first recurrence will refer to the first occurrence of a relapse. Any recurrence will include all recurrences 5+ years post diagnosis; even those with an earlier recurrence that took place in the initial 5 years post-diagnosis.

In addition to relapse status, risk factors for late relapse and survival after relapse will be assessed. Knowledge resulting from this analysis will be used to form recommendations on long-term monitoring of pediatric cancer survivors.

Specific Aims/ Hypotheses:

1. Assess the risk of first relapse and any relapse 5-years or more after original diagnosis in survivors of childhood and adolescent cancer.
    - Hypothesis: Greater than 5% of 5-year survivors of childhood and adolescent cancers will relapse 5-years or more after their original diagnosis.
2. Assess diagnosis-specific risk of late relapse 5-years or more after original diagnosis in survivors of childhood and adolescent cancer.
    - Hypothesis: Patients with a primary diagnosis of a CNS tumor or sarcoma will be at highest risk of late relapse
3. Determine patient and treatment characteristics that affect the risk of late relapse in childhood and adolescent cancer survivors.
    - Hypothesis: 5-year survivors of childhood and adolescent cancers will have a higher risk of relapse if they have the following characteristics:
        i. Closer in time to their primary diagnosis

ii. Prior history of relapse
iii. Male gender
iv. Minority race
v. Smoker
vi. BMI ≥ 25
vii. Primary relative with history of cancer

4. Assess survival of childhood and adolescent cancer survivors with late relapse.
    - Hypothesis: Survival rates for childhood and adolescent cancer survivors will be worse for those with late recurrence versus other 5-year survivors.

Analysis Framework:

1. Outcomes of interest:
    a. Primary:
        i. Any Recurrence ≥ 5 years from diagnosis
        ii. First Recurrence ≥ 5 years from diagnosis
    b. Secondary:
        i. Timing of recurrence after initial diagnosis
            1. Any recurrence
                a. 5-9 years
                b. 10-14 years
                c. 15-19 years
                d. 20-24 years
                e. 25-29 years
                f. 30+ years
            2. First recurrence
                a. 5-9 years
                b. 10-14 years
                c. 15-19 years
                d. 20-24 years
                e. 25-29 years
                f. 30+ years
        ii. Survival
2. Subject population: All CCSS 5-year cancer survivors
3. Predictor variables:
    a. Primary diagnosis
        i. ALL
        ii. AML
        iii. CNS tumor
        iv. Hodgkin's disease
        v. Non-Hodgkin's Lymphoma
        vi. Wilm's tumor
        vii. Neuroblastoma
        viii. Osteosarcoma
        ix. Ewing's sarcoma
        x. Rhabdomyosarcoma

xi. Other soft tissue sarcoma
xii. Other tumors

b. Relapse < 5 years from diagnosis
   i. Yes
   ii. No

c. Gender
   i. Male
   ii. Female

d. Race
   i. White
   ii. Black
   iii. Hispanic
   iv. Other

e. Smoking status
   i. Smoker (≥ 100 cigarettes/lifetime)
   ii. Non-smoker (< 100 cigarettes/lifetime)

f. BMI
   i. Underweight (BMI < 18.5)
   ii. Normal (BMI 18.5-24.9)
   iii. Overweight (BMI 25-29.9)
   iv. Obese (BMI ≥ 30)

g. Age at diagnosis
   i. 0-4 years
   ii. 5-9 years
   iii. 10-14 years
   iv. 15-20 years

h. Time from diagnosis to recurrence
   i. 0-4 years
   ii. 5-9 years
   iii. 10-14 years
   iv. 15-19 years
   v. 20-24 years
   vi. 25-29 years
   vii. 30+ years

i. First degree relative with history of cancer
   i. Yes
   ii. No

4. Table and Figures
   a. Table I: Patient Characteristics of 5-year survivors with late recurrences

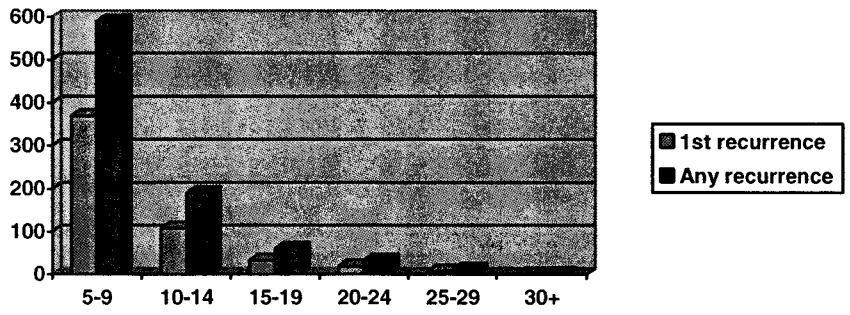
	Total patients	Any recurrence ≥ 5 years from diagnosis		First recurrence ≥ 5 years from diagnosis	
	N	N	%	N	%
Total Patients					
Gender					
Male					
Female					
Race					
White					

Black					
Hispanic					
Other					
BMI					
Underweight					
Normal					
Overweight					
Obese					
Smoking Status					
Non-smoker					
Smoker					
Family history of cancer					
Yes					
No					

b. Table 2: Clinical Characteristics of 5-year survivors with late recurrences

	Total patients	Any recurrence ≥ 5 years from diagnosis		First recurrence ≥ 5 years from diagnosis	
	N	N	%	N	%
Total Patients					
Diagnosis					
ALL					
AML					
CNS					
HD					
NHL					
Wilm's					
NBL					
OSI					
Ewing's					
Rhabdo					
Other STS					
Other					
Age at Diagnosis					
0-4 years					
5-9 years					
10-14 years					
15-20 years					

c. Figure 1: Bar graph of time from diagnosis to recurrence (X-axis = years since diagnosis; Y-axis = number of cases of recurrence)



d. Figure 2: Cumulative incidence of late recurrences (any recurrence (line #1) and first recurrence (line #2)) in the CCSS cohort (X-axis= years since diagnosis; Y-axis = cumulative incidence (%))

e. Figure 3: Survival of patients with late relapse (≥ 5 years) and without relapse from time of diagnosis (Cox regression analysis)

f. Table 3: Recurrence rates by diagnosis

	Years from diagnosis to recurrence							
	5-9 y.		10-14 y.		15-19 y.		20+ y.	
	%	95% CI	%	95% CI	%	95% CI	%	95% CI
ALL								
AML								
CNS								
HD								
NHL								
Wilm's								
NBL								
OS								
Ewing								
Other STS								
Other								

g. Table 4: Univariate and multivariable Cox regression analysis will be carried out to evaluate the impact of specific factors on the risk of late recurrence. In the event that the assumptions for Cox proportional hazards are not met, then Poisson regression analyses will be carried out. The following variables will be examined in these models: primary diagnosis, gender, race, smoking status, BMI, age at diagnosis, family history of cancer. The will be categorized as shown above.

Special Considerations:

1. Statistical analysis: This analysis is being done as a thesis project by the principal investigator, Karen Wasilewski, for the Master of Science in Clinical Research program at Emory University. All analyses for the thesis project will be done by Dr. Wasilewski under the supervision of her thesis advisory committee (Bill Woods, Lillian Meacham and John Boring), Ann Mertens, and the CCSS biostatisticians. All statistical analyses for publication will be performed or confirmed by the CCSS biostatisticians.

2. Certain analyses for predictor variables such as race and primary diagnosis may be limited by the number of patients in each category.

3. There may be a substantial number of late recurrences for certain diagnoses necessitating a more detailed analysis of these patients within this publication or as a separate analysis concept proposal.

4. As with all CCSS studies, this study will be limited by the self-report nature of the data. Wendy Leisenring will be involved in looking through ramifications of possible biases that may occur due to the self-reporting of this outcome.

References:

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3. Strauss SJ, McTiernan A, Whelan JS Late Relapse of Osteosarcoma: Implications for Follow-Up and Screening. *Pediatr Blood Cancer.* 43:692–697, 2004.

4. Sadowitz PD, Smith SD, Shuster J, Wharam MD, Buchanan GR, Rivera GK. Treatment of Late Bone Marrow Relapse in Children With Acute Lymphoblastic Leukemia: A Pediatric Oncology Group Study. *Blood* 81(3): 602-609, 1993.

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6. Shihabi S, Deutsch M, Jacobs SA. Very Late Relapse of Hodgkin's Disease: A Report of Five Patients. *Am J Clin Oncol* 24(6): 576–578, 2001.

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