Mortality Due to Colorectal Cancer Among Survivors of Childhood Cancer

Working Group and Investigators

This report will be written within the CCSS Epidemiology/Biostatistics Working Group, with secondary oversight by the Second Malignant Neoplasm (SMN) Working Group.

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Background and Rationale

The diagnosis and treatment of childhood cancer has significantly improved in recent decades, with 5-year survival rates now exceeding 85%.[1,2] As more children are cured and survive into adulthood, late effects from treatment are increasingly recognized, including subsequent malignant neoplasms (SMN). Adult survivors of childhood cancer are approximately 6 to 10 times more likely than the general population to develop SMNs, with a 30-year cumulative incidence of SMN approaching 20%.[2,3,4] Unfortunately, SMNs are the second leading cause of death in early survivorship[5] and become the primary cause of death 25 years after diagnosis.[6,7] As such, there is a pressing need to develop evidence-based SMN screening guidelines in survivors.

The Childhood Cancer Survivor Study (CCSS) is the largest and most comprehensively described cohort of childhood cancer survivors,[8] and has been used in numerous SMN studies as the median age of the cohort matures over time. The CCSS is particularly important for studying SMNs with long latency periods, such as colorectal cancer, with a median latency between primary childhood cancer diagnosis and subsequent colorectal cancer estimated at 23 years.[4]

A previous investigation within the CCSS determined that survivors of childhood cancer are at a 4.2-fold increased risk of developing colorectal cancer compared to the general population, as early as 5.5 years after their primary childhood cancer diagnosis and up to 30 years later with no plateau.[9] Cumulative incidence of colorectal SMN has been estimated at 0.4% to 2.4% by 30 years, with highest risk among survivors of Hodgkin lymphoma and Wilms tumor.[9,10] In survivors over the age of 40, colorectal cancer is one of the most common SMNs, with an absolute excess risk of 5.9 per 10,000 person-years.[11] Previous research using the CCSS cohort demonstrated increased colorectal SMN risk not only in individuals treated with abdominal radiation, a well-studied risk factor,[11,12,13] but also in those with exposure to high-dose procarbazine and platinum chemotherapy.[9,14] Despite this increased risk, there are no studies evaluating mortality after a colorectal SMN diagnosis relative to *de novo* colorectal cancer, nor any studies evaluating factors which may modify mortality risk in childhood cancer survivors.

The CCSS cohort has previously been utilized to study risk factors for SMN-related mortality, in a landmark study by Moskowitz *et al.* on survivors who subsequently developed breast cancer.[24] The study found a twofold higher risk of all-cause mortality after breast cancer in survivors compared to age-matched controls, with young age at childhood cancer diagnosis being associated with a higher risk of death. However, the most important finding in this study was that other-cause mortality after breast cancer diagnosis was 5.5 times higher in survivors compared to controls and was associated with the presence of comorbidities, particularly cardiac and pulmonary chronic conditions. These findings suggested that chronic medical comorbidities significantly contribute to the elevated mortality of survivors who develop SMNs, and that comprehensive evaluation for late effects is warranted at the time of SMN diagnosis. With the proposed study, we aim to study if there are similar factors that modify mortality risk in survivors who develop colorectal SMN.

Colorectal cancer in younger patients less than 45 years of age in the general, non-survivor population has different disease characteristics, often presenting at a more advanced stage and with higher-risk histological features.[15] This may be due to delays in diagnosis, or potentially due to intrinsic biological differences in young adults who develop colorectal cancer due to hereditary cancer syndromes. Research on the survival of young patients with colorectal cancer has had conflicting results,[15] although a 30-year retrospective review that specifically excluded hereditary syndromes found that patients less than 35 years old had a worse prognosis than older patients only if they had stage IV disease.[25] A more recent analysis of a prospective Lynch syndrome database in Europe found a 10-year survival rate of 91% for patients with Lynch syndrome who developed colorectal cancer.[26] Characteristics of colorectal cancer in childhood cancer survivors have not yet been described, although preliminary research has suggested that survivors are at higher risk for premalignant colon polyps than the general population. In one study, 28% of survivors under the age of 50 were found to have precancerous polyps on colonoscopy, a rate that is significantly higher than the average-risk population.[16] Further, there is emerging evidence of a new phenomenon termed ‘therapy-associated polyposis,’ in which childhood cancer survivors who previously received chemotherapy or radiation therapy are found to have very high numbers of

precancerous colorectal polyps.[17] Given that screening colonoscopy can detect these premalignant polyps and definitive polypectomy or resection can be performed to reduce cancer risk, survivors may benefit from earlier and more aggressive colorectal cancer surveillance protocols.

Building on our previous work characterizing the risk of colorectal SMNs in the CCSS cohort, we propose the following study to describe risk factors for mortality in childhood cancer survivors who develop colorectal SMN. An initial review of the CCSS database revealed 67 cases of invasive colorectal cancer through Follow-Up 5 in 2014, with the potential for more cases to be added when Follow-Up 6 from 2017 is incorporated. This study is critical in designing novel SMN screening guidelines for survivors, as surveillance and early detection of colorectal cancer may reduce morbidity and mortality in these high-risk survivors.[12,18-20,21]

Primary Aims and Research Hypotheses

1. To describe all-cause mortality, colorectal cancer specific-mortality, and mortality from other causes among childhood cancer survivors diagnosed with colorectal cancer, as compared to matched general population controls from the SEER database.

   Hypothesis: All-cause mortality and other-cause mortality will be higher among childhood cancer survivors as compared to sex-, age-, race-, stage- and calendar year of diagnosis-matched controls with colorectal cancer from the SEER database. Colorectal cancer-associated mortality may be higher, but we expect to see a larger difference in other-cause mortality associated with the presence of medical comorbidities in survivors as compared to non-survivor controls, as addressed in Aim 3 below.

2. To determine if the development of colorectal SMN increases the risk of mortality compared to all survivors in the CCSS cohort, after adjusting for all risk factors for mortality.

   Hypothesis: We hypothesize that survivors who develop colorectal SMN will have higher risk of all-cause mortality than other survivors, including after adjustment for confounders such as presence of medical comorbidities.

3. To describe risk factors, including comorbidities, specific chemotherapeutics, abdominopelvic radiation and age at initial childhood cancer diagnosis, that modify the risk of mortality in survivors who develop colorectal SMN as compared to matched general population controls.

   Hypothesis: Survivors with grade 3 or 4 chronic medical conditions and with a younger age at initial childhood cancer diagnosis (< 5 years of age) will have higher mortality than age-matched controls, as has been previously demonstrated in survivors with breast cancer.[24] Further, receipt of abdominopelvic radiation, particularly in patients who were < 5 years of age at time of initial childhood cancer diagnosis, will also be associated with higher mortality, assuming we have a sufficient number of patients who did not receive abdominopelvic radiation in order to be able to perform this analysis.

Exploratory Aims

1. To describe colorectal cancer disease characteristics in childhood cancer survivors, such as disease histology, stage and tumor location, in comparison with matched general population controls with colorectal cancer from the SEER database.

   Hypothesis: Childhood cancer survivors will not have differences in disease stage or tumor location compared to age-matched controls, but will have more aggressive histologies. This comparison with age-matched controls will enable us to determine if these colorectal cancer risk groups, young survivors and young non-survivors, are biologically comparable.

Analysis Framework

Outcomes of Interest:

1. All-cause mortality (overall survival)
2. Colorectal cancer-specific mortality
3. Mortality from other causes

Study Population:

All CCSS participants who have developed a subsequent colorectal cancer (see Appendix for specific SEER codes). An initial review of the CCSS database revealed 67 cases of invasive colorectal cancer through Follow-Up 5 in 2014, with the potential for more cases to be added when Follow-Up 6 from 2017 is incorporated.

For the cohort of the general population with colorectal cancer, case listings for controls will be extracted from the SEER database.

Explanatory variables:

The following predictor variables will be tested for association with the aforementioned outcomes of interest as potential risk factors for mortality in childhood cancer survivors who develop a colorectal cancer SMN. The specific data sources for each variable are indicated. Demographic and patient characteristics will be obtained for the study population from the baseline and follow-up CCSS surveys. For the purposes of this proposal, Follow-Up 5 from 2014 (or Follow-Up 6, if available) will serve as the data source for all follow-up data. Some of the explanatory variables are time dependent and they will be treated as such.

Demographics and Patient Characteristics

> Age at the time of these questionnaires will be required to compare with the age at which the patient was diagnosed with colorectal SMN, to ensure that only risk factors prior to the diagnosis of colorectal SMN are included.

1. Race / Ethnicity (Baseline, A5)
2. Sex (Baseline, A2)
3. Tobacco history
    a. Baseline: O1-O8
    b. Follow-up: N7-N14
4. Alcohol history
    a. Baseline: O9-O14
    b. Follow-up: N1-N6
5. Physical activity
    a. Baseline: O15-O20
    b. Follow-up: N15-N24
6. Insurance
    a. Baseline: U1-U5
    b. Follow-up: A10
7. Chronic health conditions: The presence of Grade 3 or 4 chronic conditions as a binary ‘yes’ or ‘no’ in the database.

Colorectal Cancer-Specific Screening Information

> Age at the time of these questionnaires will be required to compare with the age at which the patient was diagnosed with colorectal SMN, to ensure that only risk factors prior to the diagnosis of colorectal SMN are included.

1. History of colorectal screening (Follow-up: C1f)
2. History of colon polyps (Follow-up: I5)
3. Family history of colorectal cancer
    a. Baseline: Q4
    b. Follow-up: W4
4. Genetic conditions that predispose to colorectal cancer
    a. Baseline: Q1a-Q1b
    b. Follow-up: W1a-W1b

Childhood Cancer Variables

1. Childhood cancer diagnosis type (Medical Record Abstract Form, A)
2. Age at childhood cancer diagnosis (Medical Record Abstract Form, date of diagnosis minus date of birth)
3. History of chemotherapy and dose for childhood cancer treatment (Medical Record Abstract Form, D). These chemotherapy categories were selected *a priori* based on previous research demonstrating their association with gastrointestinal malignancies in childhood cancer survivors.[9,22]
    a. Alkylating agents: yes/no, cyclophosphamide equivalent dose[23]
        i. Procarbazine: yes/no, cumulative procarbazine dose
    b. Platinum agents: yes/no, cumulative platinum exposure dose
    c. Anti-metabolites: yes/no
    d. Anthracyclines: yes/no, cumulative anthracycline exposure dose
    e. Plant alkaloids: yes/no
    f. Epipodophyllotoxins: yes/no
4. History of radiation therapy for childhood cancer treatment (Medical Record Abstract Form, F)
    a. Radiation: yes/no
    b. Pelvic RT: yes/no
    c. Abdominal RT: yes/no
    d. Spinal RT: yes/no
    e. Total body irradiation: yes/no
5. History of surgery for childhood cancer treatment (Medical Record Abstract Form, E), specifically abdominal or pelvic surgeries
6. History of hematopoietic stem cell transplant (Medical Record Abstract Form, B1 and B2)

Colorectal SMN Characteristics

1. Age at colorectal SMN diagnosis: 0-19 years, 20-29 years, 30-39 years, 40-49 years, >50 years (Follow-up: S1-S10)
2. Year of colorectal cancer diagnosis
3. Treatment for colorectal cancer SMN (Follow-up: T1-T2c)
    a. Received radiation for colorectal cancer: yes, no, unknown
    b. Received chemotherapy for colorectal cancer: yes, no, unknown
4. Pathologic characteristics: We will attempt to collect pathologic characteristics of colorectal SMN from pathology reports and confirmation medical records, although these data may be incomplete or not available.
    a. Histology
    b. Degree of differentiation
    c. Stage (I, II, III, IV, unknown)
    d. T Stage (TX, T0, Tis, T1, T2, T3, T4a, T4b)
    e. N Stage (NX, N0, N1, N1a, N1b, N1c, N2, N2a, N2b)
    f. Location (left-sided colon, right-sided colon, transverse colon, rectal, anal, unknown)
5. SMNs other than colorectal cancer (Follow-up: S1-S10)

Analytic Plan

1. All-cause mortality (overall survival) will be defined as the time from colorectal cancer diagnosis until death and will be estimated using the Kaplan-Meier estimate. Overall survival will also be estimated by colorectal cancer stage at diagnosis.
2. Cumulative incidence of cause-specific mortality (from colorectal cancer or from other causes) will be estimated using a nonparametric estimate treating the competing cause(s) of death as a competing risk.
3. All-cause and cause-specific mortality will be compared between the CCSS and SEER control cohorts using proportional hazards models adjusted for sex, race, age at colorectal SMN diagnosis, calendar year at colorectal SMN diagnosis, and stage at diagnosis.
    a. The primary analysis will be unadjusted for self-reported receipt of chemotherapy or radiation therapy for treatment of colorectal SMN.
    b. An exploratory analysis will be performed to adjust for self-reported receipt of chemotherapy, radiation therapy, and receipt of both chemotherapy and radiation therapy.
    c. We recognize that self-reported data has intrinsic limitations and the database may not be complete, but we assert that this exploratory analysis is necessary to query if mortality differs due to receipt of chemotherapy or radiation therapy for colorectal SMN.
4. To determine if development of a colorectal SMN increases mortality among childhood cancer survivors, Cox proportional hazards regression models will be used, treating a colorectal SMN as a time-dependent covariate.
5. Cox proportional hazards modeling will be used to evaluate the association of potential primary cancer and treatment-related risk factors with mortality among childhood cancer survivors.
    a. If the data is available, we will perform an exploratory analysis of the association of stage of colorectal SMN at diagnosis with mortality.
6. Colorectal cancer tumor characteristics will be compared with general population controls and within childhood cancer survivors by age at colorectal cancer diagnosis using logistic regression.

Special Consideration

This work will contribute significant data toward our ancillary study of an intervention to increase colorectal cancer screening in childhood cancer survivors.

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Example Tables and Figures

Table 1. Characteristics of participants in the Childhood Cancer Survivor Study diagnosed with colorectal cancer as a subsequent neoplasm.

Characteristic	**Number (%)**
Number of participants	
Sex	
Race	
Primary childhood cancer	
Hodgkin lymphoma	
Non-Hodgkin lymphoma	
Leukemia	
ALL	
AML	
Other	
Sarcoma	
Soft tissue sarcoma	
Ewing sarcoma	
Osteosarcoma	
Other sarcoma	
Central nervous system malignancy	
Renal cancer	
Neuroblastoma	
Age at diagnosis with primary childhood cancer (years)	
0-9 years	
10-14 years	
>15 years	
Age at subsequent colorectal cancer diagnosis (years)	
0-19 years	
20-29 years	
30-39 years	

40-49 years	
>50 years	
Grade 3-4 chronic condition prior to colorectal cancer diagnosis (yes or no)	
Chemotherapeutic treatment of primary childhood cancer	
Alkylating agents	
Procarbazine	
Platinum agents	
Anti-metabolites	
Anthracyclines	
Plant alkaloids	
Epipodophyllotoxins	
Radiation treatment of primary childhood cancer	
Abdominopelvic radiation	
Spinal radiation	
Total body irradiation	
History of surgery for childhood cancer treatment	
History of hematopoietic stem cell transplant	
Vital status	
Alive at last contact	
Death due to colorectal cancer	
Death due to other causes	

Table 2. Characteristics of colorectal cancer diagnosed in childhood cancer survivors.

Characteristic	**Number (%)**
Stage	
I	
II	
III	
IV	
Unknown	
Location	
Left-sided colon	
Right-sided colon	
Transverse colon	
Rectal	
Anal	
Unknown	
T staging (depth of invasion): TX, T0, Tis, T1, T2, T3, T4a, T4b	
N staging (extent of nodal involvement): NX, N0, N1, N1a, N1b, N1c, N2, N2a, N2b	
Histology	
Degree of Differentiation	

Table 3. Multivariable associations with mortality after diagnosis of subsequent colorectal cancer.

	All-Cause Mortality		Colorectal Cancer-Specific Mortality		Other Causes of Mortality	
Variable	**Number**	**HR (95% CI)**	**Number**	**HR (95% CI)**	**Number**	**HR (95% CI)**
Primary Childhood Cancer Hodgkin lymphoma Non-Hodgkin lymphoma Leukemias Sarcomas CNS malignancy Renal cancer Neuroblastoma						
Age at diagnosis with primary childhood cancer (years) 0-9 10-14 >15						
Age at subsequent colorectal cancer diagnosis (years) 0-19 20-29 30-39 40-49 >50						
Race White Black American Indian / Alaska Native Asian or Pacific Islander Other Unknown						
Ethnicity Yes, Hispanic No, Hispanic Unknown						
Sex Male Female						
Grade 3-4 chronic condition prior to colorectal cancer diagnosis (yes or no)						
Colorectal cancer stage Stage I Stage II Stage III Stage IV						
Location Left-sided colon Right-sided colon Transverse colon Rectal Anal Unknown						

Histology						
Degree of Differentiation						
Chemotherapeutic treatment of primary childhood cancer						
Alkylating agents						
Procarbazine						
Platinum agents						
Anti-metabolites						
Anthracyclines						
Plant alkaloids						
Epipodophyllotoxins						
Radiation treatment of primary childhood cancer						
Yes in-field radiation						
No in-field radiation						

Figure 1. Kaplan-Meier curves for overall survival, colorectal cancer-specific survival, and other-cause survival for childhood cancer survivors with colorectal cancer compared to matched patients in the general population with colorectal cancer.

Figure 2. Kaplan-Meier curves for overall survival after subsequent colorectal cancer diagnosis, stratified by stage at diagnosis.

Appendix: SEER coding for colorectal cancer

Site Group	ICD-O-2 Site	ICD-O-2 Histology (Type)	Recode
Colon and Rectum			
Colon excluding Rectum			
Cecum	C180	excluding 9590-9989, and sometimes 9050-9055, 9140**+**	21041
Appendix	C181		21042
Ascending Colon	C182		21043
Hepatic Flexure	C183		21044
Transverse Colon	C184		21045
Splenic Flexure	C185		21046
Descending Colon	C186		21047
Sigmoid Colon	C187		21048
Large Intestine, NOS	C188-C189, C260		21049
Rectum and Rectosigmoid Junction			
Rectosigmoid Junction	C199	excluding 9590-9989, and sometimes 9050-9055, 9140**+**	21051
Rectum	C209		21052
Anus, Anal Canal and Anorectum	C210-C212, C218		21060