Title: Second Malignancies of the Gastrointestinal Tract: A Report from the Childhood Cancer Survivor Study

Working Group: This report will be written within the Second Malignancy Working Group. Proposed investigators include:

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1. Background and Rationale

The treatment of childhood cancers has become increasingly successful, with current 5-year survival rates approaching 80%.[1, 2] Despite these high cure rates, and subsequent treatment modifications, many patients are at risk for late effects including second cancers. Second malignant neoplasms (SMN) have been observed in childhood cancer survivors at rates of 5-15%.[3-6] SMN are the second leading cause of death in childhood cancer survivors [7] Colorectal adenocarcinoma is extremely rare in childhood, and adenocarcinoma as a SMN is also rare. While the Late Effects Study Group reported a 63.9 fold increase in risk of gastric cancers and 36.4 fold increase in risk for colorectal cancers in Hodgkin's lymphoma survivors,[8] no large studies have described the development of SMN of the entire gastrointestinal tract (GI), or evaluated the risk factors (such previous treatment, familial cancer syndromes and behavioral risk factors) associated with their development.

The Childhood Cancer Survivor Study (CCSS) is the largest and most comprehensively described cohort of childhood cancer survivors.[9] Bassal and colleagues described 71 second carcinomas in the CCSS cohort, of which 16 were of the gastrointestinal tract.[10] Since that analysis, there have been 11 more cases reported by the cohort, bringing the total to 27. This is by far the largest series described in the literature in a heterogeneous population of childhood cancer survivors. The median age of the cohort is still young (36 years) relative to the age at which these malignancies typically occur. Based on the SEER database, the National Cancer Institute reported in that the median age at diagnosis for cancer of the colon and rectum was 71 years of age for the period 2001-2005.[2] Since cancers of the GI tract, particularly colorectal cancers, can be detected with surveillance, potentially resulting in early detection and reduced morbidity and mortality, [11] it is important that any increased and premature risk of GI malignancies in the CCSS cohort be investigated and reported so that we can develop appropriate GI SMN surveillance recommendations for this population.

SPECIFIC AIMS AND RESEARCH HYPOTHESES:

Aim 1: To describe the cumulative incidence, standardized incidence ratio and absolute excess risk of second malignant neoplasms (SMN) of the gastrointestinal (GI) tract among childhood cancer survivors.

Hypothesis: Childhood cancer survivors have an increased risk of GI cancers at an earlier age than the general population.

Aim 2: To describe the risk factors (treatment related, familial and behavioral) associated with the development of SMN of the GI tract among childhood cancer survivors.

Hypothesis: GI SMN in childhood cancer survivors are associated with previous radiation therapy, family history of colorectal cancers and history of smoking.

ANALYSIS FRAMEWORK:

1. **Outcome of Interest**: Second Cancers of the gastrointestinal tract (see appendix)
2. **Population**: Entire CCSS cohort
3. **Predictor variables to be analyzed**
    a. Previous diagnosis
    b. Age at previous diagnosis
    c. History of Radiation Therapy (Yes/No)
    d. In Field Radiation Therapy (Yes/No)
    e. Out of Field Radiation Therapy (Yes/No)
    f. Chemotherapy
        i. Type (Alkylators, Heavy Metals (Platinum based drugs), Anti-Metabolites, Anthracyclines, Anti-Tumor Antibiotics (Bleomycin), Corticosteroids, Enzymes, Plant Alkaloids, Epipodophyllotoxins,
        ii. Dose
    g. Family History of GI Cancer (Yes/No)
    h. Tobacco History (Answers to baseline survey questionnaire O1, O2, O3, O4, O5, O6, O7, O8)
    i. Alcohol Use History (Answers to baseline survey questionnaire O9, O10, O11, O12, O13, O14)
    j. Hematopoietic stem cell transplant(Yes/No)

4. **Analysis**
    a. The analytic plan will be to determine age, gender and calendar year adjusted standardized incidence ratios and absolute excess risk for subsequent GI cancers among childhood cancer survivors, using SEER rates to evaluate expected numbers of digestive tract cancers from Poisson regression models. Cumulative incidence of digestive tract cancers will be evaluated from entry to the cohort (5 years post diagnosis), treating death as a competing risk event.
    b. To the extent possible, with 27 cancer cases, we will evaluate the association between previously discussed predictor variables, treatment modalities (radiation

therapy, chemotherapy, and stem cell transplant) with GI SMN in multivariable piecewise Poisson models. Due to the small number of events, the primary focus will be on evaluating impact of treatment, with additional predictor variables included in sequential pairwise models to determine the most important confounders, for which only 2-3 factors will be selected for inclusion in final model.

c. Family history of malignancies will be examined. The majority of the genetic and family history data will be descriptive.

Tables/Figures

a. Table 1. Characteristics of the CCSS cohort, including separately for survivors who have and have not developed a GI SMN

Characteristic	Patients with secondary GI Cancer (N; %)	Cohort Members without secondary GI cancers (N; %)
Median age at last follow-up, years (Range)		
Median duration of follow-up, years (Range)		
Sex Male Female		
Race White Black Other Unknown		
Age at Primary Diagnosis, years Mean (SD) Median (Range)		
Current Age Mean (SD) Median (Range)		
Primary Diagnosis Leukemia Brain/CNS Tumor Hodgkin disease Non-Hodgkin Lymphoma Kidney Tumor Neuroblastoma Soft Tissue Sarcoma Bone Tumor		
Radiation Therapy		

Yes No		
Smoking History Never Former Current		
Chemotherapy for Primary Malignancy Alkylators Heavy Metals (Platinum based drugs) Anti-Metabolites Anthracyclines Plant Alkaloids Epipodophyllotoxins		
Radiation Therapy for Primary Malignancy In-Field Out of Field		
Family History of any cancer Yes No		
Family History of GI tract cancer Yes No		
Stem Cell Transplant for Primary Malignancy Yes No		
Other Second Malignant Neoplasm Yes No		
Treatment Era 1970-1974 1975-1979 1980-1986		
Vital Status		

Alive Deceased		
Median Time from primary diagnosis to diagnosis of GI SMN, years (Range)		N/A
Age at diagnosis of GI SMN, years Quartiles to be determined		N/A
Site of GI Cancer Esophagus Colon Stomach Rectum Anus Other		N/A
Radiation Exposure for Treatment of Primary Cancer GI Cancer in radiation field GI Cancer distant from radiation field No radiation from primary cancer Unknown primary radiation data Unknown site of GI Cancer		N/A
Cause of Death of GI SMN Participants Primary Cancer GI Cancer Late Effects Toxicities Other Unknown		N/A

b. Figure 1 Cumulative Incidence Curve (vs cumulative incidence in general population)

c. Table 2 Standardized Incidence Ratios and Excess Absolute Risks for Development of GI SMN

	Observed Cases	Expected Cases	SIR (95% CI)	EAR (95% CI)
All subjects with GI SMN				
Sex Male Female				
Age at Primary Diagnosis (years)				
Time since primary diagnosis to GI SMN				
History of Radiation Therapy Yes No Unknown				
Primary Cancer Diagnosis Leukemia Non-Hodgkin Lymphoma Neuroblastoma CNS/Brain Tumor Hodgkin Lymphoma Bone Tumor Kidney Tumor Soft Tissue Sarcoma				
First Degree Relative with GI malignancy Yes No				

d. Table 3. Risk Factors for the Development of GI Cancers: Univariate Analysis

Variable	Relative Risk (95% CI)	*P* Value
Sex		
Race White Black Hispanic Other		

Age at Primary Diagnosis		
Current age		
Primary Cancer Diagnosis		
Radiation Therapy		
Chemotherapy		
Alkylator score		
Antimetabolite (yes/no)		
Anthracycline dose tertile		
Epipodophyllotoxins		
Family History of GI Cancer		
Tobacco Use Never Smoker Former Smoker Current Smoker		
Alcohol Use Never Drinker Former Drinker Current Drinker		
History of Stem Cell Transplant for Primary Diagnosis Yes No		
Treatment Era 1970-1974 1975-1979 1980-1986		

e. Multivariate Rate Ratios for the development of GI Second Malignant Neoplasms

Variable	RR (95% CI)	*P* Value

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Appendix: Seer coding for GI cancers

Site Group	ICD-O-2 Site	ICD-O-2 Histology (Type)	Recode
Oral Cavity and Pharynx			
Lip	C000-C009	excluding 9590-9989, and sometimes 9050-9055, 9140+	20010
Tongue	C019-C029		20020
Salivary Gland	C079-C089		20030
Floor of Mouth	C040-C049		20040
Gum and Other Mouth	C030-C039, C050-C059, C060-C069		20050
Nasopharynx	C110-C119		20060
Tonsil	C090-C099		20070
Oropharynx	C100-C109		20080
Hypopharynx	C129, C130-C139		20090
Other Oral Cavity and Pharynx	C140, C142-C148		20100
Digestive System			
Esophagus	C150-C159	excluding 9590-9989, and sometimes 9050-9055, 9140+	21010
Stomach	C160-C169		21020
Small Intestine	C170-C179		21030
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
Liver and Intrahepatic Bile Duct			
Liver	C220	excluding 9590-9989, and sometimes 9050-9055, 9140+	21071
Intrahepatic Bile Duct	C221		21072
Gallbladder	C239		21080

Other Biliary	C240-C249		21090
Pancreas	C250-C259		21100
Retroperitoneum	C480		21110
Peritoneum, Omentum and Mesentery	C481-C482		21120
Other Digestive Organs	C268-C269, C488		21130

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