I. Study Title: Risk and Risk Factors for Colorectal Cancers in Childhood Cancer Survivors: A Report from the Childhood Cancer Survivor Study

II. Working Group and Investigators:
This report will be written within the Secondary Malignancy Working Group. Proposed investigators are:

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III. Background and rationale:
Childhood cancer survivors are at risk for subsequent malignant neoplasms (SMNs) (Turcotte et al. 2018). SMNs are the second leading cause of death in childhood cancer survivors after recurrence of the primary cancer (Hawkins, Kingston, and Kinnier Wilson 1990; Mertens et al. 2008; Möller et al. 2001). One type of SMN that occurs in childhood cancer survivors is gastrointestinal cancers, which includes cancers of the esophagus, stomach, liver, pancreas, small intestine, large intestine, rectum and anus. Of gastrointestinal cancers, colorectal cancers have the highest occurrence (54%) in the Childhood Cancer Survivor Study (CCSS). Importantly, these are cancers where early surveillance can be implemented with the intent of decreasing morbidity and mortality. However, in order to initiate early surveillance, high-risk groups need to be identified through detailed risk factor analysis. Hence, the ***objective*** of this study is to identify the risks and associated risk factors for colorectal SMN in childhood cancer survivors. Such findings may influence guidelines for colorectal screening and follow up care for current and future childhood cancer survivors.

Concept Proposal Scope
For the purpose of performing a thorough risk and risk factor analysis, we narrowed the scope of this proposal to colorectal SMNs. Colorectal SMNs were chosen, as opposed to another gastrointestinal site, because it has the highest SMN occurrence (54%) of all gastrointestinal sites in the CCSS and hence will give us optimal power for our study.

Risks and Risk Factor Findings from the Original CCSS Cohort

Eight years ago, Henderson et al. reported risks and associated risk factors for gastrointestinal malignancies, including colorectal SMNs (N = 24) in the original CCSS cohort (1970 – 1986) (Henderson et al. 2012). They reported standardized incidence ratios (SIR) of 4.2 (95% CI: 2.8 – 6.3) and 2.4 (95% CI: 1.4 – 3.9) for colorectal cancers and all gastrointestinal cancers, respectively. In multivariable analysis, abdominal radiation (HR = 5.4; 95% CI: 2.6 – 11.2), high dose procarbazine (RR = 3.2; 95% CI: 1.1 – 9.4) and platinum drugs (RR = 7.6; 95% CI: 2.3 – 25.5) were independently associated with increased gastrointestinal SMN risk. Since this study (N = 24), additional colorectal SMNs (N = 47) have occurred within the CCSS cohort, yielding 71 colorectal SMNs as of October 2019. These additional 47 colorectal SMNs have not yet been included in a risk factor analysis for colorectal SMN risk.

RT Treatment-Related Risk Factors Background

Although RT exposure is frequently identified as a risk factor for SMNs (Turcotte et al. 2018), most colorectal SMN risk and associated risk studies (or SMN studies that include colorectal cases) have not included RT dose to the colorectum, but rather have used less specific dosimetry metrics including: [1] categorical classification, i.e., RT yes/no (Bassal et al. 2006; Metayer et al. 2000; Reulen et al. 2011; Swerdlow et al. 2000), [2] SMN proximity categories, i.e., in-beam, near-beam, or out-of-beam, (Bhatia et al. 2003; Henderson et al. 2012), [3] prescribed dose to the abdomen or pelvis (Teepen et al. 2017), or [4] dose to the site of the SMN (Allodji et al. 2019; Nottage et al. 2012; Teepen et al. 2018; Tukenova et al. 2012). These studies demonstrated that colorectal SMNs (or gastrointestinal SMNs with colorectal cases included) are associated with abdominal RT (Henderson et al. 2012), increase with direct abdominopelvic RT (Reulen et al. 2011), are more likely to develop in/near-beam (Bassal et al. 2006), increase with mixed-modality treatment (Swerdlow et al. 2000), and increase with increased RT dose to the site of the SMN (Allodji et al. 2019; Nottage et al. 2012; Tukenova et al. 2012).

However, there is little known about the effect of the volume of irradiated colorectum on colorectal SMN risk. Two studies have examined this effect. A study by Nottage et al., that included 19 colorectal SMN cases, demonstrated colorectal SMN risk increased with percentage of colon in-beam (Nottage et al. 2012). Here, the colon was divided into segments and the number of segments irradiated was used as a surrogate for the volume of irradiated colon. Additionally, a 2018 study by Teepen et al. estimated the proportion of the colorectal volume that was in-beam, but this data was found to not be statistically significantly associated with colorectal adenoma risk when evaluated in multivariable analysis (Teepen et al. 2018). It is important to note that in this study, the risk factor analysis was only performed for colorectal adenomas (benign tumors) and was not performed for colorectal SMNs. While the previous studies explored the role of colorectal volume irradiated in contributing to colorectal SMN risk (or adenoma risk), the role of volume irradiated along with colorectum-specific RT dose, as dose-volume metrics (i.e., colorectal volume receiving specific RT doses), was not explored. Nottage et al. evaluated radiation dose to colon segments and showed that SMN development in a segment increased with exposure to radiation at that particular segment. A limitation of this study is that radiation dose was based on dose records and was not a true measure of dose to the colon segment.

To date, no pediatric cancer survivorship study has investigated radiation dose or dose-volume to the colorectum as risk factors for colorectal SMN in childhood cancer survivors. We would like to examine these data as risk factors for colorectal SMN because other studies for breast cancer (Moskowitz et al. 2014) and late-onset cardiac disease (Bates et al. 2019) in childhood cancer survivors have shown an increased risk for the outcome assessed due to low radiation dose being delivered to large volumes. Moreover, these risk factors, at a substructure level (i.e., ascending, transverse, descending colon, sigmoid and rectum), have not been explored for the colorectum.

Assessing the dose-response relationship between colorectal substructures and the risk for colorectal SMN could potentially lead to finding dose-volume constraints that necessitate or obviate the need for early initiation of high-risk screening.

Systemic Treatment-Related Risk Factors Background

In addition to RT, many childhood cancer survivor studies have shown associations between chemotherapy and gastrointestinal/colorectal SMN risk including: alkylating agents (Bassal et al. 2006), platinum drugs, high dose procarbazine (Henderson et al. 2012) with gastrointestinal cancers; and alkylating agents (Nottage et al. 2012), anthracyclines (mostly doxorubicin), and the MOPP regimen (mechlorethamine, vincristine (Oncovin) and procarbazine, with or without prednisone) with colorectal cancers (Allodji et al. 2019). While findings were significant, the number of cases included in the studies by Allodji et al. (N = 39), Bassal et al. (N = 17) and Nottage et al. (N = 19) were small. Further investigation of the role of chemotherapy agents in contributing to SMN risk with a larger sample size is warranted to identify other possible risk factors of colorectal SMN. While the 2012 CCSS study on gastrointestinal SMNs had a slightly larger sample size (N = 45) compared to the studies mentioned above, chemotherapy agents were only evaluated in terms of their association with gastrointestinal SMNs and not specifically with colorectal SMNs. In our study, specific chemotherapeutics and their cumulative doses will be included and further investigated as risk factors specifically for colorectal SMN risk. Adjustments will be made to account for radiation dose categories for chemotherapeutics. In addition, since this study will be including RT dose-volume metrics, adjustments based on dose-volume groups will be explored.

Other Risk Factors (e.g., demographics, health behaviors and temporal)

Other commonly assessed risk factors for SMNs are primary cancer diagnosis, age at primary cancer diagnosis, smoking history, sex, race, and treatment era. Along with detailed treatment related risk factors, we will also include these conventional factors in the risk analysis.

Implications for Colorectal Screening Guidelines

In 2018, for childhood cancer survivors treated with abdominal, pelvic, spinal or total body radiation therapy, the U.S. Children's Oncology Group (COG) recommended colorectal screening every 5 years at a minimum of 5 years post radiation or at age 30, whichever occurs last (Children's Oncology Group 2018). Given that the 2018 guideline has no radiation dose cutoff, we think that it is important to investigate low radiation dose groups and assess colorectal SMN risk at these low dose groups. This may provide insight as to whether a dose cutoff should be recommended for colorectal screening in childhood cancer survivors. Additionally, no previous screening guidelines have considered the volume of the colorectum exposed to RT. The percentage of colorectum volume irradiated is worth further investigating as a SMN risk factor as other studies have shown that colorectal SMN risk increases with percentage of colon in-beam (Nottage et al. 2012). It is also worth investigating if patients treated with alkylating agents but no abdominal radiotherapy have an absolute risk that warrants initiation of screening.

IV. Specific Aims

The objective of this study is to determine the risks and associated risk factors for colorectal SMN development in childhood cancer survivors in the CCSS cohort. ***This study will investigate risks and risk factors for colorectal SMN risk in the overall CCSS cohort. We will consider factors including demographics, health behaviors and treatment exposures – including chemotherapy and RT (colorectal specific dose and dose-volume metrics) – on colorectal SMN risk.*** This will be the largest colorectal SMN study in the literature with detailed colorectal specific RT dosimetry for a heterogenous population of childhood cancer survivors treated over three decades. Unique to our study will be the development of an age-scalable colorectal model with substructures identified (i.e., ascending,

transverse, descending colon, sigmoid and rectum). With this model we will be able to calculate colorectal and substructure specific radiation data (i.e., mean doses and dose-volume metrics) and include these data as risk factors for colorectal SMN development; factors that have not yet been included in previous CCSS colorectal SMN risk studies. The rationale for the proposed research is that, once risk factors are identified, they can be incorporated into patient planning strategies for newly diagnosed pediatric patients (e.g., as objective functions in the RT treatment planning) as well as into follow up and screening strategies for current and future childhood cancer survivors.

SA1. Determine risk of colorectal SMN in the CCSS cohort. We will calculate the standardized incidence ratio (SIR), absolute excess risk (AER) and cumulative incidence rate of colorectal SMN in childhood cancer survivors.

Hypothesis 1a: Childhood cancer survivors have an increased risk of colorectal SMNs at an earlier age than the general population.

Hypothesis 1b: Childhood cancer survivors who received abdominal and/or pelvic RT have an increased risk of colorectal SMNs at an earlier age than childhood cancer survivors who did not receive abdominal and/or pelvic RT.

Hypothesis 1c: Childhood cancer survivors who received chemotherapy (e.g., alkylating agents) but no abdominal and/or pelvic radiotherapy have an increased risk of colorectal SMNs at an earlier age than the general population.

SA2. Determine the risk factors associated with colorectal SMN development in the CCSS cohort. We will determine the risk factors (e.g., treatment related and behavioral) associated with the development of colorectal SMN in childhood cancer survivors.

Hypothesis 2a: Colorectal SMNs in childhood cancer survivors will be associated with previous radiation therapy, exposure to platinum-based chemotherapy, exposure to anthracyclines, exposure to procarbazine, exposure to any alkylator, and history of smoking.

Hypothesis 2b: Decreased colorectal volume exposed to RT will be associated with decreased colorectal risk compared to larger colorectal volumes exposed to RT.

Hypothesis 2c: Colorectal RT dose will be associated with increased colorectal SMN risk compared to the general population and compared to those not exposed to RT.

Hypothesis 2d: Low RT dose delivered to a large volume of the colorectum will be associated with increased colorectal SMN risk compared to survivors without colorectal RT exposure.

Hypothesis 2e: High RT dose delivered to a small volume of the colorectum will be associated with increased colorectal SMN risk compared to survivors without colorectal RT exposure.

Hypothesis 2f: RT dose to a specific colorectal substructure will be associated with colorectal SMN risk to that substructure.

Hypothesis 2g: Colorectal SMN risk will be associated with increasing exposure to alkylating agents, anthracyclines, and platinum chemotherapy agents. We will look at each as groups. We will also look at specific agents separately and include cyclophosphamide equivalent dose (CED) and anthracycline dose as risk factors.

V. Analysis Framework

Previous colorectal SMN risk studies typically include RT data as categorical (i.e., received or not received), as proximity categories for each SMN, or as prescribed dose per body compartment. In addition to these variables, we will also examine mean RT doses and dose volume metrics to the whole colon and rectum and to each colon substructure as candidate risk factors.

The previous CCSS study on colorectal SMN risk was conducted eight years ago and included only the original cohort (N = 24). Since this study, additional SMNs (N = 47) have occurred from both the original and expanded cohorts, yielding 71 colorectal SMNs.

1. Outcome of Interest: Colorectal SMNs that developed more than 5 years post primary cancer diagnosis.
2. Population: Childhood cancer survivors from the original and expanded cohorts.
3. Exploratory Variables:
    a. Primary cancer diagnosis
    b. Prior SMNs
    c. Age at primary cancer diagnosis
    d. Location of colorectal SMNs
        i. Using ICD-O-2 site based on Surveillance, Epidemiology, and End Results (SEER) Program coding for colorectal cancers (see Appendix A)
    e. Histology of colorectal SMNs
        i. Using ICD-O-2 histology (type) based on SEER Program coding for colorectal cancers (see Appendix A)
    f. Treatment era
        i. 1970-1979
        ii. 1980-1989
        iii. 1990-1999
    g. History of radiation therapy (yes/no)
    h. Body region dosimetry for abdomen, maxTD (Gy)
    i. RT dose and dose-volume metrics to the colon, rectum and colon substructures
        i. Mean dose (Gy)
        ii. Percentage of volume receiving X dose (Gy), V_x
            1. V_5 and V_5 with dmax < 20 Gy
            2. V_{20}
            3. V_{30}
            4. V_{40}
    j. Chemotherapy
        i. Group type (as yes/no and or cumulative dose)
            1. Anthracyclines (Anthracycline dose)
            2. Platinum chemotherapy
            3. Alkylating agents (Cyclophosphamide equivalent dose)
        ii. Specific agents (as yes/no and or cumulative dose)
            1. 5-Azacytidine, ARA-G, Bleomycin, Busulfan, Carboplatin, Carmustine (BCNU), Chlorambucil, Cisplatin, Cyclophosphamide-All Routes, Cyclophosphamide-IV/IM, Cyclophosphamide-PO, Cytarabine, Dacarbazine (DTIC), Dactinomycin, Daunorubicin, Dexamethasone, Doxorubicin, Epirubicin, Etoposide (VP-16)-All Routes, Etoposide (VP-16)-IV/IM, Etoposide (VP-16)-PO, Fludarabine phosphate, Fluorouracil (5-

FU), Gemcitabine, Gemtuzimab (Mylotarg), Gleevec, Hydroxyurea, Idarubicin, Ifosfamide, Irinotecan, L-Asparaginase, Lomustine (CCNU), Mechlorethamine (N. Mustard), Melphalan-All Routes, Melphalan-IV/IM, Melphalan-PO, Mercaptopurine (6-MP), Methotrexate-All Routes, Methotrexate-IM, Methotrexate-IT/Ommaya, Methotrexate-IV, Methotrexate-PO, Mitoxantrone, Prednisone, Procarbazine, Taxol, Taxotere, Temozolomide, Teniposide (VM-26), Thioguanine (6-TG), Thiotepa-All Routes, Thiotepa-IT, Thiotepa-IV/IM, Topotecan, Vinblastine, Vincristine, Vinorelbine, ATG, Alemtuzumab (Campath), Cyclosporine (CSA), Mycophenolate (CellCept), Rituximab (Rituxan), Sirolemus, Tacrolimus, Erythropoietin (EPO), GCSF, GMCSF, Interferon, Interleukin-2, Mesna, Retinoic Acid, Zinecard (Dexrazoxane)

k. Tobacco history (answers to baseline survey questionnaire O1, O2, O3, etc.)
l. Alcohol use history (answers to baseline survey questionnaire O1, O2, O3, etc.)
m. Hematopoietic stem cell transplant (yes/no)
n. BMI

4. Methodology for Colorectal Model Development and RT Dose Reconstruction

Background: The MD Anderson dose reconstruction method uses a FORTRAN code to reconstruct treated fields on a computational phantom that can be scaled to any age at RT. The treatment fields are defined based on data abstracted from RT treatment records. Particularly relevant for this study is that, for the overall CCSS cohort, all RT records have already been coded and exist in a format that can be readily imported to reconstruct dose to any organ that is defined within the MD Anderson computational phantom. Presently, a colon has not been defined. We will develop a colon model for the MD Anderson computational phantom. However, because the colon is a complex organ, we will need to base our model on realistic three-dimensional structural data, i.e., from computed tomography (CT) images. Also, because the ages at time of RT for the CCSS cohort range from infant to adolescence, the colon model should be representative of typical anatomy across this age range.

The University of Florida (UF) and National Cancer Institute (NCI) developed a set of reference pediatric phantoms based on thousands of CT images for ages 0.1, 1, 5, 10, 15, and 18 years (Williams, Lee, and Bolch 2005). The colon is defined for each CT dataset for the designated ages. A limitation of these phantoms is that they are only available for set integer ages and individual calculations for the more than 13,500 individuals in the CCSS that received RT is not realistic from a cost or time perspective.

We will create a colorectal model in the MD Anderson computational phantom that is based on the UF/NCI reference phantoms. The colorectal model will also include colon substructures (e.g., ascending, transverse, and descending colon). However, in order to perform RT dose reconstruction, we need the colorectal model to be scaled to the MD Anderson computational phantom within FORTRAN. Since the colorectal data that we have is from the UF/NCI computational phantom, which is in DICOM format, we must first import the colorectal data from the UF/NCI phantom into a DICOM-compatible treatment planning system (TPS). The subsequent paragraph describes the workflow to extract the colorectal data and implement it into our phantom modelled in FORTRAN.

Development of a Colorectal Model: The UF/NCI reference computational phantoms contain structure data of the whole colon, whole rectum and colon substructures. The colon data was defined using definitions in the International Commission on Radiological Protection (ICRP)

publications “Basic Anatomical and Physiological Data for Use in Radiological Protection: Reference Values” (ICRP 2002) and “Human Alimentary Tract Model for Radiological Protection” (ICRP 2006) and was further verified by a pediatric radiologist. Using Python scripting within the RayStation TPS, we will extract the colon and rectum data from the UF/NCI phantoms for each discrete age. Because the colon and rectum are not as static or uniform in shape (across patients) compared to other organs, we will generate a consensus colorectal model that is based on the colons and rectums extracted from each discrete age.

Analysis of the Consensus Colorectal Model: Since the consensus colon will be scaled to ages from newborn to adult, it needs to be representative of the colon shape for this age range. To quantify the similarity of each age-specific colon to the consensus colon, various overlap metrics will be computed such as Dice similarity coefficients (DSC), and Hausdorff distances. We will use the DSC to quantify the spatial overlap between two colon models and the HD will quantify the longest distance between the boundaries of two colon models. While the DSC can detect disagreement in overlap between two colon models, the HD metric is better at detecting deviations (e.g., sharp spikes or tiny holes) that significantly alter the colon shape but do not substantially alter the volume.

Once the consensus colorectal model is developed and implemented into the FORTRAN code, we will perform RT dose reconstruction for all 13,732 individuals in the CCSS cohort. Using scaling functions that have been developed and validated by researchers in the Late Effects Research Group at MD Anderson Cancer Center, we will scale the consensus colorectal model to the size that adequately represents the size of the organ at time of RT for each patient.

Colon Anatomy and Uncertainty Analysis: We will consider variations in colon anatomy and a dosimetric uncertainty analysis of the colon model will be performed.

Potential Pitfall/Alternative Strategy: If we discover from the analysis methodology described above that the age-specific colons/rectums are not similar to the consensus colorectal model then we will develop six different colorectal models: one for each discrete age. For scaling between discrete ages, we will scale to the midpoint between the discrete ages (Fig. 1).

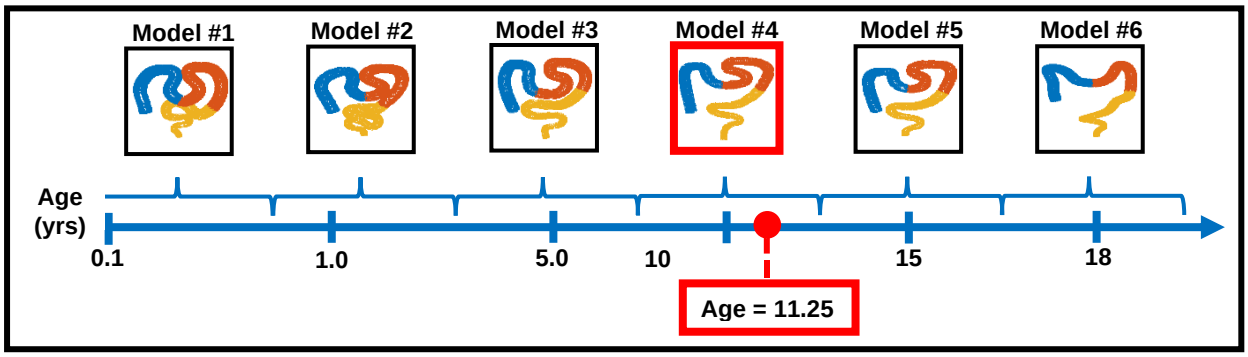

Figure 1. Alternative Colon Model Methodology. If no consensus is found across the colons/rectums of different ages, six different colorectal models will be developed: one for each discrete age of the UF/NCI phantom series. The midpoint between discrete ages will determine the colorectal model to be used for scaling to ages of integer values. For example, to extract and scale a colon/rectum for a patient that received RT at age 11.25 years, colorectal model #4 would be selected. Since colorectal model #4 is based on anatomy of a 10-year-old, the colorectal model would be scaled up to adequately represent the size of the colon/rectum for a patient of age 11.25 years.

RT Dosimetry and Quality Assurance: With a colorectal model implemented in our FORTRAN dose reconstruction code, we will perform RT dose reconstruction using methods initially developed by Stovall (Stovall et al. 2006) which have been used in over 100 radiation epidemiology studies since 2006 (Howell et al. 2019). Dose reconstruction will be performed for all individuals in the CCSS that received RT treatment using previously abstracted RT treatment records. Once this is done, we will calculate mean RT dose and dose volume metrics (listed in Part V.3.e) to the whole colon, rectum and colon substructures. To ensure the quality of the data, we will also carry out an extensive quality assurance process.

5. Analysis:

SA1. Determine risk of colorectal SMN in the CCSS cohorts. We will calculate the standardized incidence ratio, absolute excess risk and cumulative incidence rate of colorectal SMN in childhood cancer survivors.

Hypothesis 1a: Childhood cancer survivors have an increased risk of colorectal SMNs at an earlier age than the general population.

Hypothesis 1b: Childhood cancer survivors who received abdominal and/or pelvic RT have an increased risk of colorectal SMNs at an earlier age than childhood cancer survivors who did not receive abdominal and/or pelvic RT.

Hypothesis 1c: Childhood cancer survivors who received chemotherapy (e.g., alkylating agents) but no abdominal and/or pelvic radiotherapy have an increased risk of colorectal SMNs at an earlier age than the general population.

Study 1.1: Calculate SIR and AER for colorectal SMN. We will determine age, gender and calendar-year adjusted SIR and AER for colorectal SMNs among childhood cancer survivors, using SEER rates to evaluate expected numbers of colorectal SMNs from Poisson regression models. SIRs and AERs will be calculated for various subgroups of the CCSS cohort (e.g., by abdomen dose (maxTD), by RT dose/dose-volume metrics for colon and colon substructures, by chemotherapy exposure, by primary diagnosis). We will also evaluate if any trends exist with treatment era.

Study 1.2: Calculate cumulative incidence rates for Colorectal SMN. Cumulative incidence rates (absolute risk) for colorectal SMN will be calculated using the equation described by Kalbfleisch and Prentice (Kalbfleisch and Prentice 1980). Cumulative incidence rates will be evaluated from entry to the CCSS cohort (5 years post diagnosis), treating death as a competing risk. Cumulative incidence rates will be calculated for various subgroups of the CCSS cohort (e.g., by abdominal radiation exposure, by primary diagnosis, by chemotherapy exposure). We will also evaluate if any trends exist with treatment era.

For analyses comparing relative or absolute risks across treatment eras, we will censor the analyses at a time at which all eras have sufficient follow-up to make adequate comparisons. The multivariable risk factor analysis in Specific Aim 2 may also determine additional factors that will be used as subgroups for displaying SIRs, AERs or cumulative incidence estimates.

SA2. Determine the risk factors associated with colorectal SMN development in the CCSS cohorts. We will determine the risk factors (e.g., treatment related, familial and behavioral) associated with the development of colorectal SMN in childhood cancer survivors.

Hypothesis 2a: Colorectal SMNs in childhood cancer survivors will be associated with previous radiation therapy, exposure to platinum-based chemotherapy, exposure to anthracyclines, exposure to procarbazine, exposure to any alkylator, and history of smoking.

Hypothesis 2b: Decreased colorectal volume exposed to RT will be associated with decreased colorectal risk compared to larger colorectal volumes exposed to RT.

Hypothesis 2c: Colorectal RT dose will be associated with increased colorectal SMN risk compared to the general population and compared to those not exposed to RT.

Hypothesis 2d: Low RT dose delivered to a large volume of the colorectum will be associated with increased colorectal SMN risk compared to survivors without colorectal RT exposure.

Hypothesis 2e: High RT dose delivered to a small volume of the colorectum will be associated with increased colorectal SMN risk compared to survivors without colorectal RT exposure.

Hypothesis 2f: RT dose to a specific colorectal substructure will be associated with colorectal SMN risk to that substructure.

Hypothesis 2g: Colorectal SMN risk will be associated with increasing exposure to alkylating agents, anthracyclines, and platinum chemotherapy agents. We will look at each as groups. We will also look at specific agents separately and include cyclophosphamide equivalent dose (CED) and anthracycline dose as risk factors.

Study 2.1: Identify risk factors associated with the development of colorectal SMN. Univariate Cox regression analysis will be used to evaluate the association between factors (see section V.3 for list of exploratory variables) and colorectal SMN development. Using the risk factors that are found to be significant in univariate analysis ($p<0.10$), we will build multivariable Cox regression models to identify which factors will be selected as candidate risk factors for final model building. Once candidate risk factors have been selected, we will build best fitting final models for predicting colorectal SMN development using step-up and step-down procedures, basing selection on model fit statistics such as Bayesian Information Criteria (BIC) as well as statistical significance and consideration of covariates that modify the effect of other factors (as confounders). Standard asymptotic inference methods for Cox regression based on the partial likelihood will be used to construct 95% confidence intervals and to carry out two-sided tests of statistical significance (Kalbfleisch and Prentice 1980). We will also examine interactions between conventional factors (e.g., primary cancer diagnosis and treatment era), chemotherapy exposures *(e.g., procarbazine and* doxorubicin) and RT exposures. For intervening SMNs prior to a colorectal SMN, we will carry out sensitivity analyses censoring at the time of the prior SMN. For the risk factor analysis, we may also explore piecewise Poisson regression models in addition to the Cox regression approach previously described. We will also estimate absolute risks (cumulative incidence) for subgroups identified as high risk in the multivariable models. This will be done using cumulative incidence estimates for particular subgroups.

VI. Tables/Figures

1. Table 1. Characteristics of the Childhood Cancer Survivor Study Cohort.

Characteristic	Cohort members with colorectal SMN (N 71)		Cohort members without colorectal SMN (N)	
	Median	**Range**	**Median**	**Range**
Age at last follow-up (years)				
Duration of follow-up from primary diagnosis to last contact (years)				
	N	**%**	**N**	**%**
Sex (N; %) Female Male All cases				
Race (N; %) Black Hispanic White Other Unknown All cases				
Age at Primary Cancer Diagnosis (years) Less than 1 1 – 3 4 – 7 8 – 10 11 – 14 15 – 20 Total				
Current Age (years) 0 – 19 20 – 29 30 – 39 Greater than 40 Total				
Primary Diagnosis Leukemia CNS tumor Hodgkin lymphoma Non-Hodgkin lymphoma Wilms tumor Neuroblastoma Soft-tissue sarcoma Bone tumor Total				
Treatment Era 1970 – 1979 1980 – 1989				

1990 – 1999 Total				
Vital Status No. Alive Dead Total				
Radiation Therapy for Primary Malignancy Yes No Total				
Abdominal Radiation for Primary Malignancy Yes No Total				
Chest Radiation for Primary Malignancy Yes No Total				
Pelvic Radiation for Primary Malignancy Yes No Total				
Total Body Irradiation for Primary Malignancy Yes No Total				
Chemotherapy for Primary Malignancy Yes No Total				
Alkylating Agents for Primary Malignancy Yes No Total				
Platinum Agents for Primary Malignancy Yes No Total				
Anthracyclines for Primary Malignancy Yes No Total				
Stem Cell Transplant for Primary Malignancy Yes No Total				

- Additional chemotherapy agents (see section V.3.j) may be included in this table. Inclusion of additional chemotherapies will be dependent on if the specific agent has a meaningful relationship with colorectal SMN development.

2. Table 2. Clinical and Pathologic Characteristics of Colorectal SMN Cases.

Characteristic	Cohort members with colorectal SMN (N 71)	
	Median	**Range**
Age at Primary Diagnosis of Childhood Cancer		
Time from Primary Diagnosis to Colorectal SMN		
Age at Colorectal SMN		
	N	**%**
Age at Diagnosis of Colorectal SMN (years) 5 – 14 15 – 24 25 – 34 Greater than 35		
Pathologic subtype of Colorectal SMN Neoplasm, malignant Carcinoma, NOS Adenocarcinoma, NOS Adenocarcinoma in adenomatous polyp Goblet cell carcinoid Neuroendocrine carcinoma, NOS Adenocarcinoma in callous adenoma Mucinous adenocarcinoma Signet ring cell carcinoma Medullary carcinoma, NOS Leiomyosarcoma, NOS		
Anatomical Site of SMN – Based on SEER site recode ICD-O-2 (1/27/2003) definition (See Appendix A) Appendix Ascending colon Caecum Colon, unspecified Descending colon Hepatic flexure Rectosigmoid junction Rectum Sigmoid Colon Transverse colon		
Radiation Exposure for Treatment of Primary Malignancy Colorectal SMN in radiation field Colorectal SMN near field Colorectal SMN out of field No history of radiation Missing radiation data		
Cause of Death of Colorectal SMN Participants Primary cancer Colorectal SMN Other SMN		

Cardiac toxicity External causes All cases			

3. Table 3. SIRs and EARs for Colorectal SMN Development According to Sex, Childhood Cancer Diagnosis, and History of Radiation Therapy.

By Sex					
	CCSS cases	**No. Observed**	**No. Expected**	**SIR (95% CI)**	**EAR/100,000 py (95% CI)**
Male Female All subjects					
By Primary Cancer Diagnosis					
	CCSS cases	**No. Observed**	**No. Expected**	**SIR (95% CI)**	**EAR/100,000 py (95% CI)**
Leukemia CNS Hodgkin Lymphoma Non-Hodgkin Lymphoma Wilms Tumor Neuroblastoma Soft Tissue Sarcoma Bone Cancer					
By History of Abdominal RT for Primary Malignancy					
	CCSS cases	**No. Observed**	**No. Expected**	**SIR (95% CI)**	**EAR/100,000 py (95% CI)**
Abdomen RT No Abdomen RT Unknown					
By History of Alkylating Agents for Primary Malignancy					
	CCSS cases	**No. Observed**	**No. Expected**	**SIR (95% CI)**	**EAR/100,000 py (95% CI)**
Yes No Unknown					
By History of Platinum Agents for Primary Malignancy					
	CCSS cases	**No. Observed**	**No. Expected**	**SIR (95% CI)**	**EAR/100,000 py (95% CI)**
Yes No Unknown					
By History of Anthracyclines for Primary Malignancy					
	CCSS cases	**No. Observed**	**No. Expected**	**SIR (95% CI)**	**EAR/100,000 py (95% CI)**

Yes					
No Unknown					

By First Degree Relative with Colorectal Malignancy					
	CCSS cases	**No. Observed**	**No. Expected**	**SIR (95% CI)**	**EAR/100,000 py (95% CI)**
Yes No					

- A table similar to this table will be made for each individual colorectal substructure (i.e., ascending colon, transverse colon, descending colon, sigmoid colon and rectum). The table above is for the whole colon and rectum.

4. Table 4. Colorectal RT Dosimetry Metrics.

Characteristic	**Cohort members with colorectal SMN (N 71)**		**Cohort members without colorectal SMN (N)**	
Whole Colon	**N**	**%**	**N**	**%**
Volume of Whole Colorectum Receiving 5 Gy No RT 0% 0.1 – 49.9% ≥ 50%				
Volume of Whole Colorectum Receiving 5 Gy with D_{max} < 20 Gy No RT 0% 0.1 – 49.9% ≥ 50%				
Volume of Whole Colorectum Receiving 20 Gy No RT 0% 0.1 – 39.9% 40 – 79.9% ≥ 80%				
Volume of Whole Colorectum Receiving 30 Gy No RT 0% 0.1 – 39.9% 40 – 79.9% ≥ 80%				
Volume of Whole Colorectum Receiving 40 Gy No RT 0% 0.1 – 39.9% 40 – 79.9% ≥ 80%				

- A table similar to this table will be made for mean colon dose and each individual colorectal substructure (i.e., ascending colon, transverse colon, descending colon, sigmoid colon and rectum). The table above is for the whole colon and rectum.
- Doses cutoffs will be determined for each individual substructure once the dose distributions to those substructures are known.
- The final selection of tables will be dependent on which substructures have meaningful relationships with colorectal SMN development.

5. Table 5. Final Cox Multivariate Model of Risk Factors for Development of Colorectal SMN.

Risk Factor	Cohort Member with Colorectal SMN (N)		Hazard Ratio (95% CI)	P Value
	Yes	No		

6. Figure 1. Cumulative incidence for colorectal SMN (i) overall, (ii) by primary diagnosis, (iii) by abdominal radiation exposure, and (iv) by chemotherapy exposure. Other factors may be included as stratifications depending on results of multivariable modelling.

7. Figure 2. Typical and alternate colorectal configurations used for radiation dose reconstruction, as described in the analysis framework (Section V.4).

8. Appendix A. SEER Coding for Colorectal Cancers.

Site Group	ICD O 2 Site	ICD O 2 Histology (Type)	Recode
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 & Rectosigmoid Junction			
Rectosigmoid Junction	C199	Excluding 9590-9989, and sometimes 9050-9055, 9140+	21051
Rectum	C209		21052

- Based on SEER site recode ICD-O-2 (1/27/2003) definition (NIH NCI Surveillance, Epidemiology 2003)
- + The Site Recode variable can be created with or without Mesothelioma (9050-9055) and Kaposi Sarcoma (9140) as separate groupings. The table above documents both possibilities.

VII. References

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