1. Study Title
Long-term incidence of anorectal complications among childhood cancer survivors

2. Working group and investigators
This proposed project will be undertaken with the assistance of the Childhood Cancer Survivor Study (CCSS) Chronic Disease Working Group, with secondary assistance of the CCSS Epidemiology and Biostatistics and Psychology Working Groups. Proposed investigators include the following members:

Name	*Contact information*
Christopher Weldon	Christopher.Weldon@childrens.harvard.edu
Greg Armstrong	Greg.Armstrong@stjude.org
Lisa Diller	Lisa_Diller@dfci.harvard.edu
Todd Gibson	Todd.Gibson@stjude.org
Robert Goldsby	goldsbyr@peds.ucsf.edu
Rebecca Howell	rhowell@mdanderson.org
Jamie Knell	jknell1@partners.org
Kevin Krull	Kevin.krull@stjude.org
Wendy Leisenring	wleisenr@fhcrc.org
Arin Madenci	amadenci@partners.org
Kevin Oeffinger	oeffingk@mskcc.org
Leslie Robison	Les.Robinson@stjude.org
Charles Sklar	sklarc@mskcc.org
Brent Weil	Brent.Weil@childrens.harvard.edu
Yutaka Yasui	Yutaka.yasui@stjude.org

3. Background and Rationale
Long-term survivors of childhood cancer may be at elevated risk of anorectal complications driven by the late effects of abdominal surgery, chemotherapy, and radiotherapy.[1,2,3] Benign anorectal disease, including radiation colitis, stricture, fissure, and fistula-in-ano, afflict between 3-7% of the general adult population. This prevalence may be substantially greater among childhood cancer survivors, as this group is known to be at elevated risk of developing a number of lower gastrointestinal complications, including benign complications such as diverticular disease, colitis, anorectal fistula, anorectal fissure, and anorectal stricture as well as second malignant neoplasms (SMN).[1] As more childhood cancer survivors reach adulthood,[4] long-term effects of life-saving cancer multimodality treatments with radiotherapy, surgery, and chemotherapy become increasingly important to consider.

In the acute setting, abdominal and pelvic radiotherapy may cause severe, often dose-limiting mucosal damage.[3] Long-term intestinal damage is posited to be secondary to chronic ischemia and fibrosis of the tissues.[3,5] As a result, in the years and decades following radiotherapy, patients may develop treatment-related intestinal complications such as stenosis, fissure, ulceration, and fistula formation.[3,5] Similarly, up to 75% of patients treated with abdominal or pelvic radiotherapy may develop radiation enteritis.[6] The clinical presentation of radiation enteritis may include bleeding, diarrhea, stricture or fistula formation.[6] The long-term complication rates of stricture, fissure, and fistula-in-ano formation from radiotherapy are unknown.

Surgical intervention may lead to late anorectal disease by another mechanism. Post-operative anorectal stricture may occur via a number of mechanisms. After resection of a primary or metastatic colorectal tumor and primary anastomosis, stricture can form from ischemia. The incidence of anastomotic stricture in colorectal cancer patients is estimated to be 3-30%.[7] Additionally, obstructive symptoms can occur as a result of post-operative intraperitoneal adhesions. Similarly, bowel obstruction (including from stricture) is a well-known complication of surgical intervention of which childhood cancer survivors are at elevated risk.[8]

The known effects of chemotherapy on the lower gastrointestinal tract include acute mucositis.[1] However, it is unknown whether there is an increased long-term incidence of benign anorectal disease among children treated with chemotherapy and what the contribution of particular agents may be.[1,3,5] While no study clearly links chemotherapy to stricture formation, case reports of patients with non-Hodgkin lymphoma have noted intestinal stricture after chemotherapy, not related to surgery or radiotherapy.[9] In adults this prevalence is reported to be as high as 5%. While there is no direct relationship between chemotherapy and fissure or fistula-in-ano, the immunosuppressive effect of treatment regimens potentially contribute to non-healing fissures or fistula tracts.

Finally, survivors of childhood cancer may be at risk for anorectal SMN, especially in the presence of prior abdominal or pelvic radiotherapy.[10] Childhood cancer survivors are known to be at increased risk of SMN in the setting of radiotherapy.[11] However, current evidence of anorectal SMNs among children who receive radiotherapy is limited to case series. Among adults, the evidence is conflicting. An analysis of the Surveillance, Epidemiology, and End Results (SEER) registry reported a nearly two-fold higher rate of rectal cancer among adults who underwent radiotherapy for prostate cancer, compared to those who did not.[12] A recent meta-analysis conducted by Jin and colleagues documented a 50% higher standardized incidence ratio of secondary malignancy among patients with prostate cancer who underwent radiotherapy, compared to the general population.[13] Other studies have reported no relationship between pelvic radiotherapy and second primary cancers.[14]

Anorectal disease may carry a significant functional burden on the quality of life of affected individuals. Symptoms of anorectal disease, including change in bowel habits, pain, and nutritional deficiency, each substantially affect quality of life. Stigma surrounding anorectal issues may lead to underreporting and delay in presentation. In addition, among childhood cancer survivors, the rate of colostomy formation for severe treatment related complications such as stricture is unknown. In a study of adults with prostate cancer, post-radiation changes in bowel habits that had major effects on quality of life were reported by 11% of patients.[15]

The purpose of this study is to evaluate the incidence of, risk factors for, and consequences of late anorectal complications among childhood cancer to help guide treatment and counseling.

4. Specific aims/objectives/research hypotheses

A. Specific aim 1

To describe the cumulative incidence of late (≥5 years post-diagnosis) anorectal complications (i.e. anorectal stricture, anorectal fistula, anorectal fissure, radiation colitis, anorectal SMN) among childhood cancer survivors.
Hypothesis: There is a higher cumulative incidence of long-term anorectal complications among survivors compared to siblings.

B. Specific aim 2
To characterize and compare the influence of specific demographic and treatment risk factors on late (≥5 years post-diagnosis) anorectal complications (i.e. anorectal stricture, anorectal fistula, anorectal fissure, radiation colitis, anorectal SMN) among childhood cancer survivors.
Hypothesis: There is a higher cumulative incidence of late anorectal complications among survivors who have specific demographic (for example, underlying diagnosis with abdominal/pelvic tumor and younger age at diagnosis) and treatment risk factors (for example, prior abdominal or pelvic radiotherapy, resection of abdominal or pelvic tumor, and/or chemotherapy).

C. Specific aim 3
To characterize the incidence rate of ileostomy or colostomy among childhood cancer survivors who did and did not have late (≥5 years post-diagnosis) anorectal complications (i.e. anorectal stricture, anorectal fistula, anorectal fissure, radiation colitis, anorectal SMN).
Hypothesis: The incidence rate of ileostomy or colostomy is higher among childhood cancer survivors who developed late anorectal complications, compared to those who did not develop late anorectal complications.

D. Specific aim 4
To investigate the impact of late (≥5 years post-diagnosis) anorectal complications on quality of life and psychosocial outcomes among childhood cancer survivors.
Hypothesis: Late anorectal complications negatively impact quality of life among childhood cancer survivors.

5. Analysis Framework

A. Outcomes of interest

Outcomes of interest for this study will be established from CCSS surveys of survivors and siblings (Original Cohort and Expansion Cohort once data available). We will employ any CCSS survey completed by each survivor or sibling that capture relevant independent variables and outcomes. Time to first occurrence of each outcome will be used.

Primary endpoint:

- Occurrence of anorectal disease ≥5 years after enrollment including:
  - Anorectal stricture (Baseline #H18; ExpBaseline #H8; LTFU 2007 #I7)

- Anorectal fistula (Baseline #H17; ExpBaseline #H7; LTFU 2007 #I7)
- Anorectal fissure (Baseline #H11 ICD-9 code 565.0; ExpBaseline #H9 ICD-9 code 565.0; LTFU2007 #I9 ICD-9 code 565.0)
- Radiation colitis (Baseline #H14; ExpBaseline #H9 ICD-9 code 555.1 [colitis] or 555.9 [regional enteritis]; LTFU 2007 #I9 ICD-9 code 555.1 [colitis] or 555.9 [regional enteritis])
- Anorectal SMN (Baseline #K1; ExpBaseline #L1, LTFU 2003 #R1, LTFU 2005 #B1, LTFU 2007 #P1)

Secondary endpoints:

- Health-related quality of life (HRQOL), as assessed by Short Form 36 (SF-36), and Brief Symptom Inventory (BSI) surveys. The relationship between late anorectal complications and HRQOL will be evaluated.
  - HRQOL: SF-36 results for the Original Cohort are based on LTFU 2003 #F1-14 and will be included in a separate analysis among survivors who reach the primary endpoint prior to completion of the LTFU 2003 survey. Continuous and binary (>40 vs. ≤40)[15]
  - Psychosocial: BSI results are based on Baseline #J16-35 (excluding J25 and J28), Baseline Expansion #K1-K18 (anorectal outcomes that occur after baseline Original Cohort or Baseline Expansion Cohort will be excluded from this to preserve similar follow-up time between Original and Expansion Cohorts). Continuous and binary (Depression vs. no depression; anxiety vs. no anxiety; somatization vs. no somatization; <63 vs. ≥63)[15]
- Ileostomy/Colostomy: (Baseline #I12; ExpBaseline #I15; LTFU 2007 #J15)

B. Subject population

All CCSS participants diagnosed between 1970 and 1999 will be included, although for the SF-36 outcomes, only those diagnosed between 1970 and 1986 will have available data. The analyses will be stratified by tumor location, specifically pelvic tumors and non-pelvic tumors. Siblings will be analyzed as a control group wherever numbers of events allow, including sibling data from the expanded cohort, when available. In the preliminary query, 122 (original cohort baseline, n=73; expansion cohort, n=49) survivors developed anorectal stricture and 199 (original cohort baseline, n=121; expansion cohort, n=78) survivors developed anorectal fistula. For siblings in the original cohort, 34 developed anorectal fistula and 12 developed anal stricture.

C. Exploratory variables of interest

- Sociodemographic variables

- Age (time dependent; continuous and categorical; Baseline #A1; ExpBaseline #A1)
- Sex (categorical; Baseline #A2; ExpBaseline #A2)
- Race and ethnicity (categorical: non-Hispanic white, non-Hispanic black, Hispanic, other; Baseline #A4, ExpBaseline #A5)
- Annual household income ($; time dependent; categorical: <20,000, 20,000-39,999, 40,000-59,999, ≥60,000); Baseline #Q8, ExpBaseline #T1, LTFU2003 #S1-3, LTFU 2007 #A6-8)
- Tobacco use (time dependent; categorical: never, former, current smoker; Baseline #N1-2, ExpBaseline #O1-8, LTFU 2003 #L1-8, LTFU 2007 #N7-14)
- Body mass index (BMI; time dependent; continuous and categorical: <18.5, 18.5-24.9, 25-29.9, 30.0-34.9, 35.0-39.9, ≥40; Baseline #A10-11, ExpBaseline #A3-4, LTFU 2003 #7-8, LTFU 2007 #A1-2)
    - Calculated *as BMI = (weight [kg]) / (height [m])*^{2}
- Highest level of education attainment (time dependent; categorical: <high school, high school graduate, college graduate; Baseline #O1-4, LTFU2003 #1, LTFU2007 #A3)
- Health insurance coverage (time dependent; binary; Baseline #Q1-6, LTFU2000 #16, LTFU2003 #M1, LTFU2007 #B1)

o Disease variables
- Cancer diagnosis (categorical: leukemia, CNS, lymphoma, Wilms' tumor, neuroblastoma, soft tissue sarcoma, bone sarcoma, other)
- Location of tumor (categorical: pelvic vs. non-pelvic; based on ICD-O topography codes)

o Treatment variables
- Any chemotherapy (binary)
    - Alkylating agent (binary)
        - Cyclophosphamide equivalent dose (CED) score (categorical: 0, 1-3999, 4000-7999, ≥8000mg/m^2)[17]
    - Anthracycline (binary)
        - Anthracycline score (categorical: 0, <250, ≥250 mg/m^2)[18]
    - Platinum agent (binary)
        - Platinum agent score (categorical: 0, 1, 2, 3)[19]
- Abdominal/Pelvic radiotherapy
    - Continuous (Gy)
    - Dose <10 Gy vs 10-19 Gy vs >20-29 Gy vs 30-39 Gy vs 40-49 Gy vs ≥ 50 (subject to change)
- Surgery ICD-9-CM Procedure Code from MRAF
    - Abdominal/pelvic surgery as cancer treatment

D. Statistical Methods

We will compare the cumulative incidence of late anorectal complications between the following groups: 1) all survivors vs. siblings and 2) survivors with pelvic tumors vs. survivors with non-pelvic tumors vs. siblings. Mortality will be considered a competing risk and graphically displayed beside each curve if substantially different between groups. For time-to-event analyses involving siblings, age will be used as the time scale

with subjects entering the analysis at their entry to the cohort (5 years post diagnosis for survivors and corresponding age of siblings) and exiting at the age at which they have an event of interest, die, or are censored (i.e. time of last survey). Among survivors, additional analyses may examine the use of time since diagnosis as the time scale, with time zero at 5 years post cancer diagnosis.

In each cohorts, we will perform unadjusted time-independent (to concisely display characteristics of the cohort) and time-dependent analyses to identify categorical and continuous variables associated with the primary outcome. Associations will be assessed using log-rank tests for categorical variables or Cox regression analysis for continuous variables.

We will then perform a time-dependent multivariable analysis to interrogate the association between cancer treatment variables (i.e. surgery, radiotherapy, and chemotherapy) and the development of late anorectal complications among all survivors. This analysis will be adjusted by relevant clinical and demographic factors identified in univariable time-dependent analysis and stratified by pelvic tumor location, if necessary (to be determined based on unadjusted results). Multivariable Cox proportional hazards models will be used to evaluate associations. Models will be adjusted by age as appropriate. Specifically, for analyses including siblings, age will be the x-axis (because there is not time since diagnosis for siblings) and age will not be included as a covariate. For analyses with survivors only, age will be included (either as a time-dependent covariate with time since diagnosis as the x-axis or with age as the x-axis (without including age as a covariate). When a participant endorses developing a late anorectal complication, but age at that time is unknown, we will use multiple imputation methods for missing values. Regression models that include household income, current smoking status, BMI, education, and health insurance status will be evaluated using cross-sectional logistic regression models that incorporate information as of the most recent follow-up, since values of these factors are only known at the time of specific surveys and not typically known as of entry to the cohort. These results will be compared to the multivariable time-dependent analyses in order to better investigate and understand the association between the primary endpoint and risk factors.

In the subsets of subjects with available data from the Medical Outcome Short Form 36 (SF-36) and the Brief Symptom Inventory (BSI) surveys, quality of life will be compared between survivors who do and do not develop anorectal complications. Specifically, we will tabulate or graphically display summary scores for each of the SF-36 and BSI components/sub-scales. The quality of life analysis (SF-36 and BSI) will be limited to including anorectal complications that occur on the Baseline Original Cohort or Baseline Expansion Cohort (whereas the overall analysis will include anorectal complications that occur on LTFU 2003, LTFU 2005, and LTFU 2007 surveys). These will be compared between groups (survivors with late anorectal complications, survivors without late anorectal complication) using two-sample t-tests. Additionally, the quality of life outcomes will be dichotomized into impaired (vs. not impaired) using a tenth percentile cut-off values. A multivariable logistic regression analysis will then be conducted for the quality of life outcomes adjusted for demographic variables (age, sex, and race), time (years) since anorectal complication, and cancer- and treatment-related variables significant at the 0.05 level on univariable analysis. Given the expected collinearity between variables that characterize diagnosis and treatment and the problem

of subsequent steps along the causal pathway of the disease process, separate models will be fit to examine these factors. One method of creating separate models will be to first establish which diagnostic groups are at highest risk for late anorectal complications. Then, in a separate analysis, treatment-related factors will be introduced in order to investigate which treatments incur the elevated risk found in this group.

E. Examples of tables and figures

Table 1. Comparison of demographic and treatment characteristics of childhood cancer survivors who did and did not develop a late anorectal complication (LAC)

	Survivors				***Siblings***			
Variable	*Overall*	*LAC*	*No LAC*	P	*Overall*	*LAC*	*No LAC*	P
Female								
Age at cancer diagnosis, y								
0-3								
4-9								
10-14								
15-20								
Race/ethnicity								
Non-Hispanic white								
Non-Hispanic black								
Hispanic								
Other								
Cancer diagnosis								
CNS								
Leukemia								
Lymphoma								
Wilms tumor								
Neuroblastoma								
Bone/soft tissue sarcoma								
Other								
Pelvic tumor								
Surgery								
No								
Yes								
1 surgery								
2 surgeries								
>2 surgeries								
Abdominal surgery								
Colostomy								
Chemotherapy								
Alkylating agent								
CED, mg/m^2								
0								
1-3999								
4000-7999								
>7999								
Platinum agent score								

1	
2	
3	
Anthracycline dose, mg/m^2	
None	
<250	
≥250	
Abdominal/Pelvic radiotherapy, Gy	
0 (none)	
<10	
10-19	
20-29	
30-39	
40-49	
>49	
Tobacco use	
BMI, kg/m^2	
<18.5	
18.5-25	
25-30	
30-35	
35-40	
>40	
Year of diagnosis	
1970-1974	
1975-1979	
1980-1984	
1985-1989	
1990-1994	
1995-1999	
Annual household income, $	
<20,000	
20,000-39,999	
40,000-59,999	
60,000-79,999	
80,000-99,999	
>99,000	
Employment	
Unable to work	
Unemployed	
Student	
Full-time work	
Part-time work	

Education	
< high school	
High school graduate	
College graduate	
Health insurance coverage	

BMI, body mass index*; CED*, cyclophosphamide equivalent dose; *CNS*, central nervous system; *Gy*, Gray; *LAC*, late anorectal complication.

Table 2. Late anorectal complications

	Number	%	Cumulative incidence rate
Late anorectal complication			
Benign anorectal complication			
Fistula			
Fissure			
Stricture			
Radiation colitis			
Anorectal SMN			

SMN, second malignant neoplasm

Table 3. Multivariable analysis of factors associated with late anorectal complications among childhood cancer survivors[a]

Variable	*Hazard ratio*	*95% Confidence interval*	P
Female			
Age at cancer diagnosis, y			
0-3			
4-9			
10-14			
15-20			
Race/ethnicity			
Non-Hispanic white			
Non-Hispanic black			
Hispanic			
Other			
Cancer diagnosis			
CNS			
Leukemia			
Lymphoma			
Wilms tumor			
Neuroblastoma			
Bone/soft tissue sarcoma			
Other			

Pelvic tumor
Surgery
No
Yes
1 surgery
2 surgeries
>2 surgeries
Abdominal surgery
Colostomy
Chemotherapy
Alkylating agent CED, mg/m^2
0
1-3999
4000-7999
>7999
Platinum agent score
1
2
3
Anthracycline dose, mg/m^2
None
<250
≥250
Abdominal/Pelvic Radiotherapy, Gy
0 (no radiotherapy)
<10
10-19
20-29
30-39
40-49
>49
Tobacco use
BMI
<18.5
18.5-25
25-30
30-35
35-40
>40
Year of diagnosis
1970-1974
1975-1979
1980-1984
1985-1989

1990-1994	
1995-1999	
Annual household income, $	
<20,000	
20,000-39,999	
40,000-59,999	
60,000-79,999	
80,000-99,999	
>99,000	
Employment	
Unable to work	
Unemployed	
Student	
Full-time work	
Part-time work	
Education	
< high school	
High school graduate	
College graduate	
Health insurance coverage	

CED, cyclophosphamide equivalent dose; *CNS*, central nervous system

[a]The model will be separately evaluated including diagnosis (excluding treatment factors) and then including treatment factors (excluding diagnosis), so as not to incorporate two steps along the causal pathway.

Table 4. Multivariable analysis of factors associated with poor Short Form-36 outcomes among childhood cancer survivors[a,b]

	Physical function			*Physical role*			*Bodily pain*			*General health*			*Vitality*		
Variable	*No. (%)*	*OR*	*95% CI*	*No. (%)*	*OR*	*95% CI*	*No. (%)*	*OR*	*95% CI*	*No. (%)*	*OR*	*95% CI*	*No. (%)*	*OR*	*95% CI*
Late anorectal complication[c]															
Benign anorectal disease															
Second malignant neoplasm															
Female															
Age at cancer diagnosis, y															
0-3															
4-9															
10-14															
15-20															
Race/ethnicity															
Non-Hispanic white															
Non-Hispanic black															
Hispanic															
Other															
Cancer diagnosis															
CNS															
Leukemia															
Lymphoma															
Wilms tumor															
Neuroblastoma															

Bone/soft tissue sarcoma	
Other	
Pelvic tumor	
Surgery	
No	
Yes	
1 surgery	
2 surgeries	
>2 surgeries	
Abdominal surgery	
Colostomy	
Chemotherapy	
Alkylating agent	
CED, mg/m^2	
0	
1-3999	
4000-7999	
>7999	
Platinum agent score	
1	
2	
3	
Anthracycline dose, mg/m^2	
None	
<250	
≥250	
Abdominal/Pelvic Radiotherapy, Gy	

0 (no radiotherapy)	
<10	
10-19	
20-29	
30-39	
40-49	
>49	
Tobacco use	
BMI	
<18.5	
18.5-25	
25-30	
30-35	
35-40	
>40	
Year of diagnosis	
1970-1974	
1975-1979	
1980-1984	
1985-1989	
1990-1994	
1995-1999	
Annual household income, $	
<20,000	
20,000-39,999	
40,000-59,999	
60,000-79,999	
80,000-99,999	

>99,000	
Employment	
Unable to work	
Unemployed	
Student	
Full-time work	
Part-time work	
Education	
< high school	
High school graduate	
College graduate	
Health insurance coverage	

CED, cyclophosphamide equivalent dose; *CNS*, central nervous system

[a]The model will be separately evaluated including diagnosis (excluding treatment factors) and then including treatment factors (excluding diagnosis), so as not to incorporate two steps along the causal pathway.

[b]Including only Original Cohort participants (diagnosed between 1970 and 1986).

[c]Occurrence prior to completion of the LTFU 2003 survey.

(Table 4 continued)

	Emotional role			*Social function*			*Mental health*			*Physical component (summary)*			*Mental component (summary)*		
Variable	*No. (%)*	*OR*	*95% CI*	*No. (%)*	*OR*	*95% CI*	*No. (%)*	*OR*	*95% CI*	*No. (%)*	*OR*	*95% CI*	*No. (%)*	*OR*	*95% CI*
Late anorectal complication															

Benign anorectal disease	
Second malignant neoplasm	
Female	
Age at cancer diagnosis, y	
0-3	
4-9	
10-14	
15-20	
Race/ethnicity	
Non-Hispanic white	
Non-Hispanic black	
Hispanic	
Other	
Cancer diagnosis	
CNS	
Leukemia	
Lymphoma	
Wilms tumor	
Neuroblastoma	
Bone/soft tissue sarcoma	
Other	
Pelvic tumor	
Surgery	
No	
Yes	

1 surgery	
2 surgeries	
>2 surgeries	
Abdominal surgery	
Colostomy[a]	
Chemotherapy	
Alkylating agent	
CED, mg/m^2	
0	
1-3999	
4000-7999	
>7999	
Platinum agent score	
1	
2	
3	
Anthracycline dose, mg/m^2	
None	
<250	
≥250	
Abdominal/Pelvic Radiotherapy, Gy	
0 (no radiotherapy)	
<10	
10-19	
20-29	
30-39	
40-49	

>49
Tobacco use
BMI
<18.5
18.5-25
25-30
30-35
35-40
>40
Year of diagnosis
1970-1974
1975-1979
1980-1984
1985-1989
1990-1994
1995-1999
Annual household income, $
<20,000
20,000-39,999
40,000-59,999
60,000-79,999
80,000-99,999
>99,000
Employment
Unable to work
Unemployed
Student
Full-time work
Part-time work

Education												
< high school												
High school graduate												
College graduate												
Health insurance coverage												

Table 5. Multivariable analysis of factors associated with poor Brief Symptom Inventory outcomes among childhood cancer survivors[a]

	Depression			*Anxiety*			*Somatization*			*Global Status Index*		
Variable	*No. (%)*	*OR*	*95% CI*	*No. (%)*	*OR*	*95% CI*	*No. (%)*	*OR*	*95% CI*	*No. (%)*	*OR*	*95% CI*
Late anorectal complication[b]												
Benign anorectal disease												
Second malignant neoplasm												
Female												
Age at cancer diagnosis, y												
0-3												
4-9												
10-14												
15-20												
Race/ethnicity												

Non-Hispanic white
Non-Hispanic black
Hispanic
Other
Cancer diagnosis
CNS
Leukemia
Lymphoma
Wilms tumor
Neuroblastoma
Bone/soft tissue sarcoma
Other
Pelvic tumor
Surgery
No
Yes
1 surgery
2 surgeries
>2 surgeries
Abdominal surgery
Colostomy
Chemotherapy
Alkylating agent
CED, mg/m^2
0
1-3999
4000-7999
>7999

Platinum agent score
1
2
3
Anthracycline dose, mg/m^2
None
<250
≥250
Abdominal/Pelvic Radiotherapy, Gy
0 (no radiotherapy)
<10
10-19
20-29
30-39
40-49
>49
Tobacco use
BMI
<18.5
18.5-25
25-30
30-35
35-40
>40
Year of diagnosis
1970-1974
1975-1979
1980-1984

1985-1989	
1990-1994	
1995-1999	
Annual household income, $	
<20,000	
20,000-39,999	
40,000-59,999	
60,000-79,999	
80,000-99,999	
>99,000	
Employment	
Unable to work	
Unemployed	
Student	
Full-time work	
Part-time work	
Education	
< high school	
High school graduate	
College graduate	
Health insurance coverage	

CED, cyclophosphamide equivalent dose; *CNS*, central nervous system

[a]The model will be separately evaluated including diagnosis (excluding treatment factors) and then including treatment factors (excluding diagnosis), so as not to incorporate two steps along the causal pathway.

[b]Reported on Original Cohort baseline or Expanded Cohort baseline (i.e. does not include anorectal complications reported on LTFU 2003, LTFU 2005, or LTFU 2007 surveys).

Figure 1. Cumulative incidence curves of late anorectal complications[a, b, c]
Curve A: siblings
Curve B: all survivors
Curve C: survivors with abdominal/pelvic tumors
Curve D: survivors without abdominal/pelvic tumors
[a]On different plots if competing risks differ considerably
[b]May plot individual treatment curves (i.e. Abdominal/pelvic radiotherapy, Chemotherapy, Abdominal/pelvic surgery) with Figure 1 if appropriate for comparison
[c]Stratified by specific anorectal complication (i.e. by anorectal second malignant neoplasm)

Figure 2. Cumulative incidence curves of late anorectal complications based on cancer treatment[a,b]
Curve A: Abdominal/pelvic radiotherapy
Curve B: Chemotherapy
Curve C: Abdominal/pelvic surgery
[a]May plot individual treatment curves (i.e. Abdominal/pelvic radiotherapy, Chemotherapy, Abdominal/pelvic surgery) with Figure 1 if appropriate for comparison
[b]Stratified by specific anorectal complication (i.e. by anorectal second malignant neoplasm)

Figure 3. Effect of abdominal/pelvic radiotherapy dose (Gy) on cumulative incidence of late anorectal complications[a]
Curve A: <10
Curve B:10-19
Curve C: 20-29
Curve D: 30-39
Curve E: 40-49
Curve F: ≥50
[a]Stratified by specific anorectal complication (i.e. by anorectal second malignant neoplasm)

Figure 4. Bar graph comparison of mean scores on SF-36 scales[a] (Physical Health and Mental Health) between survivors with and without late anorectal complication (age-, sex-, race, and year-matched general population scores will be included for referent)[b,c]
[a]In a separate analysis for the subset of Original Cohort patients who do and do not reach the primary outcome prior to completion of the LTFU 2003 survey.
[b]Including selected SF-36 subscales, as appropriate.
[c]Stratified by specific anorectal complication (i.e. by anorectal second malignant neoplasm)

Figure 5. Bar graph comparison of mean scores on BSI scales between survivors with and without late anorectal complications (age-, sex-, race-, and year-matched general population scores will be included for referent) [a,b]
[a]Including selected subscales, as appropriate. The first survey with responses to BSI questions after occurrence of the primary endpoint will be utilized.
[b]Stratified by specific anorectal complication (i.e. by anorectal second malignant neoplasm)
[c]In a separate analysis for the subset of participants who do and do not reach the primary outcome prior to completion of the Original Cohort or Expansion Cohort baseline surveys.

References

1. Goldsby R, Chen Y, Raber S, et al. Survivors of childhood cancer have increased risk of gastrointestinal complications later in life. *Gastroenterology*. May 2011;140 (5): 1464-1471.
2. Coia LR, Myerson RJ, Tepper JE. Late Effects of Radiation Therapy on the Gatrointestinal Tract. I. J. Radiation Oncology Biol Phys. 1994; 31(5): 1213-1236.
3. Do NL, Nagle D, Poylin VY. Radiation Proctitis: Current Strategies in Management. *Gastroenterology Research and Practice.* August 2011: 1-9.
4. Robinson L, Mertens AC, Boice JD et al. Study Design and Cohort Characteristics of the Childhood Cancer Survivor Study: A Multi-Institutional Collaborative Project. *Med Pediatr Oncol* 2002; 38: 229-239.
5. Bolling T, Willich N, Ernst I. Late effects of abdominal irradiation in children: a review of the literature. *Anticancer Res.* 2010;30(1):227-231.
6. Campos-Lobato LF, Vogel JD. Enterocutaneous Fistula Associated with Malignancy and Prior Radiation Therapy. *Clinics in Colon and Rectal Surgery*. 2010; 23 (3): 176-181.
7. Schlegel RD, Dehni N, Parc R, Caplin S, Tiret E. Results of reoperations in colorectal anastomotic strictures. *Dis Colon Rectum*. 2001; 44 (10): 1464-8.
8. Kaselas C, Molinaro F, Lacreuse I, Becmeur Francois. Postoperative bowel obstruction after laparoscopic and open appendectomy in children: a 15-year experience. *Journal of Pediatric Surgery.* 2009; 44: 1581-1585.
9. Gupta G, Agarwala S, Thulkar S, Shukla B, Bakhshi S. Jejnual Stricture: A Rare Complication of Chemotherapy in Pediatric Gastrointestinal B-Cell Non-Hodgkin Lymphoma. J Pediatr Hematol Oncol. 2011; 33 (2): 69-71.
10. Jao SW, Beart RW Jr, Reiman HM, Gunderson LL, Iistrup DM. Colon and anorectal cancer after pelvic irradiation. *Dis Colon Rectum.* 1987: 30 (12): 953-8.
11. Neglia JP, Friedman DL, Yasui Y, Mertens AC, Hammond S, Stovall M, Donaldson SS, Meadows AT, Robison LL. Second malignant neoplasms in five-year survivors of childhood cancer: childhood cancer survivor study. *J Natl Cancer Inst.* 2001: 93(8):618-29.
12. Baxter NN, Tepper JE, Durham SB, Rothenberger DA, Virnig BA. Increased risk of rectal cancer after prostate radiation: a population-based study. *Gastroenterology*. 2005: 128(4): 819-24.
13. Jin T, Song T, Deng S, Wang K. Radiation-induced secondary malignancy in prostate cancer: a systematic review and meta-analysis. *Urol Int.* 2014: 93(3):279-88.
14. Kendal WS, Eapen L, Macrae R, Malone S, Nicholas G. Prostatic irradiation is not associated with any measurable increase in the risk of subsequent rectal cancer. *Int J Radiat Oncol Biol Phys.* 2006:65(3):661-8.
15. Crook J, Esche B, Futter N. Effect of pelvic radiotherapy for prostate cancer on bowel, bladder, and sexual function: The Patient's perspective. *Adult Urology*. 1996; 47 (3): 387-394.
16. Zeltzer LK, Recklitis C, Buchbinder D, Zebrack B, Casillas J, Tsao JC, Lu Q, Krull K. Psychological status in the childhood cancer survivors: a report for the Childhood Cancer Survivor Study. *J Clin Oncol*. 2009:27(14):2396-404.

17. Green DM, Nolan VG, Goodman PJ, Whitton JA, Srivastava D, Leisenring WM, Negalia JP, Sklar CA, Kaste SC, Hudson MM, Diller LR, Stovall M, Donaldson SS, Robison LL. The cyclophosphamide equivalent dose as an approach for quantifying alkylating agent exposure: a report from the Childhood Cancer Survivor Study. *Pediatr. Blood Cancer.* 2014: 61(1): 53-67.
18. Mulrooney, DA, Yeazel MW, Kawashima T, Mertens AC, Mitby P, Stovall M, Donadson SS, Green Dm, Sklar CA, Robison LL, Leisenring WM. Cardiac outcomes in a cohort of adult survivors of childhood and adolescent cancer: retrospective analysis of the Childhood Cancer Survivor Study cohort. *BMJ*. 2009: 339.
19. Henderson, TO, Whitton J, Stovall M, Mertens AC, Mitby P, Friedman D, Strong LC, Hammond S, Neglia JP, Meadows AT, Robison L, Diller L. Secondary sarcomas in childhood cancer survivors: a report from the Childhood Cancer Survivor Study. *J. Natl. Cancer Inst.* 2007: 99(4): 300-308.