

1) Study Title: Long-term Burden of Major Surgical Procedures in Survivors of Childhood Cancer: A Report from the Childhood Cancer Survivor Study

2) Working group and investigators: The study will be performed with the assistance of the Chronic Disease Working Group. Secondary oversight will be provided by the Epidemiology/Biostatistics Working Group.

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3) Background and rationale:

Multimodal cancer therapy places survivors of childhood cancer at increased risk for chronic health conditions later in life.¹⁻² As a result of the extensive investigations conducted through the Childhood Cancer Survivor Study (CCSS) and other survivorship cohorts, associations between toxic therapies received during the course of treatment for childhood cancer and later development of chronic health conditions and secondary malignancies have become well-delineated.³ In addition to providing survivors and their healthcare providers with vital information necessary to optimize future health, knowledge of the long-term consequences of cancer therapies continues to influence the design of new cancer treatment protocols that seek to minimize detrimental late effects whenever possible.⁴

Despite an abundance of existing and continually expanding knowledge regarding the nature of chronic medical conditions afflicting survivors of childhood cancer, comparatively little is known about the nature and quantity of surgical interventions that survivors undergo. Recent findings from the CCSS revealed that survivors are at significantly higher risk for intestinal obstruction requiring surgery compared to their siblings.⁵ Apart from this example and despite the fact that numerous other health conditions that predispose to a need for surgical intervention are common among childhood cancer survivors, there are few studies that investigate the long-term burden of major surgical procedures in this population.

The importance of advancing our understanding of the frequency of late major surgical procedures on the childhood cancer survivor population should not be understated. From an economic perspective, surgical hospitalizations, including those related to complications, are among the most expensive hospital service lines in terms of hospital costs in the United States and the average total hospital cost per surgical discharge far exceeds those of medical

discharges.⁶⁻⁷ For the patient, suboptimal recovery after surgery can occur in nearly a quarter of patients who may suffer lasting consequences on physical function, mental health and vitality postoperatively.⁸ More importantly, every operation comes with associated risk for morbidity and mortality as a direct result of the operation or its sequelae.⁹⁻¹⁰ While it can be inferred that the comorbidity profiles of survivors place them at higher overall risk for postoperative complications compared to the general population, it remains unclear whether survivors are also undergoing more major surgical procedures than the general population. Additionally, gaining an understanding of which subgroups of survivors are more likely to need additional surgery later in life is important for physicians who provide patient education and expectation management to this vulnerable population.

To date, there have been no reports exploring the long-term burden of major surgical procedures faced by survivors of childhood cancer over the course of their lifetime. We intend to estimate the rates and distribution of selected late major surgical operations among survivors of childhood cancer compared to their siblings as well as elaborate on the risk factors for late surgery in the survivor population.

4) Specific aims:

Aim 1 – To estimate and compare the cumulative incidence and cumulative burden (using the mean cumulative count) of late major surgical operations* undergone by survivors overall and according to initial cancer diagnosis vs. sibling controls.

Hypothesis – The cumulative incidence and cumulative burden of major surgical operations are higher over time for survivors when compared to sibling controls. With respect to specific diagnosis subgroups, cancer diagnoses that historically undergo more intensive multimodal therapies, especially those that are treated primarily by gross total resection, will result in higher incidence and cumulative counts of operations later in life.

**Major operations are defined according to the Healthcare Cost and Utilization Project definition as invasive diagnostic or therapeutic procedures requiring performance within an operating room¹¹*

Aim 2 – To estimate and compare the cumulative incidence and cumulative burden of specific types of late major surgical operations (or operation subgroups where appropriate) in survivors vs. sibling controls.

Hypothesis – Certain major surgical operations (or operation sub-groups) will be more common in survivors than siblings. For example, we hypothesize that major surgeries including joint replacements and cardiac surgery, which are often undertaken in the elderly, will be more common in survivors due to comorbidity profiles and treatment exposures.

Aim 3 – To estimate the cumulative incidence of specific late major surgical operations (or operation subgroups) by initial cancer diagnosis in survivors vs. sibling controls.

Hypothesis - Initial cancer diagnoses will be associated with differential likelihoods of undergoing certain operations.

Aim 4 – To investigate associations between childhood cancer treatment exposures and rate of late major surgical operations among survivors.

Hypothesis – Survivors who underwent multiple surgeries or received radiotherapy as treatment for their primary cancer will be at higher risk for late major surgical burden compared with survivors who did not have these exposures.

5) Methods:

a) Population

We will include all childhood cancer survivors and siblings who participated in the CCSS original and expanded cohorts.

b) Outcomes of interest

The *primary outcome* is all late major surgical operations undergone by survivors and the sibling comparison group, defined as self-report of any of the surgical procedures included in the CCSS long-term follow-up surveys and occurring ≥ 5 years after diagnosis of primary childhood cancer.

- Surgical Procedures (yes/no for each operation and reported age at operation); section I1-I31 (baseline [B]), section I1-I37 (baseline expansion [BE]), section J1-J37 (follow-up 4 [FU4]), and/or section J1-J40 (follow-up 5 [FU5]).
 - Amputation of extremity or digit (B.I1, BE.I1, FU4.J1, FU5.J1)
 - Include each reported amputation from the ‘free-text’ section
 - Joint replacement (B.I5, BE.I5, FU4.J5, FU5.J5)
 - Include each reported joint replacement from the ‘free-text’ section
 - Limb lengthening/shortening (B.I4, BE.I4, FU4.J4, FU5.J5)
 - Other bone surgery (B.I6, BE.I6, FU4.J6, FU5.J6)
 - These reported operations within the ‘free-text’ field will be reviewed but may not be included in the final analysis
 - Scoliosis surgery (B.I2, BE.I2, FU4.J2, FU5.J2)
 - Other spine surgery (B.I3, BE.I3, FU4.J3, FU5.J3)
 - These reported operations within the ‘free-text’ field will be reviewed but may not be included in the final analysis
 - Coronary artery bypass (B.I7, BE.I7, FU4.J7, FU5.J7)
 - Pericardiectomy (B.I8, BE.I8, FU4.J8, FU5.J8)
 - Valve replacement (BE.I11, FU4.J11, FU5.J11)

- Heart transplant (B.I23, BE.I25, FU4.J25, FU5.J27)
- Other heart surgery (B.I10, BE.I13, FU4.J13, FU5.J13)
 - These reported operations within the 'free-text' field will be reviewed but may not be included in the final analysis
- Heart cath/angioplasty (B.F14 or B.I9, BE.I9 or I10, FU4.J9 or J10, FU5.J9 or J10)
- Pacemaker implant (BE.I12, FU4.J12, FU5.J12)
- Any lung surgery (B.I20, BE.I23, FU4.J23, FU5.J25)
 - These reported operations within the 'free-text' field will be reviewed but may not be included in the final analysis
- Lung transplant (B.I24, BE.I26, FU4.J26, FU5.J28)
- Lumpectomy (BE.I21, FU4.J21, FU5.J23)
- Any mastectomy (BE.I22, FU4.J22, FU5.J24)
- Ex-lap for SBO (B.I11, BE.I14, FU4.J14, FU5.J14)
- Colostomy/ileostomy (B.I12, BE.I15, FU4.J15, FU5.J15)
- Partial or total colectomy (FU5.J16)
- Rectal resection (FU5.J17)
- Splenectomy (B.I16, BE.I18, FU4.J18, FU5.J20)
- Renal transplant (B.I25, BE.I27, FU4.J27, FU5.J29)
- Liver transplant (BE.I28, FU4.J28, FU5.J30)
- Any oophorectomy (BE.I32 or I33, FU4.J32 or J33, FU5.J34 or J35)
- Hysterectomy (BE.I34, FU4.J34, FU5.J36)
- Any orchiectomy (BE.I35 or I36, FU4.J35 or J36, FU5.J37 or J38)
- Prostatectomy (FU5.J39)
- Partial or total thyroidectomy (B.I15, BE.I16 or I17, FU4.J16 or J17, FU5.J18 or J19)
- Cataract surgery (B.I28, BE.I31, FU4.J31, FU5.J33)
- VP shunt (B.I17, BE.I19, FU4.J19, FU5.J21)

c) Exploratory variables

- Demographic and social variables
 - Age at last survey (continuous)
 - Sex (categorical; female, male)
 - Race/ethnicity (categorical; non-Hispanic white, non-Hispanic black, Hispanic, other)
 - Health Insurance (categorical; no, yes/Canadian resident)
- Additional Variables
 - Cancer diagnosis (categorical; CNS tumor, ALL, AML, Other leukemia, Hodgkin lymphoma, Non-Hodgkin lymphoma, Wilms tumor, Neuroblastoma, Soft tissue sarcoma, Bone cancers)
 - Years from diagnosis to late surgery (continuous)
 - Surgery as treatment for primary cancer (categorical; none, 1-2, ≥ 3)
 - Chemotherapy as treatment for primary cancer (binary; yes/no; anthracycline yes/no; alkylator yes/no)

- Radiotherapy as treatment for primary cancer (categorical; none, any, cranial, chest, abdomen/pelvis)

d) Statistical methods

Survivors will enter the cohort five years from the primary cancer diagnosis and at-risk status will end at the time of last survey or on the date of death. Sibling controls will enter the analysis five years after the date of corresponding survivor primary cancer diagnosis. Demographic and clinical characteristics will be displayed for childhood cancer survivors and sibling controls (**Table 1**). Using the method of mean cumulative count (MCC), which estimates the mean number of self-reported surgeries per person-time during the follow-up period, we will estimate the total number of self-reported late major surgical procedures undergone per individual for survivors and sibling controls overall and by primary cancer diagnosis and then determine adjusted rate ratios compared to siblings controlling for age, sex, race/ethnicity and health insurance status (**Table 2**). We will show the curve of MCC versus time for all late major surgical procedures for survivors overall and sibling controls (**Figure 1**). We will then estimate the MCC of late major surgical procedures versus time for survivors according to initial cancer diagnosis compared to siblings (**Figure 2**). Note: due to limitations of the data collected, patients who undergo multiple operations of the same type (i.e. multiple operations for small bowel obstruction) may only be captured at the first event, this will underestimate the total burden of late surgery in the cohort. The cumulative incidence of selected subcategories of late major surgical procedures will be determined for survivors and sibling controls and adjusted rate ratios calculated, adjusting for age, sex, race/ethnicity and health insurance status (**Table 3**). The distribution of late major surgical operation subcategories shown for sibling controls and survivors stratified by underlying cancer diagnosis and selected attained ages, controlling for the same variables (**Figure 3**). Multivariable polytomous logistic regression analysis will then be used to quantify late surgery burden in survivors relative to siblings (**Table 4**) initially, followed by an assessment of associations between primary cancer treatment variables and late surgical burden among survivors alone (**Table 5**), adjusting for age at the last follow up, sex, race/ethnicity and health insurance status.

6) Future Directions:

The purpose of this project is to provide a comprehensive understanding of the general burden of late surgical procedures faced by childhood cancer survivors as they age. We hypothesize that survivors will undergo more late operations relative to siblings and that there is variability in the associated surgical burden when examined by specific cancer diagnoses, likely related to the types and intensity of the cancer treatments received. Due to the heterogeneity of cancer therapies and the broad spectrum of operations captured in the CCSS dataset, we intend to identify associations between general categories of treatment exposures and late surgery. We anticipate that future projects would likely need to be tailored toward understanding the specific risk factors that predispose to a given late surgery of interest (i.e. body region radiotherapy by dose ranges, chemotherapy variables related to certain diagnoses and specific childhood cancer operations). In these future projects, we would also aim to understand the relationships between select original cancer treatments, specific late surgeries, and subsequent long-term quality of life and physical function, as well as, late all-cause mortality when appropriate.

7) Examples of tables and figures

Table 1. Demographic and treatment characteristics of childhood cancer survivors and siblings

Characteristic	Survivors (N = ***)	Siblings (N = ***)
Sex		
Female	No. (%)	No. (%)
Male		
Race/ethnicity ^a		
Non-Hispanic white		
Non-Hispanic black		
Hispanic		
Other		
Health insurance status		
No		
Yes or Canadian resident		
Cancer diagnosis		
CNS Tumor		
Acute Lymphoblastic Leukemia		
Acute Myeloid Leukemia		
Other Leukemia		
Hodgkin lymphoma		
Non-Hodgkin lymphoma		
Wilms' Tumor		
Neuroblastoma		
Soft Tissue Sarcoma		
Ewing's Sarcoma		
Osteosarcoma		
Surgery as treatment for primary cancer		
None		
1-2		
≥3		
Chemotherapy as treatment for primary cancer		
Any chemotherapy		
Any anthracycline		
Any alkylator		
Radiation therapy as treatment for primary cancer		
Any irradiation		
Cranial irradiation (ref no)		
Chest irradiation (ref no)		
Abdominal/pelvic irradiation (ref no)		
TBI		
Any late major surgical operation		
Yes		
No		
Median age at first late surgery, y (median +/- IQR)		
Median age at last survey, y (median +/- IQR)		
Time to last follow-up, y (median +/- IQR)		

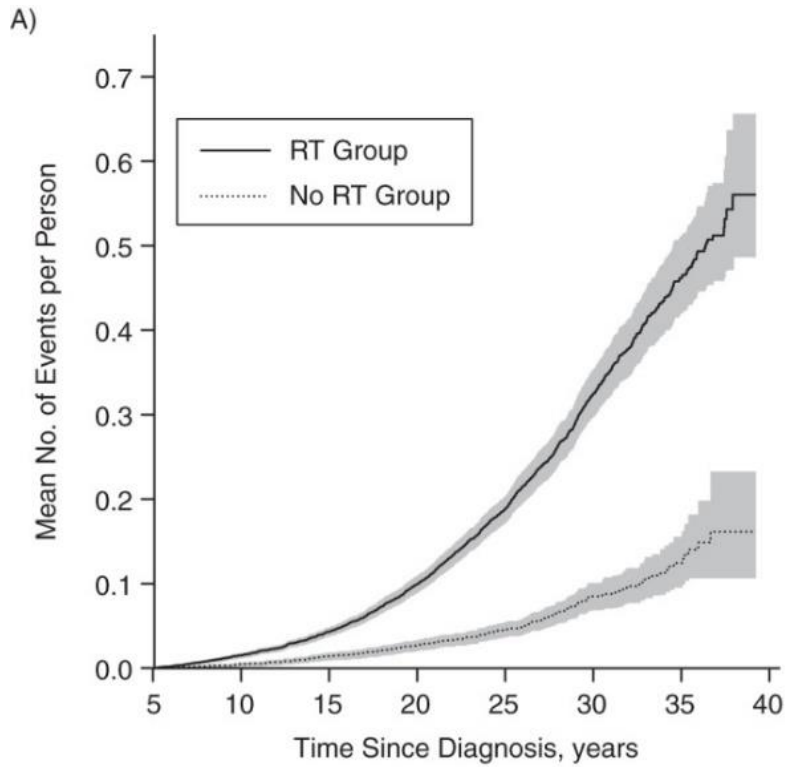
^aRace or ethnic group was reported by the participant; ^bFor siblings, any primary cancer diagnosis

Table 2. Mean cumulative count and adjusted rate ratios of late major surgical procedures for cancer survivors and siblings

	MCC (# events per person)	ARR
Siblings (n=XXX)	X	1.0
All Survivors (n=XXX)	X	X (95% CI)
<i>Primary Cancer Diagnosis</i>		
CNS Tumor (n=XXX)		
Acute Lymphoblastic Leukemia (n=XXX)		
Other Leukemia (n=XXX)		
Hodgkin Lymphoma (n=XXX)		
Non-Hodgkin Lymphoma (n=XXX)		
Wilms Tumor (n=XXX)		
Neuroblastoma (n=XXX)		
Soft Tissue Sarcoma (n=XXX)		
Ewing's Sarcoma (n=XXX)		
Osteosarcoma (n=XXX)		

Adjusted for attained age, sex, race/ethnicity and health insurance status.

Figure 1. Mean cumulative count versus time for all late major surgical procedures for survivors overall and sibling controls



From: Dong et al. *Am J Epidemiol.* 2015;181(7):532–540.

Figure 2A-J. Mean cumulative count versus time for all late major surgical operations undergone by survivors and siblings, according to initial cancer diagnosis.

- Ex. 3A – MCC of selected late major surgical operations for CNS tumor survivors and siblings; 3B – MCC of selected late major surgical operations for ALL survivors and siblings; ...; 3J – MCC of selected late major surgical operations for Osteosarcoma survivors and siblings.

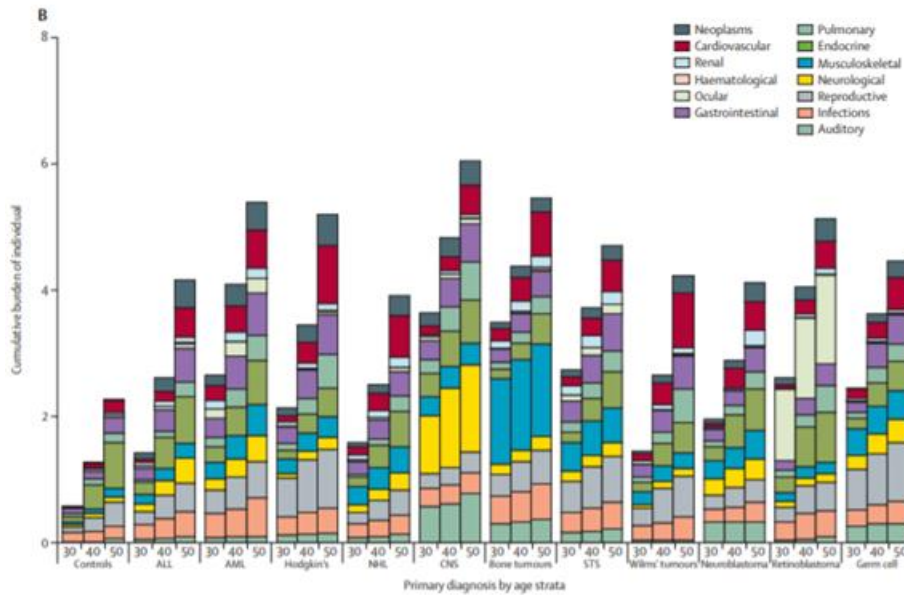
Table 3. Cumulative incidence of specific late major surgical operations and adjusted rate ratios for survivors compared to siblings.

Surgery Sub-type	Survivors	Siblings	Adjusted rate ratio
Any cardiac surgery	X	X	X (95% CI)
Valve replacement			
CABG			
Pericardiectomy			
Any colorectal surgery			
Any thyroidectomy			
Any breast surgery			
Any lung surgery			
Any female reproductive surgery			
Oophorectomy			
Hysterectomy			
Any lower extremity joint replacement			
Hip replacement			
Knee replacement			
Any lower extremity amputation			
Any spine surgery			
Cataract surgery			
Ventriculoperitoneal shunt			

Adjusted for attained age, sex, race/ethnicity and health insurance status.

- Similar to ‘Table 3’ in Oeffinger et al. *NEJM* 2006.
- May present as composites by surgery sub-type instead of specific procedures

Figure 3. Distribution of late major surgical operation subtypes among survivors and sibling controls by diagnosis group and attained age.



- Similar to 'Figure 4' in Bhakta et al. *Lancet* 2017.
- Late surgeries to be subdivided into the following categories: orthopedic, spine, cardiac, colorectal, other abdominal, breast, lung, neurological, GU/reproductive and other. We will group by primary cancer diagnosis and stratify by attained age 30, 40 and 50 (as above).

Table 4. Relative Risk of Late Surgical Disease among Cancer Survivors by Treatment Exposures as Compared with Siblings*

Exposure as Treatment for Primary Cancer	Any Late Surgery	≥2 Late Surgeries
	Relative Risk (95% Confidence Interval)	
Siblings	1.0	1.0
Surgery		
None		
1		
≥2		
Chemotherapy		
Any		
Radiation therapy		
Any irradiation		
TBI		
<i>Specific Combinations</i>		
Surgery plus chemotherapy		
Surgery plus radiation		
Surgery plus chemotherapy plus radiation		
Chemotherapy plus radiation		

*Each row represents an individual multivariate regression model, adjusted for the age at the time of the study, sex, race/ethnicity and insurance status.

- Note: we may perform sub-analysis investigation specific chemotherapy agents (e.g. alkylating agents, anthracyclines) or radiotherapy body-regions of interest (e.g. cranial, chest, abdomen/pelvis).

Table 5. Multivariable model of factors associated with late surgery burden among survivors.

Treatment Exposures for Primary Cancer	Adjusted Odds Ratio (95% Confidence Interval)	
	1 vs. 0 Late Surgery	2+ vs. 0 Late Surgery
Surgery		
1 (ref none)		
≥2 (ref none)		
Chemotherapy		
Any (ref no)		
Alkylating agent (ref no)		
Anthracycline (ref no)		
Radiation therapy		
Any irradiation (ref no)		
Cranial irradiation (ref no)		
Chest irradiation (ref no)		
Abdominal/pelvic irradiation (ref no)		
TBI (ref no)		

* additionally, adjusted for age at the time of the study, sex, race/ethnicity and health insurance status

8) Special considerations: N/A

References

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