Analysis Concept Proposal

Study Title: Long-term outcomes of survivors of childhood Acute Lymphoblastic Leukemia (ALL) across 30-years of treatment: a report from the Childhood Cancer Survivor Study

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1. Background and Rationale

   Acute lymphoblastic leukemia (ALL) is the most common childhood cancer, accounting for 25% of all malignancies among children <15 years of age and 20% among those <20 years.[1] Cure rates improved dramatically over the last six decades, from 5-year overall survival (OS) of approximately 10% in the 1960s to near 80% by the late 1980s and approached 90% by the year 2000.[2-9] These improvements were achieved through increased understanding of the biology of ALL, leading to improved risk stratification, appropriate chemotherapeutic intensification, disease monitoring and supportive care. Additionally, many therapeutic changes occurred over this timeframe; there was a successive decline in the proportion of patients receiving cranial radiation therapy,[9-12] increased dexamethasone and asparaginase use[13] and higher dose methotrexate exposure.[5]

   While the majority of ALL patients treated in the current era are expected to be cured of their disease, many will go on to experience excess morbidity and mortality as a result of their cancer experience. Mody et al. previously reported on long-term outcomes of ALL survivors among the CCSS original cohort (diagnosed from 1970-1986). These findings included a cumulative mortality conditioned on 5-year survival of 13%, which was a significantly higher rate of occurrence than expected in the general US population. All-cause mortality in the entire CCSS cohort, diagnosed from 1970-99, was most recently evaluated by Armstrong et al. ALL 5-year survivors followed for 15

years from diagnosis were found to have a standardized mortality ratio (SMR) of 15.2 compared to the general US population. The 15-year cumulative mortality conditioned on 5-year survival was reduced from 10.7% for ALL survivors treated in the 1970s to 3.1% for those treated in the 1990s.[14]

ALL survivors are also known to be at increased risk for subsequent neoplasms compared to the general US population.[15,16] Mody et al. reported a cumulative incidence of second neoplasms (excluding non-melanoma skin cancer) of 5.2% in the ALL survivors in the original CCSS cohort. Turcotte et al. recently evaluated the overall CCSS cohort and found the 15-year cumulative incidence of subsequent neoplasms and subsequent malignant neoplasms to be lower in survivors who received treatment in later decades. However, there was no significant change in cumulative incidence of subsequent malignant neoplasms observed in the subgroup of ALL survivors by decade.[16]

ALL survivors are also at an increased risk for chronic health conditions compared to siblings. The Mody et al. study of ALL survivors in the original cohort observed a cumulative incidence of any chronic health condition at 25 years from diagnosis of 50.0% among survivors compared to 37.8% in siblings. ALL survivors were 3.7 times as likely as siblings to report a severe or life-threatening condition, with a cumulative incidence among ALL survivors 25 years from diagnosis of 21.3%. [15] A recent analysis of temporal trends in chronic health conditions by Gibson et al. utilizing the entire CCSS cohort reported findings overall and by cancer diagnosis groups. By 15 years after diagnosis, they observed no significant difference across treatment decades in the cumulative incidence of any severe, disabling, life-threatening or fatal chronic health condition for ALL survivors (15.7% for 1970s vs. 14.5% for 1980s vs. 14.6% for 1990s). Additionally, there was no observed decline in the prevalence of chronic conditions at 5 years post-diagnosis across treatment decades in survivors of ALL. Finally, although a decrease in the rate of incident chronic conditions among survivors of ALL from 5-15 years post-diagnosis was observed, the inclusion of treatment variables (anthracycline, cranial radiation, epipodophyllotoxin, methotrexate and steroids) into the model attenuated the association.[17]

In the Mody et al study, ALL survivors more frequently reported poor general health status, mental health problems, activity limitations and functional impairment compared to siblings; however, Essig et al. observed that in the subset of survivors treated most similarly to contemporary ALL therapy (without cranial radiation, with low to moderate anthracycline doses and low overall alkylating agent exposure), differences from siblings health status were seen only with regards to functional limitations.[18] A recent analysis of the overall CCSS cohort by Ness et al. observed an increase in the percentage of ALL survivors reporting poor general health, cancer-related pain and anxiety across treatment decade. After adjustment for treatment exposures, differences in poor general health and cancer-related pain became nonsignificant, they were not changed by adjustment for grade 3 or 4 chronic health conditions.[19] Similarly, while ALL survivors in the Mody et al. study reported significantly lower rates of marriage, college graduation and health insurance coverage compared to siblings, Essig et al observed that survivors treated most similarly to contemporary therapy did not differ from siblings in terms of household income, educational attainment, marital status, likelihood of living independently, or rates of insurance coverage. With the exception of the study by Essig et al., prior CCSS studies did not evaluate ALL survivors by treatment grouping, which may provide additional information regarding specific risk factors, or combinations of risk factors, contributing to these outcomes.

Since the initial ALL specific evaluation of the CCSS cohort, an additional 1819 ALL survivors have been added to the cohort from the expansion cohort (diagnosed from 1987-1999). Many survivors from the expansion cohort would have received treatment more similar to contemporary ALL therapy including fewer patients exposed to cranial radiation, intensification of intrathecal chemotherapy, increased asparaginase use, increased dexamethasone use[13] and higher dose methotrexate.[5] With fewer patients exposed to cranial radiation, neurocognitive impairment within this group will be less;[20] however IV methotrexate and dexamethasone have been linked to impaired executive function and attention[12,20] and dexamethasone use to memory impairments.[21] Both treatments are utilized in contemporary protocols. While dexamethasone use has demonstrated improved control of CNS leukemia as well as other dose related anti-leukemic benefits compared to prednisone, it has also been linked to increased adverse effects including bone fracture, osteonecrosis and myopathy.[22] Additionally, more patients in this expansion cohort will have had anthracycline exposure; however, among those exposed, the median cumulative dose will be less.[14]

Given the improved OS in recent decades, more of these survivors will be expected to be living into middle and late adulthood and therefore be at-risk of experiencing the late effects of their prior treatment. There is a need to understand how changes in therapy over time have impacted morbidity and mortality of survivors of childhood ALL. While we have a number of studies detailing effects of specific therapeutic exposures or decade of treatment on outcomes of childhood cancer survivors, few have been able to analyze late effects by treatment grouping which may be more clinically meaningful when thinking of care of survivors of childhood ALL. Additionally, specific outcomes of adult survivors of childhood ALL have not been reported in a single study since the expansion of the CCSS cohort. This study aims to provide a comprehensive description of long-term outcomes of ALL survivors across 30-years of treatment and describe these findings in the context of therapeutic changes over this time span. Outcomes will include mortality, subsequent neoplasms, chronic medical conditions, overall health status, neurocognitive and socioeconomic outcomes.

2. Specific Aims
   2.1. Evaluate all-cause and cause-specific late mortality (death ≥ 5 years after diagnosis) among ALL survivors in the CCSS cohort compared to the US population overall. Further, analyze all-cause and cause-specific late mortality by mutually exclusive treatment groups created to summarize treatment changes over time and then by specific therapeutic exposures.

   2.2. Describe the prevalence of chronic health conditions among ALL survivors in the CCSS cohort compared to sibling controls overall. Further, analyze chronic health conditions among survivors by mutually exclusive treatment groups and then by specific therapeutic exposures. We will specifically examine bone health (non-digit fracture, osteoporosis, osteonecrosis, joint replacement) with regard to type of steroid exposure, endocrine/metabolic outcomes such as obesity and diabetes with respect to radiation to the brain, stroke with respect to radiation to the brain, cardiac conditions with respect to anthracycline exposure and dose given changes in therapy over time which may lead to differential effects by treatment exposure, neuropathy and fertility with respect to alkylator exposure and testicular irradiation in males.

      2.2.1. Describe late neurocognitive outcomes among ALL survivors in the CCSS cohort compared to siblings using the NCQ. Impairment will be graded using a scale detailed in the methods similar to prior grading in the St Jude Lifetime Cohort.[23] Further, analyze neurocognitive outcomes by treatment group and then by cranial radiation exposure. Further evaluation

among survivors with specific therapeutic exposures will not be performed as it is in conflict with an ongoing CCSS study.

2.3. Describe the incidence of subsequent neoplasms (benign and malignant) among ALL survivors in the CCSS cohort compared to the US population overall. Further, analyze subsequent malignant neoplasms by treatment group and then by specific therapeutic exposures.

2.4. Describe overall health status among ALL survivors compared to sibling controls including general health, mental health, functional status, activity limitations, treatment related pain and anxiety overall, by treatment group and then by specific therapeutic exposures.

2.5. Describe socioeconomic outcomes among ALL survivors compared to siblings including marriage, employment, education and insurance status overall, by treatment group and then by specific therapeutic exposures.

3. Exploratory Aim

3.1. As an exploratory outcome, we will evaluate the above aims by treatment era, stratifying by 5 year time blocks similar to prior CCSS study by Mody et al (i.e. 1970-74, 1975-89, 1980-84, 1985-89, 1990-94 and 1995-99) acknowledging that many of these assessments (late mortality, SMNs) have previously occurred, but that since the time of those analyses there have been additional data obtained from the NDI (deaths now through 2013) and updated SMN data (through FU5).

4. Hypotheses

4.1. Late mortality will be significantly higher among the cohort of ALL survivors compared to the age- and gender-matched general US population. Within the cohort of survivors, late mortality rates will be lower in patients treated without cranial radiation.

4.2.

4.2.1. ALL survivors will experience significantly higher rates of any (grade 1-5) and severe, life threatening or fatal (grade 3-5) chronic medical conditions when compared to siblings.

4.2.2. Within the cohort of survivors, survivors treated with any radiation, compared to survivors who were not exposed to radiation, will be at the highest risk for any chronic health condition.

4.2.3. Within the cohort of survivors, survivors treated with dexamethasone, compared to survivors who received only prednisone, will be a highest risk for musculoskeletal morbidities.

4.2.4. ALL survivors will experience significantly worse neurocognitive function when compared to siblings. Within the cohort of survivors we anticipate that the rate and degree of impairment will be greatest in those patients treated with cranial radiation.

4.3.

4.3.1. ALL survivors will experience significantly more subsequent neoplasms including malignant neoplasms, meningiomas and non-melanoma skin cancers compared to the general US population.

4.3.2. Within the cohort of survivors, the rate of malignant CNS tumors, meningiomas and non-melanoma skin cancers will be significantly higher in patients whose therapy included cranial radiation.

4.4. ALL survivors will be more likely to report poor general health, mental health problems, activity limitations, and poor functional status when compared with siblings; however, survivors treated within the group of *1990's standard risk-like therapy* (defined in the methods) will only be observed to have poor functional status when compared to siblings, similar to findings from Essig et al.

4.5. ALL survivors will report lower rates of marriage, educational attainment, employment, insured status and independent living when compared with siblings with these differences being most pronounced in those treated with radiation.

5. Methods

Specific, mutually exclusive, treatment groupings identified to represent clinically relevant therapy combinations used during different eras of therapy and capture a large percentage (though not all) of the CCSS population were developed and described in the below table.

Dosing Thresholds for mutually exclusive groups

	1970s –like (n=716)	**1980s SR-like (n=645)**	**1980s HR-like (n=373)**	**1990s SR/Essig (n=1115)**	**1990s HR-like (n=492)**	**Relapse/Transplant (n=1090)**
Radiation (Gy)	>20 Gy	0<RT ≤20 Gy	>0 Gy	None	NS	NS
Dexamethasone (Y/N)	No	No	No	NS	Yes	NS
Anthracycline (mg/m2)	NS	≤120 mg/m2	>120 mg/m2	≤120 mg/m2	>120 mg/m2	NS
Cyclophosphamide (mg/m2)	NS	NS	NS	≤1000 mg/m2	>1000 mg/m2	NS
Cytarabine, IV**	N	NS	Y	NS	NS	NS
Relapse or Transplant ever	N	N	N	N	N	Y

SR (Standard Risk); HR (High Risk)

NS indicates that this variable is not a differentiator for the group, the cell can assume any value (ie Y or N dexamethasone, no radiation or any amount of radiation).

**Y is any Cytarabine in expansion cohort or any IV Cytarabine in Original cohort. N is no Cytarabine in expansion cohort or no IV Cytarabine in original cohort. Cytarabine in original cohort MRAF was differentiated into IV/IM and IT while in the expansion cohort MRAF it was only cumulative dose but not specified route of administration. N for 1970s like will include original cohort participants with No IV/IM Cytarabine; however, we will not exclude those original cohort participants who received only IT Cytarabine. Additionally if there were any expansion cohort participants who received no Cytarabine and met the other criteria for 1970s-like therapy, they would also be included. Y for 1980s HR-like therapy will include original cohort participants who received any IV Cytarabine as well as expansion cohort participants who received any Cytarabine (either IV or IT) and otherwise met the inclusion criteria for the group. Although there may be some expansion cohort patients included in the 1980s HR like group who received only IT Cytarabine, since they were treated after 1986 and otherwise meet the 1980s HR like therapy requirements we feel it is reasonable to include these patients.

When referencing therapeutic exposures we will include: cranial radiation (None, >0 to 20 Gy, >20 Gy), Craniospinal irradiation (CSI) (Y/N), Testicular irradiation (Y/N), Total body irradiation (TBI) (Y/N), anthracycline (None, >0 and <120 mg/m^2, ≥120 mg/m^2 and <250 mg/m^2, ≥250 mg/m^2), alkylators (Cyclophosphamide equivalent dose (CED); None, >0 to <1000 mg/m^2, ≥1000 to <4000 mg/m^2, ≥4000 to <8000 mg/m^2 and ≥8000 mg/m^2), IV methotrexate (None, <4.3 g/m^2, ≥4.3 g/m^2),

IT methotrexate (none, <230 mg/m^2, ≥230 mg/m^2), epipodophyllotoxins (Y/N), and dexamethasone (Y/N); Cytarabine exposure (Y/N) will also be included descriptively in table 1.

5.1. Study Population: All 5-year survivors of ALL in the overall CCSS cohort (diagnosed between 1970 and 1999). For the mortality analysis, all eligible subjects will be included. For subsequent aims, the subset of eligible CCSS participants who completed a baseline survey will be included (n= 6148). For the treatment group analysis, numbers of eligible subjects for analysis will be: total (n = 4431), 1970s-like (n=716), 1980s SR-like (n=645), 1980s HR-like (n=373), 1990s SR-like (n=1115), 1990s HR-like (n=492), relapse or HSCT (n=1090).

5.2. Outcome Measures: Outcomes of interest will be gathered from CCSS surveys of survivors and siblings, the US National Death Index (NDI) and the Surveillance, Epidemiology, and End Results (SEER) program. Any CCSS survey completed by each survivor and sibling that captures any of the outcome or explanatory variables will be utilized, up to and including follow-up #5. Mortality, subsequent neoplasms, and chronic health conditions will be evaluated as time-to-event outcomes and all relevant information will be collected from all questionnaires. For the remaining outcome variables, we will utilize cross-sectional information from the most recently completed questionnaire that assessed the outcome of interest.

5.2.1. Mortality: We will use vital status (alive/dead) to identify a) cumulative mortality and b) standardized mortality ratios (SMR). The NDI will be the source for vital status. The CCSS currently has NDI data updated through 2013. Standardized mortality rates will be calculated using age- and sex-specific mortality rates for the U.S. population from the National Center for Health Statistics as per the method established by Mertens et al for previous CCSS publications.[24] Underlying cause of death has been determined from death certificates and will be grouped into three mutually exclusive categories as[14]:

5.2.1.1. Recurrence/progression of primary childhood malignancy

5.2.1.2. External cause (e.g. accidents, injuries, suicides)

5.2.1.3. Non-recurrence/non-external cause (attributable to chronic health conditions) sub-classified as subsequent neoplasms, cardiac, pulmonary and all other causes.

5.2.2. Chronic health conditions: Chronic health conditions identified using the standard approach of scoring the severity of each condition using the Common Terminology Criteria for Adverse Events (CTCAE) version 4.0, will be used in the analysis in accordance with prior CCSS studies[25]. Conditions are separated by organ system (i.e. cardiac, endocrine, metabolism and nutrition, neurologic, musculoskeletal etc.) and graded as mild (grade 1), moderate (grade 2), severe (grade 3), life-threatening or disabling (grade 4) or fatal (grade 5). If a condition reported was not listed in the CTCAE criteria, it will be included as "Other, specify" according the organ system affected. If there is insufficient information to distinguish between grades, the lower score will be selected. We will describe results for any chronic health conditions and separated by grade 1-2 and grade 3-5 conditions.

5.2.2.1. Neurocognitive outcomes: Neurocognitive impairment in survivors will be assessed using the CCSS-NCQ (Q1-33 on FU5) which was developed for use and validated within the CCSS cohort using 4 factors; Task Efficiency, Emotional Regulation, Organization, and Memory. Raw scores referenced to the sibling cohort, with scores ≥90th percentile of siblings classified as impairment has been the

threshold used in the validation studies of the CCSS-NCQ and prior CCSS studies.[26] Additionally, we will grade the degree of neurocognitive impairment modelling the grading scale after studies using the St. Jude Lifetime Cohort[23] where impairment will be defined as ≥1 and < 2 standard deviations (SDs) (Grade 1, mildly impaired), ≥ 2and <3 SD (Grade 2, moderately impaired), and ≥ 3 SD (Grade 3, severely impaired) below the mean age-adjusted population normative score on any one measure. Moderate impairment (scores below the lowest 3rd percentile for population norms) would be expected to impact instrumental activities of daily living, while severe impairment (scores below the lowest 0.3 percentile for population norms) would be expected to impact self-care activities of daily living.

5.2.3. Subsequent neoplasms: Subsequent neoplasms identified by self- or next-of-kin proxy report or death certificate and confirmed using pathology report or, when unavailable, death certificate, medical records or both will be included in this analysis. For subsequent malignant neoplasms, only those occurring 5 years or more after initial cancer diagnosis will be included. Subsequent neoplasm will be categorized into three mutually exclusive groups as in prior CCSS studies[16]:

5.2.3.1. Subsequent malignant neoplasms, which include invasive neoplasms classified as International Classification of Diseases for Oncology (ICD-O, third version) behavior code of 3, excluding non-melanoma skin cancers

5.2.3.2. Benign meningiomas

5.2.3.3. Non-melanoma skin cancers, including ICD-O morphology codes 8070, 8071, 8081, 8090 and 8094.

5.2.4. Overall health status: Overall health status will be evaluated using the methodology of Hudson et al. including the six domains of general health, mental health, functional status, activity limitations, cancer-related pain and cancer-related anxiety/fears.[27] Classification of poor general health will be based on “poor” or “fair” response to the question, “Would you say that your health is excellent, very good, good, fair, or poor?”[28] Adverse mental health status will be assigned to participants whose responses to the Brief Symptom Inventory 18 resulted in a sex-specific T-score of 63 or higher on the Global Severity Index or any two of the Depression, Anxiety, or Somatization subscales.[29] Participants will be categorized with functional impairment if they reported that a health problem resulted in needing help with personal care or routine needs or resulted in difficulty attending work or school. Activity limitations will be assigned to participants who reported that health limited moderate activities (i.e. walking upstairs, climbing a few flights of stairs, or walking one block) three or more months out of the past two years. Survivors will be dichotomized as having medium, a lot, or very bad, excruciating pain related to their cancer/treatment versus none or a small amount of pain. Similarly, survivors will be categorized as having medium, a lot, or very many, extreme fears or anxiety related to their cancer/treatment versus no or a small amount of anxiety or fears. Siblings will be categorized in the overall health, mental health, functional impairment and activity limitation categories only. This is modeled after the methods of Hudson et al and Ness et al.[19,28]

5.2.5. Socioeconomic outcomes: Cross-sectional information from the last completed questionnaire will be used to assess socioeconomic characteristics of ALL survivors compared to siblings including:

5.2.5.1. Household income in 2016 dollars (≤$19,999, $20,000 - $59,999, $60,000 - $99,999, ≥$100,000)
5.2.5.2. Education (Not high school graduate, high school graduate, college graduate)
5.2.5.3. Marital status (married/living with a partner/widowed, divorced/separated, never married)
5.2.5.4. Dependent living status (Independent vs Dependent ("live with parent" " live with brothers and/or sisters" "live with other relatives" or nursing or caregiver support under "other"))
5.2.5.5. Health insurance coverage (public health insurance, private health insurance, Canadian, uninsured)

5.3. Explanatory variables:

Sociodemographic and health behavior variables:

5.3.1. Age at cancer diagnosis
5.3.2. Age at follow-up
5.3.3. Sex
5.3.4. Race or ethnic group
5.3.5. Treatment era (1970-74, 1975-79, 1980-84, 1985-89, 1990-94, 1995-99)
5.3.6. Smoking status (never/past/current)
5.3.7. Heavy alcohol consumption (7+/week female, 14+/week male)
5.3.8. Education attainment (high school or less vs some college)
5.3.9. Insurance status
5.3.10. Marital status
5.3.11. Income

Treatment related variables:

1. Cranial irradiation (Y/N) and dose (none, >0 and <20 Gy, >20 Gy)
2. Craniospinal irradiation (CSI) (Y/N)
3. Testicular irradiation (Y/N)
4. TBI (Total body irradiation)
5. Cumulative anthracycline in doxorubicin equivalent dose (none, >0 and <120 mg/m^2, ≥120 mg/m^2 and <250 mg/m^2, ≥250 mg/m^2)
6. Cumulative alkylators in cyclophosphamide equivalent dose (none, >0 and <1000 mg/m^2, ≥1000 and <4000 mg/m^2, ≥4000 and <8000 mg/m^2, ≥8000 mg/m^2)
7. IV methotrexate (none, IV methotrexate not high-dose (>0 and <4.3 g/m^2), High-dose methotrexate (≥4.3 g/m^2))[19,30]
8. IT methotrexate (none, >0 and <230 mg/m^2, ≥230 mg/m^2)
9. Epipodophyllotoxins (Y/N)
10. Corticosteroid exposure (none, prednisone only, any dexamethasone)
11. Cytarabine (Y/N)

5.4. Statistical Analysis Framework:

5.4.1. Mortality: To assess our primary outcome of late-mortality (death ≥5-years after diagnosis) in survivors of ALL in the entire cohort overall and by treatment group, a descriptive analysis of the cohort overall and by treatment group will be performed. Additionally, we will perform the analysis by specific therapeutic exposures. To address our exploratory aim, the mediation analysis will be performed over treatment era, using the method used by Armstrong et al. and Turcotte et al. Since mortality data are available

for all CCSS eligible subjects (except Canadians) from NDI, we will use the eligible cohort (rather than participants only) for the mortality analysis using the methods consistent to the previous CCSS mortality publications (Armstrong et al.). Standardized mortality ratios (SMR) and absolute excess risk (AER) will be calculated for all cause and cause-specific (recurrence/progression or non-recurrence/non-external causes including health-related causes) mortality. We will utilize US population based age-, year- and sex-specific mortality rates to calculate expected number of deaths each year since diagnosis in order to compare the CCSS mortality with that expected in the US population. Multivariable piecewise-exponential regression will be used to assess the simultaneous impact of multiple factors on overall and cause-specific SMRs, adjusting for sex, age at diagnosis, attained age, and year at diagnosis. Finally, we will perform analyses conditioned on 10 year survival intervals for survivors overall and by treatment group to assess if any novel patterns emerge.

5.4.2. Chronic health conditions: We will evaluate the cumulative incidence of chronic conditions among survivors and siblings as any condition (grades 1 through 5), severe, life-threatening or fatal conditions (grade 3-5) and multiple conditions (≥2) overall and by treatment group. Additionally, analysis by specific therapeutic exposures will be performed. We will only include patients with available treatment data for those analyses that examine treatment group and treatment doses: this applies to all analyses except the mortality analysis above. In participants with more than one condition, the earliest development of a condition meeting the grade of interest will be used in analysis. For deceased survivors, the follow-up time is terminated at death and conditions before death will be used in analysis.[25] We will use multivariable piecewise-exponential regression to estimate rate ratios with 95% confidence intervals. Sibling and survivor comparisons will be adjusted for sex, race/ethnicity and attained age, accounting for potential intra-family correlation between survivors and siblings. Finally, we will perform analyses conditioned on 10 year intervals for survivors overall and by treatment group.

5.4.2.1. Neurocognitive outcomes: We will evaluate the age-specific prevalence of neurocognitive impairment, any, grade 2-3, and grade 3, in each of the four domains characterized by the CCSS-NCQ among survivors and siblings and among survivors by treatment group. Adjusted comparisons of age-specific prevalence of impairment between survivors and siblings and among survivors by cranial radiation exposure will be evaluated, using GEE-modified logistic regression, adjusting for sex, age at diagnosis and age at the NCQ assessment. Finally, we will perform analyses conditioned on 10 year intervals for survivors overall and by treatment group.

5.4.3. Subsequent Neoplasm: We will evaluate cumulative incidence of subsequent neoplasms (overall and categorized as above) estimated using time from the CCSS cohort entry and treating death as a competing risk event. Following the methodology from the recent CCSS analysis by Turcotte et al., standardized incidence ratios (SIRs) and AER per 1000 person-years for specific SMNs will be calculated using age-, sex-, and calendar-year–specific US cancer incidence rates from the SEER program to determine expected numbers of events. Multivariable piecewise-exponential models will be used to assess the incidence rate of subsequent neoplasm types, in association with treatment group, adjusting for attained age, sex, and other clinical/demographic variables: a separate analysis will adjust for 5-year treatment era in place of treatment exposures. Multiple subsequent neoplasm

occurrences within individual survivors will be included and accounted for in the models by modifications of the models using generalized estimating equations (GEE) as previously performed by Turcotte et al. Adjusted relative rates (RRs) and 95% confidence intervals will be estimated. Finally, we will perform analyses conditioned on 10 year intervals for survivors overall and by treatment group.

5.4.4. Overall health status: The prevalence of adverse outcomes in each health status domain will be estimated for survivors and siblings. Multivariable log-binomial models will be used to adjust for demographic variables, compare between survivors and siblings and, among survivors, assess associations with treatment group and then treatment exposures. Generalized estimating equations will be used to account for potential intra-family correlation between survivors and siblings. Finally, we will perform analyses conditioned on 10 year survival intervals for survivors overall and by treatment group.

5.4.5. Socioeconomic outcomes: Age-standardized rates by direct adjustment method of marriage, educational attainment, employment, health insurance coverage and income will be calculated. Multivariable log-binomial regression models will be used to assess associations with treatment group and then treatment exposures, adjusting for sex, race/ethnicity and attained age, after binalizing each outcome. Generalized estimating equations will be used to account for potential intra-family correlation between survivors and siblings. Finally, we will perform analyses conditioned on 10 year survival intervals for survivors overall and by treatment group.

5.4.6. Exploratory Aim: we will perform the mediation analysis over treatment era to address our exploratory aim, using the methods used by Armstrong et al. and Turcotte et al.

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Table 1. Demographic and Treatment Characteristics										
				Therapy Groupings						
	All ALL survivors, (N=) n (%)	Siblings (N=) n (%)	P	1970s-like	1980s SR-like	1980s HR-like	1990s SR-like	1990s HR-like	Relapse/ Transplant	p
Sex, n (%)										
Male										
Female										
Race/ethnicity, n (%)										
Non-Hispanic White										
Non-Hispanic Black										
Hispanic										
Other										
Unknown										
Age at diagnosis, n (%)										
0-4										
5-9										
10-14										
15-21										
Age at most recent follow-up, n (%)										
<20 yrs										
20-29 yrs										
30-39 yrs										
40-49 yrs										
≥50 yrs										
Year of diagnosis, n (%)										
1970-74										
1975-79										
1980-84										
1985-89										
1990-94										
1995-99										
Radiation exposure, n (%)										
Cranial radiation										
None										
>0 to ≤20 Gy										
>20 Gy										
Craniospinal radiation										
Yes										
No										
Testicular radiation										
Yes										
No										
TBI										

Yes										
No										
Chemotherapy, n (%)										
Anthracycline exposure (mg/m^2)*										
None										
>0 and <120										
≥120 and <250										
≥250										
Alkylator exposure (mg/m2)**										
None										
>0 and <1000										
≥1000 and <4000										
≥4000 and <8000										
≥8000										
IV Methotrexate dose (g/m^2)										
None										
>0 and <4.3										
≥4.3										
IT Methotrexate (mg/m^2)										
None										
<230										
≥230										
Corticosteroid										
None										
Prednisone only										
Any dexamethasone										
Epipodophyllotoxin exposure (Y/N)										
Yes										
No										
Cytarabine exposure (Y/N)										
Yes										
No										

TBI (Total body irradiation)
Cranial radiation, craniospinal radiation and testicular irradiation are all excluding body site scatter.
Weighting of ALL survivors due to differences in sampling in the expansion cohort were accounted for using:

* Anthracycline dose reported as doxorubicin equivalent dose where conversions are idarubicin x 5, daunorubicin x 0.833, mitaxantrone x 4 and epirubicin x 0.67.
**Alkylator dose reported as cyclophosphamide equivalent dose were conversions are ifosfamide x 0.244, procarbazine x 0.857, BCNU x 15, CCNU x 16, melphalan x 40, Thio-TEPA x 50, nitrogen mustard x 100 and Busulfan and 8.823.[31]

Table 2. Late mortality in survivors: overall and cause-specific rate (deaths per 1,000 person-years) and standardized mortality ratios (SMR) comparing ALL survivors and age-, sex- and race-matched US population.

	All cause				Recurrence/Progression				External Causes (accident/injury)				Non-recurrence/non-external			
	No. of deaths	Rate	SMR	95% CI	No. of deaths	Rate	SMR	95% CI	No. of deaths	Rate	SMR	95% CI	No. of deaths	Rate	SMR	95% CI
All survivors																
Sex																
Male																
Female																
Survival after diagnosis (yrs)																
5-9																
10-14																
15-19																
20-24																
25-29																
30-34																
35-39																
40-45																
≥45																
Treatment group																
1970s like																
1980s SR-like																
1980s HR-like																
1990s SR-like																
1990s HR-like																
Relapse/HSCT																

	SMN				Cardiac				Pulmonary				Other (nonrecurrence/nonexternal)			
	No. of deaths	Rate	SMR	95% CI	No. of deaths	Rate	SMR	95% CI	No. of deaths	Rate	SMR	95% CI	No. of deaths	Rate	SMR	95% CI
All survivors																
Sex																
Male																
Female																
Survival after diagnosis (yrs)																
5-9																
10-14																
15-19																
20-24																
25-29																

30-34																
35-39																
40-45																
≥45																
Treatment group																
1970s like																
1980s SR-like																
1980s HR-like																
1990s SR-like																
1990s HR-like																
Relapse/HSCT																

SMN: Subsequent malignant neoplasm

Table 3. Subsequent Neoplasms: observed, expected and SIR comparing ALL survivors and age-, sex- and race-matched US population.

	Subsequent malignant neoplasm						Nonmelanoma skin cancer		Meningioma	
	Number at risk	Cases/1000py observed	Cases/1000py Expected	SIR (95% CI)	AER/1000 py (95% CI)	Cumulative Incidence (%) (95% CI)	Cases/1000py observed	Cumulative Incidence (%) (95% CI)	Cases/1000py observed	Cumulative Incidence (%) (95% CI)
All survivors										
Sex										
Male										
Female										
Age at diagnosis										
0-4										
5-9										
10-14										
15-21										
Treatment group										
1970s like										
1980s SR-like										
1980s HR-like										
1990s SR-like										
1990s HR-like										
Relapse/HSCT										
Treatment era										
Every 5 years										
Radiation exposure, n (%)										
Cranial radiation										
None										
>0 to ≤20 Gy										
>20 Gy										
Craniospinal radiation										
Yes										
No										
Testicular radiation										
Yes										
No										
TBI										
Yes										
No										
Chemotherapy, n (%)										
Anthracycline exposure (mg/m^2)*										
None										

>0 and <120										
≥120 and <250										
≥250										
Alkylator exposure (mg/m2)**										
None										
>0 and <1000										
≥1000 and <4000										
≥4000 and <8000										
≥8000										
Epipodophyllotoxin exposure (Y/N)										
Yes										
No										

SIR: Standardized incidence ratio; AER: Absolute excess risk

Cumulative incidence will be explored at varying timepoints (15- and 30- year etc for the overall analysis and by treatment group)

* Anthracycline dose reported as doxorubicin equivalent dose where conversions are idarubicin x 5, daunorubicin x 0.833, mitoxantrone x 4 and epirubicin x 0.67.

**Alkylator dose reported as cyclophosphamide equivalent dose were conversions are ifosfamide x 0.244, procarbazine x 0.857, BCNU x 15, CCNU x 16, melphalan x 40, Thio-TEPA x 50, nitrogen mustard x 100 and Busulfan and 8.823.[31]

Table 4. Neurocognitive function of ALL survivors compared to siblings.

	Task Efficiency						Emotional Regulation					
	Mean (SD)	% any impairment	Rel Risk (95% CI)	% Grade1	% Grade2	% Grade3	Mean (SD)	% any impairment	Rel Risk (95% CI)	% Grade1	% Grade2	% Grade3
All survivors												
Siblings			1.0						1.0			
Sex												
Male												
Female												
Age at diagnosis												
0-4												
5-9												
10-14												
15-21												
Treatment group												
1970s like												
1980s SR-like												
1980s HR-like												
1990s SR-like												
1990s HR-like												
Relapse/HSCT												

	Organization						Memory					
	Mean (SD)	% any impairment	Rel Risk (95% CI)	% Grade1	% Grade2	% Grade3	Mean (SD)	% any impairment	Rel Risk (95% CI)	% Grade1	% Grade2	% Grade3
All survivors												
Siblings			1.0						1.0			
Sex												
Male												
Female												
Age at diagnosis												
0-4												
5-9												
10-14												
15-21												
Treatment group												
1970s like												
1980s SR-like												
1980s HR-like												
1990s SR-like												
1990s HR-like												
Relapse/HSCT												

Relative risk adjusted for age and sex, sibling as reference grou

Table 5. Relative Risk of Chronic Health Condition among ALL survivors, according to treatment and selected chronic conditions, as compared with siblings.

	Grade 1-5, n (%)	Relative Risk (95% CI)	Grade 3-5, n (%)	Relative Risk (95% CI)
Siblings		1.0		1.0
All survivors				
Sex				
Male				
Female				
Age at diagnosis				
0-4				
5-9				
10-14				
15-21				
Treatment group				
1970s like				
1980s SR-like				
1980s HR-like				
1990s SR-like				
1990s HR-like				
Condition				
Major joint replacement§				
Congestive heart failure				
Coronary artery disease				
Cerebrovascular accident				
Obesity				
Ovarian failure§§				
Male infertility§§				
Diabetes				
Neurocognitive impairment				
Treatment Groups				
Chemotherapy				
CNS radiation				
Relapse/HSCT				
Radiation exposure, n (%)				
Cranial radiation				
None				
>0 to ≤20 Gy				
>20 Gy				
Craniospinal radiation				
Yes				
No				
Testicular radiation				
Yes				
No				
TBI				
Yes				
No				
Chemotherapy				
Anthracycline exposure (mg/m^2)*				
None				
>0 and <120				
≥120 and <250				
≥250				
Alkylator exposure (mg/m2)**				
None				
>0 and <1000				
≥1000 and <4000				
≥4000 and <8000				

≥8000				
Corticosteroid exposure				
None				
Prednisone only				
Any dexamethasone				

§ For survivors, major joint replacement was not included if it was part of cancer therapy.

§§Values are for women only for ovarian failure and male only for male infertility

* Anthracycline dose reported as doxorubicin equivalent dose where conversions are idarubicin x 5, daunorubicin x 0.833, mitaxantrone x 4 and epirubicin x 0.67.

**Alkylator dose reported as cyclophosphamide equivalent dose were conversions are ifosfamide x 0.244, procarbazine x 0.857, BCNU x 15, CCNU x 16, melphalan x 40, Thio-TEPA x 50, nitrogen mustard x 100 and Busulfan and 8.823.[31]

Table 6.1. Prevalence ratios of adverse health outcomes in ALL survivors, compared to siblings.

	Poor General Health, PR (95% CI)	Poor Mental Health, PR (95% CI)	Functional Impairment, PR (95% CI)	Activity Limitations, PR (95% CI)	Adverse outcome in any domain, PR (95% CI)
Survivor Status					
Sibling					
Survivors					
Age at most recent follow-up					
<20 yrs					
20-29 yrs					
30-39 yrs					
40-49 yrs					
≥50 yrs					
Race/ethnicity					
Non-Hispanic White					
Non-Hispanic Black					
Hispanic					
Other					
Unknown					

Table 6.2. Prevalence ratios of adverse health outcomes among ALL survivors, according to treatment groups.

	Poor General Health, PR (95% CI)	Poor Mental Health, PR (95% CI)	Functional Impairment, PR (95% CI)	Activity Limitations, PR (95% CI)	Cancer-Related Pain, PR (95% CI)	Cancer-Related Anxiety, PR (95% CI)	Adverse outcome in any domain, PR (95% CI)
Sex							
Male							
Female							
Age at most recent follow-up							
<20 yrs							
20-29 yrs							
30-39 yrs							
40-49 yrs							
≥50 yrs							
Race/ethnicity							
Non-Hispanic White							
Non-Hispanic Black							
Hispanic							
Other							
Unknown							
Treatment group							
1970s like							
1980s SR-like							
1980s HR-like							
1990s SR-like							
1990s HR-like							
Relapse/HSCT							

Table 7. Prevalence and odds ratios for socioeconomic outcomes in siblings and ALL survivors, overall and according to treatment groups.

					ALL Survivors by Treatment Groupings (compared to siblings)											
	Siblings, n (%)	ALL survivors, n (%)	Odds Ratio (95% CI)	p-value	1970s-like OR ()	p-value	1980s SR-like OR (CI	p-value	1980s HR-like OR (CI)	p-value	1990s SR-like OR(CI)	p-value	1990s HR-like OR(CI	p-value	Relapse HSCT OR(CI)	p-value
Marital status, n (%)																
Never married																
Married																
No longer married																
Education, n (%)																
Not high school graduate																
High school graduate																
Any college or post-HS																
College graduate																
Employment, n (%)																
Unable to work																
Unemployed																
Employed/Student																
Health insurance, n (%)																
Public health insurance																
Private health insurance																
Uninsured																
Canadian																
Living independently																
Yes																
No																
Household income $*, n (%)																
<20,000																
20-59,999																
60-99,999																
≥100,000																

Odds Ratio adjusted for gender, age at response to questionnaire, race/ethnicity, year of diagnosis and age at diagnosis.

*Income in 2016 dollars