CONCEPT PROPOSAL

STUDY TITLE: Changes in Long-Term Outcomes in Neuroblastoma Survivors Treated with Contemporary Therapies: A Report from the Childhood Cancer Survivor Study

WORKING GROUP: This report will be written within the Chronic Disease, Second Malignancy, Cancer Control Working Groups. Proposed investigators include:

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BACKGROUND AND RATIONALE

Neuroblastoma, the most common extracranial solid tumor of childhood, is marked by its clinical heterogeneity.[1,2] While advances in multimodality therapy have resulted in 5-year survival rates exceeding 95% for those with low risk disease, long-term survival remains suboptimal (<50%) for those with high risk disease.[3] In recognition of this discrepancy, therapeutic efforts over the past four decades have focused on de-intensifying treatment for those with low/intermediate risk disease and intensifying treatment for those with high-risk disease, where risk is defined by a constellation of factors including clinical stage, age at diagnosis, histopathology and biologic features such as amplification of the MYCN proto-oncogene.[1]

Historical treatment of neuroblastoma: 1970-1999

Looking back to the 1960s, patients with neuroblastoma were treated with surgery with or without radiotherapy for local control.[4] The majority of patients, however, presented with unresectable or widely disseminated disease, which had a uniformly dismal prognosis.[4] Given the need for improved treatment options, individual and combined chemotherapeutic regimens were evaluated in the 1970s, including pulses of cyclophosphamide and vincristine; cyclophosphamide, vincristine, and doxorubicin;[5] and vincristine, doxorubicin, nitrogen mustard, and imidazole carboxamide (DTIC).[6] Limited efficacy, however, was noted in high-risk patients older than 12 months of age with metastatic disease.

During the 1980s, it became clear that localized, low-risk neuroblastoma was treatable with surgery alone and therapy was accordingly de-intensified.[7,8] At the same time, systemic therapy for high-risk neuroblastoma became more aggressive, incorporating more aggressive chemotherapy and myeloablative therapy followed by autologous or allogeneic transplantation.[9-12] Monoclonal antibody-based immunotherapy that targeted the surface ganglioside GD2, which is highly expressed on neuroblastoma cells, with or without GM-CSF, was introduced during this decade as well.[13-15] These therapeutic modifications resulted in improved outcomes for those with low and intermediate-risk disease, however, survival rates for patients with stage 4 neuroblastoma remained less than 20% through the late 1980s.[16]

In the 1990s, treatment was increasingly tailored to tumor biology and risk stratification. Data emerged that patients with low and intermediate risk disease (non-stage 4 disease without evidence of MYCN amplification and stage 4 infants without MYCN amplification) could be cured without cytotoxic therapy.[17,18] Conversely, for those age > 12 months with metastatic disease, it became clear that further therapeutic intensification was required. Accordingly, a randomized trial of high-risk neuroblastoma patients conducted between January 1991 and April 1996 demonstrated that event-free survival was significantly improved in patients treated with myeloablative chemotherapy, total body irradiation, and autologous bone marrow transplantation, when compared to those treated with chemotherapy alone.[19] A second randomization showed that treatment with 13-cis-retinoic acid (isotretinoin) after transplantation or chemotherapy further improved outcomes.[19] Pilot studies, performed in the setting of relapsed disease, also demonstrated the safety of administering the chimeric human/murine anti-GD2 monoclonal antibody (ch14.18) in combination with either GM-CSF or interleukin-2.[20,21] **Supplementary Table 1** highlights some of the key neuroblastoma trials conducted in North America between 1970-1999.

While the cooperative groups have each reported short-term overall and event free survival, it is unclear how these treatment changes will impact all-cause and cause-specific mortality over time. In the recent landmark study by Armstrong et al on changing trends in late mortality among childhood cancer survivors enrolled in CCSS, neuroblastoma survivors were one of the only diagnostic sub-groups found to have an increase in late mortality among individuals treated in more recent decades.[22] Yet granular data are lacking on how therapeutic shifts over time have impacted neuroblastoma survivors' risk for specific causes of late mortality and other long-term chronic medical conditions. Additionally, we do not have a clear understanding of the risk of the late effects associated with the novel combination of cis-retinoic acid, immunotherapy, MIBG or tandem transplant, either alone or in combination. The current proposal seeks to address some of these gaps by: (1) analyzing changes in late mortality, chronic condition risk, rate of subsequent neoplasms, and health status in CCSS low/intermediate risk neuroblastoma survivors diagnosed between 1970 and 1999; (2) analyzing changes in late mortality, chronic condition risk, rate of subsequent neoplasms, and health status in CCSS neuroblastoma survivors in the expansion cohort who were treated in the early biologic era.

Late effects in survivors of neuroblastoma

Medical conditions

The largest report of long-term morbidity and mortality in neuroblastoma survivors emerges from Laverdiere *et al*.'s CCSS study of 954 5-year neuroblastoma survivors, diagnosed between 1970 and 1986, and 3899 siblings.[23] Survivors had an increased rate of mortality and second malignancies, when compared to age- and sex-matched US population controls, and an eight-fold increased risk of chronic health conditions, when compared to CCSS siblings.[23] The most prevalent chronic medical conditions involved the neurological, sensory, endocrine, and musculoskeletal systems. Survivors treated with multimodality therapy were 2.2-fold more likely to develop a chronic health condition, when compared to survivors treated with surgery alone. Given the dates of diagnosis of the original cohort, it is likely that the majority of these 5-year survivors of neuroblastoma had low- or intermediate-risk disease.

Several subsequent late effect analyses, focusing on high-risk neuroblastoma survivors, have reported a high prevalence of long-term medical problems.[23-29] One single institution study of 63 advanced stage neuroblastoma survivors, the majority of whom were treated with multimodality therapy between 1970 and 2001, detected late complications in 95% of survivors.[25] Most of these complications, however, were mild-moderate in severity and included hearing loss (62%), primary hypothyroidism (24%), and ovarian failure (41%

of females). Others have highlighted the increased prevalence of endocrinopathies,[24,30-32] metabolic dysfunction,[33,34] and subsequent malignancies[35,36] among survivors of high-risk neuroblastoma. There are limited data,[35,37] however, on long-term outcomes among larger cohorts of high-risk neuroblastoma survivors. **Supplementary Table 1** highlights the changes in key therapeutic exposures between survivors diagnosed from 1970-1986 (original cohort) and those diagnosed between 1987-1999 (expansion cohort). The expansion cohort should include a sizable number of high-risk survivors treated with intensive multimodality therapy, which can be inferred based on their therapeutic exposures to key agents, such as cis-retinoic acid (n=98), autologous stem cell transplant, and total body irradiation (n=74).

Health status

Prior analyses have demonstrated that long-terms neuroblastoma survivors may be at increased risk for adverse health status and inferior psychosocial outcomes. Existing studies on long-term health status health-related quality of life (HRQL) in this cohort have produced conflicting results.[38-42] One prior CCSS report found that adult neuroblastoma survivors did not differ from population norms on most HRQL measures; however, they did score significantly below the population mean score on the Mental Component Summary of the SF-36 (population mean=50; neuroblastoma mean=42.4; p< 0.0001), thus reflecting decreased emotional health.[42] In a separate CCSS report by Laverdiere and colleagues, neuroblastoma survivors were less likely to have ever been employed; had lower individual and household incomes; and were less likely to have ever married, when compared to siblings, thus suggesting decreased social integration.[23] It is unclear whether more contemporarily treated neuroblastoma survivors experience similar HRQL outcomes. A recent report by Ness and colleagues on self-reported health status of all adult survivors of childhood cancer enrolled in CCSS found no improvement in health status among those treated in more recent decades;[43] it is unclear whether the same will hold true among survivors of neuroblastoma.

Expected outcomes

Given the marked shifts in treatment approaches for neuroblastoma between 1970 and 1999, it is reasonable to expect that late effect profiles will accordingly change over time in this cohort. While data exist on temporal trends in late mortality,[22] subsequent malignant neoplasm (SMN) risk,[44] and health status[43] in the overall cohort of childhood cancer survivors enrolled in CCSS, the changing risk of these parameters effects in subgroups of survivors in whom treatment has evolved remains understudied. The current proposal seeks to assess late mortality, chronic condition risk, subsequent neoplasm risk, and health status in low or intermediate risk neuroblastoma survivors treated between 1970 and 1999, in relation to temporal trends and the introduction of risk-adapted therapy.

In this proposal, we will treat the era of the original cohort (1970-1986) as the time period which preceded risk-stratification; while we do not have definitive data on disease stage in the original cohort, we will assume that any survivor diagnosed at age < 1 year and treated in this era had low or intermediate risk disease.[45] We will compare mortality outcomes, chronic condition risk, second malignant neoplasm risk, and health status among patients diagnosed with neuroblastoma between 1970-1986 (pre-biologic era) to those diagnosed between 1987-1999 (the era of “early risk stratification”) by era of treatment. Since age at diagnosis and details of disease stage are available for participants enrolled in the expansion cohort, we will perform a separate analysis analyzing outcomes in this cohort among patients diagnosed with neuroblastoma at age ≥ 1 year between 1987-1999 with low/intermediate risk (stage 1/2) vs high-risk (stage 4) disease. Given the complexities involved in definitions of stage 3 disease, we have decided to include these patients as a separate risk group in the analysis.

Thus, Analysis I will analyze long-term outcomes of babies with neuroblastoma (diagnosed 1970-1999 at <1 year of age) which will ensure that the same assumptions are made across all subjects, despite the lack of definitive stage data in the original cohort. Analysis II will be restricted to individuals diagnosed with neuroblastoma at age ≥1 year between 1987-1999 and will include separate analyses for patients with stage 1/2 and stage 4 disease (ignoring patients with stage 3 disease since they could theoretically be in either risk group). The details of the analyses are outlined below:

Note: Tara Henderson and Lisa Diller are leading a large effort through COG to assess late effects in high-risk neuroblastoma survivors treated after 2000. The current proposal will provide important foundational data for that analysis. Both Drs. Diller and Henderson are key investigators on the current proposal.

ANALYSIS I: Given the lack of information on NMYC status, metastatic disease, or disease stage in the original cohort, we have confined the first analysis to individuals diagnosed with neuroblastoma at age < 1 year in the original or expansion cohorts (**n=947**). We assume that all patients in this cohort had low or intermediate risk disease. For comparisons of chronic health conditions and health status, we will also evaluate siblings in the overall cohort.

Aim 1. Determine all-cause and cause-specific cumulative incidence mortality, standardized mortality ratios (SMRs) and excess absolute risk (EARs) for 5-year survivors of neuroblastoma diagnosed at age < 1 year between 1970 and 1999. We will assume that all patients in the original cohort diagnosed at age < 1 year (1970-1986, n=525) had low or intermediate risk disease at diagnosis.

Hypothesis: We expect decreased mortality rates, SMRs and EARs among patients with low/intermediate risk neuroblastoma diagnosed in more recent eras (1990s vs 1980s vs 1970s). We hypothesize that decreased mortality will reflect de-intensification of treatment in the more contemporary era in individuals with low/intermediate risk disease.

Aim 2: Estimate the cumulative incidence of chronic health conditions (any condition, grade 3-5 conditions, multiple grade 3-5 conditions) among 5-year survivors of neuroblastoma diagnosed at age < 1 year between 1970 and 1999 overall and by treatment era (10 year and 5 year intervals), as well as within a sibling cohort. We will assume that all patients diagnosed at age < 1 year had low or intermediate risk disease at diagnosis. The specific primary chronic conditions of interest include**:** sensory issues (primarily hearing loss); cardiopulmonary outcomes; and endocrinopathies (growth, hypothyroidism, gonadal dysfunction, diabetes mellitus).

Hypothesis: While elevated compared to a sibling comparison group, we expect to find a decreased incidence of: sensory complications (after high-dose platinum therapy); endocrinopathies (high-dose alkylating agents), cardiometabolic disease (anthracyclines + abdominal/chest radiation at a young age), pulmonary complications (chest radiation), and gonadal dysfunction (high-dose alkylating agents) in those treated with low/intermediate disease with less intensive therapies in the more recent era when compared to the earlier eras (1990s vs 1980s vs 1970s). As described in the background, beginning in the 1980s, therapy was increasingly de-intensified for patients with low or intermediate disease; given these reductions in therapy, we expect to accordingly find a lower burden of chronic conditions in low/intermediate risk neuroblastoma survivors treated in the more recent era. **Supplementary Table 2** outlines changes in treatment in the overall cohort of neuroblastoma survivors enrolled in CCSS.

Aim 3. Assess the cumulative incidence, standardized incidence ratios (SIRs) and EARs of subsequent neoplasms in patients diagnosed with neuroblastoma at < 1 year of age between 1970 and 1999 overall and by treatment era (10 year and 5 year intervals).

Aim 3a. Describe the most prevalent subsequent neoplasms in this cohort in the original versus expansion cohorts.

Aim 3b. Determine risk factors associated with the development of the subsequent neoplasms delineated in Aim 3a in the cohort of neuroblastoma survivors diagnosed at age < 1 between 1970 and 1999.

Hypothesis: Since risk of subsequent neoplasms should be related to specific therapeutic exposures, we expect that low/intermediate patients treated in the more recent era (1990-1999) will have fewer subsequent malignant neoplasms, relative to those treated between 1970-1979 or 1980-1999. Specifically, we expect that a decrease in the use of radiation therapy in the more recent era will result in fewer second malignant neoplasms in this cohort in the more recent era.

Aim 4. Evaluate proportions of self-reported adverse health status outcomes among adult neuroblastoma survivors (attained age ≥ 18 years) diagnosed at age < 1 year between 1970 and 1999, as well as within a sibling cohort.

Hypothesis: We expect health status to improve in this cohort as therapy is de-intensified in more recent decades.

ANALYSIS II Changes in therapy and long-term outcomes for patients ≥ 1 year of age at diagnosis:
Given the lack of information on NMYC status, metastatic disease, or disease stage in the original cohort, we are unable to make definitive assumptions about risk status. We will limit our second analysis to survivors in the expansion cohort who were diagnosed between 1987-1999 at age ≥ 1 year (**n=512**). We will use abstracted data on age at diagnosis and disease stage to compare mortality, chronic condition, SMN, and health status outcomes within stratum of patients with stage 1/2 (**n=137**) versus stage 3 (**n=78**) versus stage 4 (**n=145**) disease in this cohort. An additional **104** patients do not have staging data available or use another staging system; to the extent possible with available data, we will infer stage data for these patients based on the protocols with which they were treated and include those for whom we have confidence in that classification.

Aim 1. Determine cumulative incidence, SMRs and EARs for all-cause and cause-specific mortality for 5-year survivors of neuroblastoma diagnosed at age ≥ 1 year between 1987 and 1999 and compare outcomes among those diagnosed 1987-1993 versus 1994-1999, within disease risk stratum with a focus on stage 1 / 2 (n=137) and stage 4 (n=145). The era of 1987-1993 reflects pre/testing of cis-retinoic acid prior to the testing of tandem transplant; by 1994-1999, the efficacy of cis-retinoic acid is established and tandem transplant was being tested for stage 4 disease.

Hypothesis: With the introduction of risk-adapted therapy, we expect to find decreased mortality rates among patients ≥ 1 year of age at diagnosis with stage 1/2 disease diagnosed in 1994-1999, versus 1987-1993. This decreased mortality will reflect de-intensification of treatment in the more contemporary era in individuals with low/intermediate risk disease. Conversely, we hypothesize that treatment-related mortality rates will increase across eras in patients with stage 4 disease diagnosed at ≥1 year of age in due to intensification of therapy over time.

Aim 2: Estimate the incidence of chronic health conditions (any condition, grade 3-5 conditions, multiple grade 3-5 conditions) among 5-year survivors of neuroblastoma diagnosed at age ≥ 1 year between 1987 and 1999 with stage 1/2 versus stage 3 versus stage 4 disease; compare outcomes among those diagnosed 1987-1993 versus 1994-1999 within stratum defined by risk status. Compare each stratum by era of treatment to siblings. The primary chronic conditions of interest include**:** sensory issues (primarily hearing loss); cardiopulmonary outcomes; and endocrinopathies (growth, hypothyroidism, gonadal dysfunction, diabetes mellitus).

Hypothesis: Given the introduction of risk-adapted therapy in the 1990's, we expect we expect to find a decreased burden of chronic conditions in patients with stage I-II disease in 1994-1999, relative to those diagnosed in 1987-1993. In contrast, we expect to find an increased prevalence of: sensory complications (after high-dose platinum therapy); endocrinopathies (TBI, high-dose alkylating agents), cardiometabolic disease (anthracyclines + abdominal/chest radiation at a young age), pulmonary complications (chest radiation), and gonadal dysfunction (high-dose alkylating agents, TBI) in patients with stage 4 disease diagnosed at ≥1 year of age treated in the most recent era (1994-1999) versus those treated between 1987-1993.

Aim 3. Assess the cumulative incidence, SIRs and EARs for subsequent neoplasms in CCSS survivors diagnosed with neuroblastoma at age ≥ 1 year between 1987 and 1999, and within the sibling comparison group.

Aim 3a. Describe the most prevalent subsequent neoplasms in this cohort of neuroblastoma survivors.

Aim 3b. Determine risk factors associated with the development of the subsequent neoplasms delineated in Aim 3a in the cohort of neuroblastoma survivors diagnosed at age ≥ 1 year within risk level (stage 1/2 vs. 4) between 1987 and 1999.

Hypothesis: Since risk of subsequent neoplasms should be related to specific therapeutic exposures, we expect that stage 1 and 2 patients treated in the most recent era (1994-1999) will have fewer subsequent malignant neoplasms, relative to those treated between 1987-1993. We expect that the risk of subsequent neoplasms in patients with stage 4 disease will remain unchanged during this time.

Aim 4. Evaluate proportions of self-reported adverse health status outcomes among adult neuroblastoma survivors (attained age ≥ 18 years) diagnosed at age ≥ 1 year within risk groups, between 1987 and 1999. Compare these proportions to the sibling comparison group.

Hypothesis: When comparing health status for those diagnosed from 1987-1993 versus 1994-1999, we expect health status to improve among patients with stage 1 or 2 disease and remain unchanged in those with stage 4 disease.

Analytic Framework:

1. Population of interest:

Aim 1 (mortality analysis).

a) Analysis I, Aim 1: We will include all neuroblastoma survivors diagnosed at age < 1 year who are eligible for participation in the CCSS overall cohort (diagnosed between 1970 and 1999).[46]
b) Analysis II, Aim 1: We will include all neuroblastoma survivors diagnosed at age ≥ 1 year who are eligible for participation in the CCSS expansion cohort (diagnosed between 1987 and 1999).

Aims 2 and 3 (chronic condition, subsequent neoplasms).

a) Analysis I, Aim 2 and 3: We will include all neuroblastoma survivors diagnosed at age < 1 year who are enrolled in the CCSS overall cohort (diagnosed between 1970 and 1999),[46] as well as siblings in the overall cohort.
b) Analysis II, Aims 2 and 3: We will include neuroblastoma survivors diagnosed at age ≥ 1 year who are stage 1/2, stage 3, or stage 4 enrolled in the CCSS expansion cohort (diagnosed between 1987 and 1999) for the chronic condition and subsequent neoplasm analyses, as well as siblings from the same time period.

Aim 4 (health status). In accord with prior analyses,[43,47] we will limit our population to neuroblastoma survivors ≥ 18 years of age at the time of any questionnaire completion; because health status was completed by a proxy for those < 18 years of age at the time of questionnaire completion, these data will not be included in the health status analysis. Patients must be living at the time of the survey to be included.

a) Analysis I includes those diagnosed with neuroblastoma at age < 1 year with attained age ≥ 18 years in the overall cohort, as well as siblings from the overall cohort.
b) Analysis II includes those diagnosed at age ≥ 1 year with stage 1/2, stage 3, or stage 4 neuroblastoma with attained age ≥ 18 years in the CCSS expansion cohort, as well as siblings from the same time period.

For all time-to-event analyses, follow-up will start at 5 years from original cancer diagnosis and end on the date of death or date of last completed questionnaire. Health status, which is cross-sectional, will be examined at each questionnaire on which the subject was alive and over the age of 18.

2. Outcome measures:

a. Mortality:

For Analysis I and II, we will use vital status to identify: (a) cumulative incidence of mortality, and (2) standardized mortality ratios (SMR) and excess absolute risk (EAR). The National Death Index will be the source for vital status. Mortality will be calculated from 5 years after diagnosis until either date of death or December 31, 2013.[22] For deaths that predate the NDI (1975–1978), death certificates from states where the deaths had occurred will be requested.

We will calculate standardized mortality ratios to compare the rate of death in neuroblastoma survivors enrolled in the CCSS cohort as compared to age-, sex-, and calendar year specific mortality rates in the U.S. population, using data from the National Center for Health Statistics. Information on the underlying cause of death will be obtained from death certificates for cases that resided in the United States. In accord with prior CCSS analyses,[22,48] cause of death will be categorized into three mutually exclusive categories based on International Classification of Diseases, Ninth Revision (ICD-9) coding and International Classification of Diseases, Tenth Revision (ICD-10) coding:

1. Recurrence/progression of primary childhood malignancy
2. External causes (e.g. accidents, injuries, suicide)
3. Non-recurrence/non-external cause (attributable to chronic health conditions): subsequent neoplasm, cardiac, pulmonary, infections, other

b. Chronic conditions:

For Analysis I and II, the standard approach of identifying chronic conditions and scoring the severity of each condition using Common Terminology Criteria for Adverse Events (CTCAE) criteria will be used in the current analysis, in accord with prior CCSS analyses.[49] Chronic conditions will be graded as: grade 1 (mild); grade 2 (moderate), grade 3 (severe), grade 4 (life-threatening or disabling), and grade 5 (fatal). In addition to severity, chronic conditions will be categorized into one of four groupings:

1. No chronic condition
2. Any chronic condition (grade 1-5)
3. At least one grade 3-5 condition
4. Multiple grade 3-5 conditions

We are specifically interested in the following chronic conditions: sensory complications; endocrinopathies (thyroid dysfunction, growth, diabetes mellitus, gonadal dysfunction), cardiometabolic disease, and pulmonary complications. Chronic conditions of all grades with be compared by treatment era for Analyses I and II, and within disease-risk stratum for Analysis II, and will be compared to those reported by the sibling cohort (overall sibling cohort for Analysis I or siblings of survivors diagnosed between 1987-1999 for Analysis II). We will use chronic condition data collected through FU5.

c*. Subsequent neoplasms:*

For both Analysis I and II, the standard approach for identifying subsequent neoplasms via self- or next-of kin proxy report or death certificate and confirming by pathology report or, when unavailable, death certificate, medical records, or both, will be used for this analysis. Only subsequent malignant neoplasms occurring 5 years or more after initial cancer diagnosis will be included; this analysis will thus not account for the vast majority of treatment-related secondary leukemias, which have been reported among neuroblastoma patients treated with intensive multimodality therapy.[35,36,50]

Subsequent neoplasm will be classified into three mutually exclusive groups:

1. Subsequent malignant neoplasms, which include invasive neoplasms classified as International Classification of Diseases for Oncology (*ICD-O*) behavior code of 3, excluding nonmelanoma skin cancer;
2. Benign meningiomas;

3. Nonmelanoma skin cancers

Standardized incidence ratios (SIRs, or the ratio of the observed to expected number of events) and excess absolute risk (EAR) per 1000 person-years will be calculated using age-, sex-, and calendar-year–specific US cancer incidence rates from the Surveillance, Epidemiology, and End Results program to determine expected numbers of events. Following the methodology from the analysis by Turcotte and colleagues (JAMA 2017), SIRs for specific SMNs will be calculated by stratifying on 10-year age intervals in orders to avoid confounding of calendar effects by attained age.

d*. Health status*

In accord with the recent publication by Ness and colleagues,[43] adverse health status will be determined using established definitions in the following domains:

1. General health (survivors and siblings): (Baseline N15; Expansion O21)
2. Mental health (survivors and siblings): (Baseline J16-35; Expansion K1-K18)
3. Functional impairment (survivors and siblings): (Baseline N14.b, N14.c, N14.e; Expansion O20.b, O20.c, O20.e)
4. Activity limitations (survivors and siblings): (Baseline N10-N12; Expansion O16-18)
5. Pain related to cancer treatment (survivors only): (Baseline J36; Expansion K20)
6. Fears or anxiety related to cancer treatment (survivors only): (Baseline J37; Expansion K20)

For Analysis I, reports of adverse health status will be compared between survivors and siblings in the overall cohort by treatment era (1970-1979; 1980-1989; 1990-1999).

For Analysis II, reports of adverse health status will be compared between survivors by treatment era (1987-1993 versus 1994-1999) and within disease stage (1/2 versus 4) stratum, and compared to siblings with their related cancer survivor diagnosed between1987-1999. Associations between era of treatment and adverse health status outcomes will be explored in both analyses.

3. Explanatory variables:

General variables:

1. Sex (Baseline A2, Baseline – expanded A2)
2. Race or ethnic group (Baseline A4, A4.a, Baseline – expanded A5, A5.a)
3. Treatment era (1970–1979; 1980–1989; 1990–1999)
4. Age at primary cancer diagnosis (years)
5. Attained age at most recent assessment (DOB – assessment)
6. Survival after diagnosis (years)
7. Education attainment (high school or less vs some college): (Baseline O1-O4; Expansion R1-R4)
8. Insurance status (Baseline Q2, Q3, Q3.a, Q3.b; FU 2000 16; FU 2003 M1; FU 2007 B9; Expansion U2, U3, U3.a, U3.b)
9. Smoking status [never/past/current]: (Baseline N1.a, N1.b, N1.c, N1.d; Expansion O1-O3)
10. Heavy alcohol consumption [7+/week female, 14+ week/male] (Baseline)
11. Physical activity
12. Body mass index
13. Recurrence prior to five-years post diagnosis
14. Vital status

Treatment variables:

We will also include data about specific radiation fields and all administered chemotherapeutic agents in those so exposed. However, we anticipate that key therapeutic exposures will include:

- Abdominal radiation (yes/no; maximum tumor dose [maxTD])
- Chest radiation (yes/no; max TD)
- Total body irradiation (yes/no; dose)

- Cranial radiation (yes/no; max TD)
- Doxorubicin equivalent dose (yes/no; cumulative dose)
- Cyclophosphamide equivalent dose (CED cumulative dose)
- Epipodophyllotoxin (yes/no; cumulative dose)
- Platinum agents (yes/no; cumulative dose)
- Cis-Retinoic acid (yes/no)
- Surgery (thoracotomy; nephrectomy)
- Transplant (yes/no); expansion cohort only

4. Statistical analysis

a. Mortality:

Analysis I:
Among low/intermediate risk patients diagnosed at age < 1 year in the overall cohort, mortality will be assessed by decade (1970-1979 vs 1980-1989 vs 1990-1999). Overall survival probabilities will be calculated using Kaplan-Meier estimates and will be presented separately by treatment era from time of diagnosis, with censoring at ~15 years to allow for comparability across eras. A nonparametric estimate of the cumulative incidence function will be used to estimate cause-specific mortality by treatment era and by binary risk grouping accounting for the competing risk of death from other causes.

Analysis II:
In order to assess mortality among survivors diagnosed at age ≥ 1 year in the expansion cohort by treatment era (1987-1993 versus 1994-1999) and by risk grouping (stage 1/2 versus stage 4), a descriptive analysis of the entire cohort based on age at diagnosis, disease stage, and treatment era will be performed. Overall survival probabilities will be calculated using Kaplan-Meier estimates and will be presented separately by treatment era and by risk groupings. A nonparametric estimate of the cumulative incidence function will be used to estimate cause-specific mortality by treatment era and by binary risk grouping accounting for the competing risk of death from other causes.

For both analyses, within their respective analytic populations, standardized mortality ratios (SMR) and excess absolute risk (EAR) by treatment era will be calculated for all-cause and cause-specific mortality. To compare mortality of CCSS neuroblastoma survivors with that expected in the US population, an expected number of deaths per year since diagnosis will be calculated based on US population age-, year- and sex-specific mortality rates. Multivariable Poisson regression will be used to assess the impact of calendar era on the overall and cause-specific SMRs, potentially adjusting for sex, age at diagnosis, current age and/or years since diagnosis and, for Analysis II, examine era effects within stratum defined by stage of disease via interaction terms.

In accord with the recent CCSS analysis by Armstrong et al, we will use multivariable piecewise exponential models in both analyses to assess relative rates, with 95% confidence intervals, of death from health-related causes in specific treatment eras, as compared with a reference treatment era (1970-1979 in Analysis I; 1987-1993 in Analysis II), after adjustment for sex, age at diagnosis, and attained age. This methodology will allow for the evaluation of changes in mortality by comparing treatment-era effects with and without adjustment for the treatment variables in the model, after adjustment for sex, age at diagnosis, and attained age to evaluate whether any observed changes in mortality over era are explained by adjustment for treatment factors. For Analysis II, models will be examined within disease stage stratum.

b. Chronic health conditions:

Cox proportional hazards models will be used to compare any grade (1-5), grade 3-5, and multiple grade 3-5 chronic conditions across decade of treatment (1970s vs 1980s vs 1990s) for Analysis I, and for treatment era (1987-1993 vs 1994-1999) within binary risk stratum (stage 1/2 vs stage 4) for Analysis II. Age will be used as the time scale. Models will be adjusted for age at diagnosis (Analysis II), sex and race or ethnic group.

The cumulative incidence of any grade (1-5), grade 3-5, and multiple grade 3-5 chronic conditions will be estimated nonparametrically treating death as a competing risk event. For each outcome, the cumulative incidence will be computed based on time to the earliest reported occurrence of the event of interest and treating deaths not relevant to the outcome of interest as competing risk events. Curves will be presented overall and split by the key variables and stratification factors for Analysis I and II. Cumulative incidence plots will be stratified by era of cancer diagnosis, and compared to siblings of survivors. Using Cox regression, hazard ratios will be estimated and reported as relative risks with 95% confidence intervals. Comparisons between survivors and siblings will use age as the time scale and will be adjusted for sex and race or ethnic group. Like the mortality analysis, we will also assess changes in chronic conditions by comparing treatment-era effects with and without adjustment for the key treatment variables in the model, after adjustment for sex and attained age to evaluate whether any observed changes in chronic condition risk over era are explained by adjustment for treatment factors. For Analysis II, models will be examined within disease stage stratum.

Additionally, we will create layered curves demonstrating the cumulative incidence of any grade 3-5 chronic condition as well as the cumulative incidence of any grade 5 condition in the survivor cohort, illustrating the proportion of subjects with maximum grades 3-4 as the area between the curves.

c. Subsequent neoplasms:

Cumulative incidence of second neoplasms will be estimated using time as the time scale from 5 years after initial diagnosis, treating death as a competing event. For subsequent malignant neoplasms, standardized incidence ratios (SIRs) and excess absolute risk (EAR) per 1000 person years will be calculated using age-, sex- and calendar year specific US cancer incidence rates.

For the current analysis exploring changing trends in rates of subsequent neoplasms among neuroblastoma survivors, we will follow the approach used by Lucie Turcotte and colleagues in their recent JAMA publication.[44] We will use multivariable piecewise-exponential models to assess the incidence rate of subsequent neoplasm types, in association with demographic variables, adjusting for attained age, and treatment era (1970s vs 1980s vs 1990s in Analysis I; 1987-1993 vs 1994-1999 in Analysis II). Additional models will be fit with treatment variables added to evaluate whether treatment changes mediate changes in subsequent neoplasms over time. Multiple subsequent neoplasm occurrences within individual survivors will be included and accounted for in the models using generalized estimating equations. Adjusted relative rates (RRs) and 95% confidence intervals will be estimated.

d. Health status

Reports of each adverse health status outcome will be compared between siblings and survivors using generalized linear regression models adjusted for sex, race/ethnicity, and attained age. In accord with the analysis performed by Ness and colleagues,[43] three models among survivors will be explored:

1. Association between era of treatment and adverse health status [Analysis I and II]
2. Association between era of treatment and adverse health status, stratified by risk grouping (era-risk group) [Analysis II]
3. Association between era of treatment and adverse health status, adjusted for grade 3 or 4 chronic condition (decade-chronic condition) [Analysis I and II]

Models will be adjusted for demographic characteristics, second malignant neoplasms (as a surrogate for additional treatment) and health habit variables (smoking, heavy drinking, body mass index) with p-values < 0.1 in univariate analysis. Intra-family correlation will be accounted for in these generalized estimating equations with robust variance estimates.

For each of the outcomes outlined above, we will use mediation analysis methods,[51] used in the Turcotte analysis,[44] to estimate changes in rates of each outcome of interest (mortality, subsequent neoplasms, chronic conditions, health status) across treatment eras with and without adjustment for treatment variables in the same model. This will allow us to assess whether treatment modifications mediate changes in subsequent neoplasm rates over time. Nonparametric bootstrap will be used to test statistical significance of the changes in the regression coefficient associated with the relevant treatment era variable with and without adjustment for treatment variables. For Analysis II, these models will be stratified by risk level.

SUPPLEMENTARY DATA TABLES

Supplementary Table 1. Key neuroblastoma regimens utilized in North America between 1970-1999

Regimen	***Induction Cumulative Chemotherapy Exposures***	***Consolidation***	***Radiation***	***Study question/ comments***	***Years of study***
Hospital for Sick Children; Stage III-IV (n=77)	Vincristine Cyclophosphamide +/- Adriamycin		RT to bulk and/or residual disease (400-4000 cGy)	CV vs CAV	1970-1977
POG 8743/Int risk (n=172)	Cyclophosphamide Doxorubicin Cisplatin Teniposide			Can neuroblast ploidy be used to guide treatment in infants with unresectable or metastatic tumors?	1987-1991
CCG-3881/Infant (n=116)	Cisplatin 519 mg/m^2 Cyclophosphamide 8100 mg/m^2 Doxorubicin 170 mg/m^2 Etoposide 2495 mg/m^2		Local radiation to residual disease		1989-1995
POG 9340/1/2/ High risk (n=84)	Cisplatin 400 mg/m^2 Etoposide 1050 mg/m^2 Cyclophosphamide 2 g/m^2 Doxorubicin 60 mg/m^2 Vincristine 4.5 mg/m^2 Ifosfamide 10 g/m^2 Carboplatin 1000 mg/m^2	Single (CEC*)	24 Gy to primary tumor volume with 2 cm margin	Use of induction with carboplatin and ifosfamide	1993-1995
CCG 3891/High risk (n=539)	Cisplatin 300 mg/m^2 Etoposide 1000 mg/m^2 Doxorubicin 150 mg/m^2 Cyclophosphamide 10 g/m^2 2nd random assignment: +/- cis-RA	Single (CEM/TBI) vs chemotherapy; 2nd random assignment: +/- cis-RA	10 Gy to local sites of gross residual disease (+10 Gy from TBI dose for ABMT group)	High-dose therapy vs continuing chemotherapy; Inferior non-transplant consolidation may have been used in some surviving patients (ifos/dox/etoposide/cisplatin)	1991-1996
COG A3961/Int risk, MYCN neg (n=479)	Carboplatin (1680 mg/m^2 vs 2800 mg/m^2) Etoposide (1080 mg/m^2 vs 1800 mg/m^2) Cyclophosphamide (2000 mg/m^2 vs 5000 mg/m^2)			Reduced chemotherapy for int risk patients	1997-2005

	Doxorubicin (60 mg/m^2 vs 120 mg/m^2)				
POG-9243/Int risk non-NMYC (n=479)	Cyclophosphamide 7350 mg/m^2 (Arm A) vs 1050 mg/m^2 (Arm B) Ifosfamide (4800 - Arm B) Doxorubicin (245 mg/m^2 Arm A; 35 mg/m^2 Arm B) Etoposide (400 mg/m^2 Arm A vs 3360 mg/m^2 Arm B) Cisplatin (180 mg/m^2 Arm A) Carboplatin (3360 mg/m^2 Arm B)			Can biologically based treatment assignment lead to reduction in chemotherapy duration and doses?	1992-1996
COG P9641/ Low risk (n=915)	Carboplatin 2800 mg/m^2 Etoposide 600 mg/m^2 Cyclophosphamide 5 g/m^2 Doxorubicin 120 mg/m^2		None	Surgery alone vs surgery + chemotherapy	1998-2004
POG 9640	Cisplatin 400 mg/m^2 Etoposide 1050 mg/m^2 Vincristine 4.5 mg/m^2 Doxorubicin 60 mg/m^2 Cyclophosphamide 4 g/m^2 Ifosfamide 8 g/m^2 Carboplatin 1000 mg/m^2	Double (CEC / CyThio)	24 Gy to primary tumor site	Pilot tandem transplant (no melphalan or TBI)	1998-2000
MSK N6/N7	Cyclophosphamide Doxorubicin Vincristine Etoposide Cisplatin 3F8	None	21 Gy to primary tumor site	No transplant	1990-1999
DFCI[52,53] High risk (n=97)	Cisplatin Etoposide Doxorubicin Vincristine Cyclophosphamide Ifosfamide Carboplatin	Tandem ASCR (CEC/Mel-TBI)	Local XRT	PBSC-supported tandem transplant	1994-2002

**CEC=Carboplatin/Etoposide/Cyclophosphamide

Supplementary Table 2. Treatment Exposure During First 5 Years After Neuroblastoma Diagnosis with Complete Abstraction of Medical Records

Agent		Original cohort		Expansion cohort	
Total		835	100.0	873	100.0
Any radiation	Yes	**411**	49.3	240	27.7
	No	422	50.7	625	72.3
Max dose to brain[1]	Non	424	51.8	649	76.2
	1-19.9	362	44.2	177	20.8
	20-29.9	8	1.0	18	2.1
	30-49.9	13	1.6	5	0.6
	>=50	12	1.5	3	0.4
Max dose to chest	Non	424	51.8	648	76.1
	1-19.9	**288**	35.2	165	19.4
	20-29.9	**60**	7.3	30	3.5
	>=30	46	5.6	9	1.1
Neck	Yes	93	11.3	84	9.7
	No	727	88.7	781	90.3
Spine	Yes	**26**	**3.2**	**81**	**9.4**
	No	793	96.8	784	90.6
Abdomen	Yes	231	28.2	196	22.7
	No	588	71.8	669	77.3
Pelvis	Yes	150	18.3	120	13.9
	No	669	81.7	745	86.1
Limb	Yes	20	2.4	89	10.3
	No	799	97.6	776	89.7
TBI	Yes	**16**	2.0	**74**	8.6
	No	803	98.0	791	91.4
Any chemotherapy	Yes	495	59.4	546	63.1
	No	338	40.6	319	36.9
Alkylating agents (CED,	None	346	45.6	331	41.8
	>0 - <4000	57	7.5	108	13.6
	>=4000 -	**118**	**15.5**	**182**	**23.0**
	>=8000 -	74	9.7	45	5.7
	>=12000 -	58	7.6	53	6.7
	>=16000 -	38	5.0	31	3.9
	>=20000	68	9.0	42	5.3
Anthracycline dose	None	605	74.1	386	46.7
	>0 - <100	29	3.5	94	11.4
	>=100 - <250	105	12.9	**287**	**34.7**
	>=250 - <400	50	6.1	50	6.1
	>=400	28	3.4	9	1.1
Carboplatin		**8**	**1.0**	**218**	**24.9**
Cisplatin		**107**	**12.8**	**381**	**43.5**
Cyclophosphamide-All		479	57.5	552	61.6
Cyclophosphamide-IV/IM		358	43.0	463	53.5
Cyclophosphamide-PO		225	27.0	129	14.9

Dacarbazine (DTIC)		**164**	**19.7**	**35**	**4.0**
Doxorubicin		**223**	**26.8**	**488**	**55.6**
Etoposide (VP-16)-All		**18**	**2.2**	**447**	**50.1**
Etoposide (VP-16)-IV/IM		**17**	**2.0**	**418**	**48.3**
Ifosfamide		**4**	**0.5**	**111**	**12.8**
Mechlorethamine		35	4.2	10	1.2
Melphalan – IV/IM		27	3.2	90	10.4
Teniposide		84	10.1	29	3.4
Topotecan		1	0.1	55	6.3
Vincristine		307	36.9	165	19.0
GCSF		1	0.1	168	19.0
GMCSF		0	0.0	17	2.0
Retinoic acid		1	0.1	98	11.2
IL-2		0	0.2	7	0.8

Adapted from Overall CCSS Cohort Demographic and Treatment Exposure Tables, which are publicly available at: https://ccss.stjude.org/public-access-data/treatment-exposure-tables.html

Supplementary Table 3. Body Region Dosimetry Data of Neuroblastoma Patients Enrolled in CCSS original and expanded cohorts

Body Region Dose	Decade	CCSS Cohort	# of pts with region irradiated	Min of prescribed doses	Maximum of prescribed doses	Median of prescribed doses
Other Head	1970's	Original	17	810	6000	2030
	1980's	Original	18	450	6000	2300
		Expanded	4	1980	5075	3870
	1990's	Expanded	16	590	4800	1630
	2000's	Expanded	4	1100	3400	2250
Max Brain segment	1970's	Original	18	450	6000	2300
	1980's	Original	30	300	6500	3500
		Expanded	9	1000	5100	2700
	1990's	Expanded	34	450	6600	1750
	2000's	Expanded	1	-	-	2000
Chest	1970's	Original	106	450	6000	2010
	1980's	Original	83	300	4650	2000
		Expanded	8	300	3000	2000
	1990's	Expanded	50	450	4500	2100
	2000's	Expanded	5	1050	2250	1400
Abdomen	1970's	Original	136	260	5300	2060
	1980's	Original	92	200	6600	2000
		Expanded	18	360	3200	1170
	1990's	Expanded	143	450	5100	1800
	2000's	Expanded	14	940	2550	2100

ANALYSIS TABLES

Table 1. Demographic and treatment characteristics of 5-year survivors of neuroblastoma, overall and by treatment era

Characteristic	All patients	1970–1986	1987–1999
Sex Male Female			
Race or ethnic group White, non-Hispanic Black, non-Hispanic Hispanic/Latino Other Unknown			
Age at diagnosis, years Mean (SD) Median (Range) < 1 year 1-4 5-9 10 or older			
Risk group Low/intermediate High		 N/A N/A	
Survival after diagnosis, years 5–9 10–14 15–19 20–24 25–29 30–34 ≥35			
Treatment exposure, No. (%) Surgery only Surgery and chemotherapy Surgery and radiation Surgery, chemotherapy, and radiation *Surgery, chemotherapy, radiation, and transplant* Any chemotherapy Any radiation *Any transplant*			
Abdominal radiation Yes No			
Abdominal radiation dose, median (range), Gy			
Total body irradiation Yes No			
Total body irradiation dose, median (range), Gy			
Cranial radiation Yes			

No			
Alkylating agents Yes No			
Cyclophosphamide equivalent dose, median (range), mg/m^2			
Anthracycline Yes No			
Anthracycline dose, median (range), mg/m^2			
Epipodophyllotoxin Yes No			
Epipodophyllotoxin, median dose (range), mg/m^2			
Platinum agent Yes No			
Platinum agent, median dose (range), mg/ m^2			
Retinoic acid Yes No			
Mean age at last follow up, years (range)			
Mean duration of follow-up since diagnosis, years (range)			
Vital Status Alive Deceased			

Table 2. All cause and cause-specific standardized mortality ratios (SMRs) in 5-year survivors of neuroblastoma age < 1 year at diagnosis

	All Cause	Health-related cause	Subsequent neoplasm	Cardiac cause	Pulmonary cause	Other health-related cause
	SMR (95% CI)	SMR (95% CI)	SMR (95% CI)	SMR (95% CI)	SMR (95% CI)	SMR (95% CI)
All survivors						
Treatment era						
1970-1979						
1980-1989						
1990-1999						
Sex						
Male						
Female						
Race or ethnicity						
Non-Hispanic white						
Non-Hispanic black						
Other						
Years since original diagnosis						
5-9						
10-14						
15 or more						

(Parallel table will be constructed illustrating excess absolute risks [EARS])

Table 3. Burden of chronic health conditions in neuroblastoma survivors age < 1 year at diagnosis and siblings, according to treatment era

Health Condition	All Patients No. (%)	1970-1979 No. (%)	1980-1989 No. (%)	1990-1999 No. (%)	Siblings No. (%)	All patients vs siblings HR (95% CI)
Any condition (Grade 1-5)						
Grade 3-5 conditions						
Multiple conditions						
Any						
Grades 3-5						

† Comparisons between survivors and siblings adjusted for age at enrollment, sex, and race/ethnicity

Table 4. Relative risk of select grade 1-5 chronic conditions among patients diagnosed with neuroblastoma at age < 1 year, according to multivariable analysis

	Any chronic condition	Endocrine condition	Sensory condition	Cardiac condition	Pulmonary condition	Second malignant neoplasm
	RR (95% CI), p value	RR (95% CI), p value	RR (95% CI), p value	RR (95% CI), p value	RR (95% CI), p value	RR (95% CI), p value
Sex						
Male						
Female						
Era of diagnosis						
1970-1979						
1980-1989						
1990-1999						
Radiation						
Any						
Abdomen						
Cranial						
Chemotherapy						
Any						
CED						
Doxorubicin equivalent dose						
Epipodophyllo-toxin						
Platinum						
Retinoic acid						

Table 5. Relative risk of select grade 3-5 chronic conditions among patients diagnosed with neuroblastoma at age < 1 year, according to multivariable analysis

	Any chronic condition	Endocrine condition	Sensory condition	Cardiac condition	Pulmonary condition	Second malignant neoplasm
	RR (95% CI), p value	RR (95% CI), p value	RR (95% CI), p value	RR (95% CI), p value	RR (95% CI), p value	RR (95% CI), p value
Sex						
Male						
Female						
Era of diagnosis						
1970-1979						
1980-1989						
1990-1999						
Radiation						
Any						
Abdomen						
Cranial						
Chemotherapy						
Any						
CED						
Doxorubicin equivalent dose						
Epipodophyllo-toxin						
Platinum						
Retinoic acid						

Table 6. Relative risk of subsequent neoplasm among neuroblastoma survivors < 1 year of age at diagnosis, overall and by subtypes, according to multivariable analysis

	Subsequent neoplasm	Subsequent malignant neoplasm	Meningioma	Nonmelanoma skin cancer
	RR (95% CI), p value	RR (95% CI), p value	RR (95% CI), p value	RR (95% CI), p value
Sex				
Male				
Female				
Era of diagnosis				
1970-1979				
1980-1989				
1990-1999				
Radiation				
Any				
Abdomen				
Cranial				
Chemotherapy				
Any				
CED				
Doxorubicin equivalent dose				
Epipodophyllo-toxin				
Platinum				
Retinoic acid				

Table 7. Observed and expected subsequent malignant neoplasms, standardized incidence ratios, excess absolute risks and median time to occurrence, by treatment decade, among neuroblastoma survivors diagnosed at < 1 year of age

	Observed	Expected	SIR (95% CI)	EAR (95% CI)	Median time to occurrence, y, IQR
All survivors					
Decade of diagnosis					
1970-1979					
1980-1989					
1990-1999					

Abbreviations: IQR, interquartile range; SIR, standardized incidence ratio.
[This table will be expanded to show different types of SMNs observed in this cohort]

Table 8. Relative risk of adverse health status outcomes of patients diagnosed with neuroblastoma at age < 1 year, by treatment era, demographics, and health habits

	Poor general health	Functional impairment	Activity limitation	Poor mental health	Cancer-related pain	Cancer-related anxiety
	RR (95% CI)	RR (95% CI)	RR (95% CI)	RR (95% CI)	RR (95% CI)	RR (95% CI)
Treatment decade						
1970-1979						
1980-1989						
1990-1999						
Sex						
Male						
Female						
Race/ethnicity						
White, Non-Hispanic						
Other						
Smoking status						
Never						
Former						
Current						
Heavy alcohol use						
No						
Yes						
Body mass index						
Underweight						
Normal						
Overweight						
Obese						
Meets physical activity guidelines						
Yes						
No						

ANALYSIS II:

Table 9. Table 2. All cause and cause-specific standardized mortality ratios (SMRs) in 5-year survivors of neuroblastoma age ≥ 1 year at diagnosis

	All Cause	Health-related cause	Subsequent neoplasm	Cardiac cause	Pulmonary cause	Other health-related cause
	SMR (95% CI)	SMR (95% CI)	SMR (95% CI)	SMR (95% CI)	SMR (95% CI)	SMR (95% CI)
All survivors						
Race/ethnicity						
Non-Hispanic white						
Non-Hispanic black						
Other						
Sex						
Male						
Female						
Treatment era						
1987-1993						
1994-1999						
Age at diagnosis, year						
1-4						
5-9						
10 or older						
Years since original diagnosis						
5-9						
10-14						
15 or more						

(Parallel table will be constructed illustrating excess absolute risks [EARS])

Table 10. Burden of chronic health conditions in neuroblastoma survivors age ≥ 1 year at diagnosis and siblings, according to treatment era

	All patients	Low-risk patients		High-risk patients		Siblings	All patients vs siblings
Health Condition	1987-1999 No. (%)	1987-1993 No. (%)	1994-1999 No. (%)	1987-1993 No. (%)	1994-1999 No. (%)	1987-1999 No. (%)	HR (95% CI)
Any condition (Grade 1-5)							
Grade 3-5 conditions							
Multiple conditions							
Any							
Grades 3-5							

† Comparisons between survivors and siblings adjusted for age at enrollment, sex, and race/ethnicity

Table 11. Relative risk of select grade 1-5 chronic conditions among patients diagnosed with neuroblastoma at age ≥ 1 year between 1987-1999, according to multivariable analysis

	Any chronic condition	Endocrine condition	Sensory condition	Cardiac condition	Pulmonary condition	Second malignant neoplasm
	RR (95% CI), p value	RR (95% CI), p value	RR (95% CI), p value	RR (95% CI), p value	RR (95% CI), p value	RR (95% CI). P value
Sex						
Male						
Female						
Age at diagnosis						
1-4						
5-9						
10 or older						
Era of diagnosis						
1987-1993						
1994-1999						
Risk group*						
Low (Stage 1 or 2)						
High (Stage 4)						
Radiation						
Any						
Abdomen						
Total body						
Cranial						
Chemotherapy						
Any						
CED						
Doxorubicin equivalent dose						
Epipodophyllotoxin						
Platinum						
Retinoic acid						

*interactions between era of diagnosis and risk group will be evaluated and results may be stratified by risk group.

Table 12. Relative risk of select grade 3-5 chronic conditions among patients diagnosed with neuroblastoma at age ≥ 1 year between 1987-1999, according to multivariable analysis

	Any chronic condition	Endocrine condition	Sensory condition	Cardiac condition	Pulmonary condition	Second malignant neoplasm
	RR (95% CI), p value	RR (95% CI), p value	RR (95% CI), p value	RR (95% CI), p value	RR (95% CI), p value	RR (95% CI), p value
Sex						
Male						
Female						
Age at diagnosis						
Era of diagnosis*						
1987-1993						
1994-1999						
Risk group*						
Low (Stage 1 or 2)						
High (Stage 4)						
Radiation						
Any						
Abdomen						
Total body						
Cranial						
Chemotherapy						
Any						
CED						
Doxorubicin equivalent dose						
Epipodophyllo-toxin						
Platinum						
Retinoic acid						

*Interactions between era of diagnosis and risk group will be evaluated and results may be stratified by risk group.

Table 13. Relative risk of subsequent neoplasm among neuroblastoma survivors ≥ 1 year of age at diagnosis, overall and by subtypes, according to multivariable analysis

	Subsequent neoplasm	Subsequent malignant neoplasm	Meningioma	Nonmelanoma skin cancer
	RR (95% CI), p value	RR (95% CI), p value	RR (95% CI), p value	RR (95% CI), p value
Sex				
Male				
Female				
Age at diagnosis				
1-4				
5-9				
10 or older				
Era of diagnosis*				
1987-1993				
1994-1999				
Risk group*				
Low/intermediate				
High				
Radiation				
Any				
Abdomen				
Cranial				
Chemotherapy				
Any				
CED				
Doxorubicin equivalent dose				
Epipodophyllo-toxin				
Platinum				
Retinoic acid				

*Interactions between era of diagnosis and risk group will be evaluated and results may be stratified by risk group.

Table 14. Observed and expected subsequent malignant neoplasms, standardized incidence ratios, and median time to occurrence, by treatment decade, among neuroblastoma survivors ≥ 1 year of age at diagnosis

	Observed: All patients	Observed: Low/int risk	Observed: High risk	Expected	SIR: Low/int risk (95% CI)	SIR: High risk (95% CI)	Median time to occurrence, y, IQR
All survivors							
Decade of diagnosis							
1987-1993							
1994-1999							

Abbreviations: IQR, interquartile range; SIR, standardized incidence ratio.
[This table will be expanded to show different types of SMNs observed in this cohort]

Table 15. Relative risk of adverse health status outcomes of patients diagnosed with neuroblastoma at age ≥ 1 year, by treatment era, risk group, demographics, and health habits

	Poor general health	Functional impairment	Activity limitation	Poor mental health	Cancer-related pain	Cancer-related anxiety
	RR (95% CI)	RR (95% CI)	RR (95% CI)	RR (95% CI)	RR (95% CI)	RR (95% CI)
Treatment decade*						
1987-1993						
1994-1999						
Risk group*						
Low/intermediate						
High						
Sex						
Male						
Female						
Race/ethnicity						
White, Non-Hispanic						
Other						
Smoking status						
Never						
Former						
Current						
Heavy alcohol use						
No						
Yes						
Body mass index						
Underweight						
Normal						
Overweight						
Obese						
Meets physical activity guidelines						
Yes						
No						

*Interactions between era of diagnosis and risk group will be evaluated and results may be stratified by risk group.

ANALYSIS I FIGURES:

Figure 1. All-cause and cause-specific cumulative mortality among 5-year survivors of neuroblastoma diagnosed at age < 1 year, according to treatment era (1970s vs 1980s vs 1990s)

1A. Death from any cause
1B. Death from recurrence or progression
1C. Death from chronic conditions

X axis: Year since diagnosis
Y axis: Cumulative mortality (%)

Figure 2. Cumulative incidence of chronic conditions among 5-year survivors of neuroblastoma diagnosed at age < 1 year, according to treatment era (1970s vs 1980s vs 1990s)

2A. Any chronic condition
2B. Grade 3-5 chronic conditions
2C. Multiple chronic conditions
2D. Multiple grade 3-5 conditions

X axis: Years since diagnosis
Y axis: Cumulative incidence (%)

Figure 3. Cumulative incidence of select chronic conditions among 5-year survivors of neuroblastoma diagnosed at age < 1 year, according to treatment era (1970s vs 1980s vs 1990s)

3A. Endocrine conditions
3B. Sensory conditions
3C. Cardiac conditions
3D. Pulmonary conditions
3E. Subsequent neoplasms
3F. Subsequent malignancies

X axis: Years since diagnosis
Y axis: Cumulative incidence (%)

Figure 4. Cumulative Incidence of Subsequent Neoplasms among 5-year survivors of neuroblastoma diagnosed at age < 1 year, by type and by era of initial cancer diagnosis (1970s vs 1980s vs 1990s)

4A. Cumulative incidence of subsequent neoplasms by years since diagnosis (stratified by decade of initial cancer diagnosis)
4B. Cumulative incidence of subsequent malignant neoplasms by years since diagnosis (stratified by decade of initial cancer diagnosis)
4C. Cumulative incidence of benign meningiomas by years since diagnosis (stratified by decade of initial cancer diagnosis)
4D. Cumulative incidence of nonmelanoma skin cancer by years since diagnosis (stratified by decade of initial cancer diagnosis)

Figure 5. Adverse health status outcome among neuroblastoma survivors among 5-year survivors of neuroblastoma diagnosed at age < 1 year, by treatment era (1970s vs 1980s vs 1990s)

5A. Poor general health
5B. Functional impairment
5C. Activity limitation
5D. Poor mental health
5E. Cancer-related pain
5F. Cancer-related anxiety

ANALYSIS II FIGURES:

Figure 6. All-cause and cause-specific cumulative mortality among 5-year survivors of neuroblastoma diagnosed at age ≥ 1 year, according to treatment era (1987-1993 vs 1994-1999) and according to risk grouping (low/intermediate vs high risk)

6A. Death from any cause
6B. Death from recurrence or progression
6C. Death from chronic conditions

X axis: Year since diagnosis
Y axis: Cumulative mortality (%)

Figure 7. Cumulative incidence of chronic conditions mortality among 5-year survivors of neuroblastoma diagnosed at age ≥ 1 year, according to treatment era (1987-1993 vs 1994-1999) and according to risk grouping (low/intermediate vs high risk)

7A. Any chronic condition
7B. Grade 3-5 chronic conditions
7C. Multiple chronic conditions
7D. Multiple grade 3-5 conditions

X axis: Years since diagnosis
Y axis: Cumulative incidence (%)

Figure 8. Cumulative incidence of select chronic conditions among 5-year survivors of neuroblastoma diagnosed at age ≥ 1 year, according to treatment era (1987-1993 vs 1994-1999) and according to risk grouping (low/intermediate vs high risk)

8A. Endocrine conditions
8B. Sensory conditions
8C. Cardiac conditions
8D. Pulmonary conditions
8E. Subsequent neoplasms
8F. Subsequent malignancies

X axis: Years since diagnosis
Y axis: Cumulative incidence (%)

Figure 9. Cumulative Incidence of Subsequent Neoplasms among neuroblastoma survivors diagnosed at age ≥ 1 year between 1987-1999, by type and by era of initial cancer diagnosis (1987-1993 vs 1994-1999)

9A. Cumulative incidence of subsequent neoplasms by years since diagnosis (stratified by decade of initial cancer diagnosis)
9B. Cumulative incidence of subsequent malignant neoplasms by years since diagnosis (stratified by decade of initial cancer diagnosis)
9C. Cumulative incidence of benign meningiomas by years since diagnosis (stratified by decade of initial cancer diagnosis)
9D. Cumulative incidence of nonmelanoma skin cancer by years since diagnosis (stratified by decade of initial cancer diagnosis)

Figure 10. Risk grouping (low/intermediate vs high risk) and adverse health status outcome among neuroblastoma survivors diagnosed at age ≥ 1 year between 1987-1999

10A. Poor general health
10B. Functional impairment
10C. Activity limitation
10D. Poor mental health
10E. Cancer-related pain
10F. Cancer-related anxiety

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