THERAPY-RELATED NEUROSENSORY DEFICITS AND THEIR EFFECTS ON NEUROCOGNITIVE FUNCTION, HEALTH-RELATED QUALITY OF LIFE AND SOCIAL ATTAINMENT IN CHILDHOOD CANCER SURVIVORS

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1. Background and Rationale:

Due to advances in treatment and supportive care, the five-year survival rate for most childhood cancers has increased dramatically over the past three decades to over 80%.[1] It has been estimated that over 500,000 childhood cancer survivors currently live in the United States.[2] However, treatment of childhood cancer continues to leave a burden of chronic health conditions and functional morbidities. Studies have reported that as many as 10-25% of childhood cancer survivors in their adult years report adverse health status including poor general and mental health, functional impairments, activity limitations, cancer-related pain and cancer-related anxiety.[3] Treatment modalities in the modern era have focused on reducing toxicities and preserving function; but recent data demonstrate that children treated in the contemporary era may be at even higher risk for poor general health.[3] This paradox may be due to the intensification of treatment for higher risk cancers.

Neurosensory deficits reflect impaired sensory input to the visual, vestibular, and peripheral nervous systems. Chemotherapy agents and radiation therapy used in the treatment of childhood cancers may lead to a broad scope of neurosensory complications. In children, the developing neurosensory systems are susceptible to neurotoxic effects of cancer therapy.[4,5] Neurosensory complications can be mild or subtle and can be unrecognized in childhood cancer survivors.[5-7] Although neurotoxic consequences of therapy including loss of sight, hearing loss, vestibular dysfunction and peripheral neuropathy have been described, the effects of having more than one moderate to severe deficits and their long-term impact on health-related quality of life and social functioning are largely unknown.

Visual impairment

Depending upon the cancer diagnosis and treatment exposure(s), childhood cancer survivors have an elevated risk of blindness, decreased visual acuity, cataracts, diplopia, dry eyes, and glaucoma when compared to age-matched siblings.[8] Visual impairment is commonly reported in childhood cancer survivors with a diagnosis of central nervous system (CNS) tumor; deficits are related to tumor location and radiotherapy.[9,10] Childhood leukemia survivors are also at an increased risk for developing cataracts compared to their siblings.[11] Cataracts are observed in upwards of 4.1% of patients with a history of leukemia[12] and the cumulative incidence of cataracts continues to increase up to 20 years after diagnosis.[8] Cataracts can lead to visual impairment and the need for surgery. Radiotherapy to the orbital region is the major risk factor for several ocular complications,[13] including cataracts.[14] Corticosteroids and busulfan are associated with increased risk of cataracts, whereas vincristine, cytarabine or doxorubicin are associated with increased risk of optic neuropathy, keratoconjunctivitis and conjunctivitis, respectively.[13]

Visual impairment in childhood can pose lifelong challenges for children and their families. Visual impairments may affect self-perception, cognitive development, educational attainment, ability to drive and be employed.[15] A number of studies have examined visual loss and quality of life in brain tumor survivors and have noted negative effects on health-related quality of life in physical, social and emotional domains.[16-19] In adults, visual deficits can cause significant impairments in physical functioning and well-being, leading to decreased health-related quality of life.[20-22] Within CCSS, de Blank et al investigated the impact of vision loss on academic and social development among adult survivors of childhood CNS astroglia tumors, a group of low grade tumors that are prone to result in vision impairment and blindness. The study showed that survivors with bilateral blindness were less likely to be married, live independently, attend college and be employed compared with those without vision impairments.[23] Retinoblastoma survivors also experience reduced qualify of life due to poor vision[24] and bilateral disease,[25] although those treated in more recent eras have overall good outcomes.[26] Beyond these observations in these tumor groups, there is scarce literature examining the effect of multiple neurosensory deficits on health-related quality of life in childhood cancer survivors with limited vision or blindness.

Hearing and vestibular system

Hearing loss is a well-established side effect of platinum and radiation therapy in childhood survivors of CNS tumors, high risk neuroblastoma and non-otologic solid tumors.[27-30] Hearing impairment may be particularly detrimental to developing children and has been associated with impaired language acquisition and speech, poor academic performance, and decreased quality of life in the general population.[31-33] Survivors of a variety of childhood cancer diagnoses demonstrate speech and hearing problem in childhood[34] and young adulthood.[35] Sensorineural hearing loss among survivors of embryonal brain tumors is associated with cognitive deficits[36-39] and reduced social attainment.[19] Academic difficulties and special education needs that significantly impact quality of life also have been reported among child and adolescent survivors of neuroblastoma with hearing loss.[40] Among adults, survivors of non-CNS tumor with hearing loss were twice as likely to perceive negative impact of cancer on social functioning, live dependently, never have married and not graduate from high school or be unemployed, compared to survivors of non-CNS tumor without hearing impairment.[41] Detrimental effects of hearing loss on perceived impact of cancer on social functioning and social attainment were also found among CNS-tumor survivors.[41] Qualitatively, social isolation emerges as a critical problem for survivors with hearing loss.[42]

Treatment with platinum agents can also lead to damage of organs of the inner ear that impair vestibular function,[43,44] which in turn can cause delayed development of motor skills, recurrent episodes of tinnitus and vertigo.[45] Vestibular impairment in children with sensorineural hearing loss ranges between 20-70%.[46-48] Dysfunction in vestibular function can translate into problems with balance.[49,50] Children with acquired unilateral deafness displayed poor balance function when compared to their peers.[51] Child and adult survivors of pediatric CNS tumors[22,52] report impaired balance that can be secondary to the location of the tumor and the exposure to CNS radiation or other chemotherapy agents. Interestingly, a recent study showed that hearing loss is associated with over 11-fold elevated risk for balance impairment among adults survivors of CNS tumors and vestibular deficits are the most frequent contributor to impaired balance.[53] Deficits in balance can affect functional performance and increase the risk of falls and injuries.[54-57] Overall, hearing and vestibular impairments in children can lead to decreased function in daily life such as poor receptive and expressive language, slower rates of educational progress and impairments in physical activities such as riding a bike or crossing the street.[58-60]

Peripheral neuropathy

Peripheral neuropathies encompass several different conditions including altered or diminished sensation, painful dysesthesia, and loss of vibratory, temperature and proprioceptive sensation.[61,62] Vinca alkaloids such as vincristine and vinblastine have been shown to cause sensorimotor neuropathies that compromise proprioceptive feedback to muscles and joints.[63] Loss of motor functions has been associated with platinum agents and vinca alkaloids.[64-66] Peripheral neuropathies are often seen during the acute phase of therapy in leukemia, CNS, and solid tumor patients, but many survivors face life long neuropathies leading to chronic pain, limitation in occupational pursuits and activities in daily living.[67]

Previous cross-sectional studies have shown that adult survivors of acute lymphoblastic leukemia with neuromuscular deficits have increased problems with balance and walking efficiency,[68] whereas adult survivors of extracranial solid tumors with chemotherapy-induced sensory impairment were at elevated risk for mobility and endurance problems.[69] Among adolescent survivors of neuroblastoma, peripheral neuropathy was associated with increased risk for anxiety/depression and attention deficits. In addition, a recent study with long-term childhood cancer survivors of mixed diagnoses demonstrated that neuromuscular dysfunction (including motor or sensory dysfunction) was associated with concurrent or subsequent obesity, anxiety, depression, frailty and physical limitation, as well as reduced likelihood of graduating from college or being employed.[70] These findings underscore how sensory deficits can interfere with function in survivors who otherwise appear to be doing well.

Neurosensory deficits and cognitive and emotional outcomes

Cancers of the central nervous system (CNS), the most common solid malignancies in childhood, are associated with a number of sequelae including dysfunction in neurologic, endocrine, social, psychological and neurocognitive areas.[71-73] A CCSS study examining neurocognitive deficits in CNS childhood cancer survivors found that medical complications, including hearing deficits, paralysis and cerebrovascular incidents resulted in a greater likelihood of reported deficits in memory, task efficiency and organization.[74] Associations between neurosensory deficits and cognitive and emotional outcomes have been reported also among survivors who are not typically exposed to CNS-directed therapies. For example, among survivors of soft tissue sarcomas having a moderate to severe neurologic condition (mostly peripheral neuropathy) or hearing deficit was associated with worse neurocognitive performance and poor HRQOL.[75] ***In spite of this evidence from disease-specific studies, no studies to date have examined the prevalence of multiple neurosensory deficits and their effects on cognitive and emotional outcomes in all diseases.***

Combination effects

In older adults, the *patterns of unisensory and multisensory morbidities* (i.e., impairments in single or multiple senses; e.g., hearing only, vision only, hearing + vision, hearing + touch, hearing + vision + vestibular), have been described,[76] and a higher number of impaired senses has been associated with greater risk of dementia,[77] depressive symptoms and poorer quality of life.[78] Together, deficits in vision, hearing, and sensation can have substantial impact on the long-term health and productivity for childhood cancer survivors.

Neurosensory deficits, alone and in combination, also have implications on personal safety of long-term survivors, both in public (e.g., crossing streets, riding a bike) and private (e.g., not hearing smoke alarms at home) settings. Research shows that cancer patients within 5 years from their diagnosis have 60% higher risk of death due to accidental causes compared to the matched general population, and the risk remains significant even after excluding patients with history of self-harm related behavior.[85] This suggests that aspects related to the cancer diagnosis and treatment, including neurosensory deficits, may pose a risk of mortality. An ongoing study in CCSS found a significantly increased risk of unintentional injury-related deaths among survivors of childhood CNS tumor or neuroblastoma; however, this analysis did not examine the impact of sensory deficits, which are common in these diagnostic groups.

This proposal will analyze the CCSS database organizing neurosensory impairments as defined in the CCSS Chronic Conditions Matrix Common Terminology for Adverse Events (CTCAE) 4.03. First, we will estimate the *prevalence* of impairment in each and any sensory organ system in non-mutually exclusive categories (e.g., vision impairment yes/no, regardless of the other sensory domains) and examine the *patterns of unisensory and multisensory morbidities* in this population in mutually exclusive categories (e.g., vision only vs. vision + hearing vs. vision + hearing + vestibular, etc.), overcoming the limitations of past research that studied different organ systems in isolation in different cohorts. Together, these approaches will allow us to comprehensively characterize the frequency and patterns of neurosensory deficits in this cohort. We will then be able to assess the impact of these patterns of neurosensory morbidities on the outcome measures of this proposal, namely neurocognitive functioning, health-related quality of life, emotional distress, and social attainment. Given the association of individual neurosensory deficits with poor outcomes, patients with more than one deficit may be even more severely impacted. We hypothesize that survivors who develop multisensory impairments may experience even more profound effects on their overall quality of life and cognitive and psychosocial functioning. Most neurosensory deficits are not considered life threatening, but to date the impact on quality of life, cognition, emotional and social functioning of having multiple chronic neurosensory deficits in childhood cancer survivors has not been fully assessed.

2. Specific Aims & Hypotheses

Aim 1: Describe the prevalence of neurosensory impairments (visual, hearing, vestibular and/or neuropathy) and the patterns of neurosensory comorbidities in childhood cancer survivors compared to sibling controls.

> *Hypothesis 1a*: The *prevalence* of individual neurosensory impairments in each sensory organ system and across the four systems will be higher in childhood cancer survivors compared to sibling controls.

Hypothesis 1b: The prevalence of *neurosensory comorbidities* will be higher in childhood cancer survivors compared to sibling controls.

Aim 2: Examine associations between the patterns of neurosensory comorbidities and neurocognitive outcomes, health-related quality of life, emotional distress, and social attainment within survivors.

Hypothesis 2a: Survivors with sensory impairments will be more likely to report neurocognitive impairment, poor health-related quality of life, emotional distress, and reduced social attainment, compared to survivors with no sensory impairments.

Hypothesis 2b: Survivors with neurosensory comorbidities will be more likely to report neurocognitive impairment, poor health-related quality of life, emotional distress, and reduced social attainment, compared to survivors with no neurosensory comorbidities.

Exploratory aim: Examine associations between the patterns of neurosensory morbidities and unintentional causes of death (motor vehicle accidents, accidental poisonings, falls).

3. Analysis framework:

Population: The planned research population will include adult participants (≥18 years of age) from the original and expansion cohorts including both survivors and sibling controls.

Predictors:

- Original: Follow-up 4 or Follow-up 5 or Follow-up 7
- Expansion: Follow-up 5 or Follow-up 7

For aim 2, only neurosensory conditions with date of onset prior to NCQ completion will be considered.

The primary aim is to describe the prevalence of neurosensory impairments and the patterns of neurosensory comorbidities. To do this, we will use the CCSS Chronic Conditions Matrix Common Terminology for Adverse Events (CTCAE) 4.03. to consolidate different sensory impairments within each organ. This will allow us to analyze the impact of the impairment of the specific organ despite the nature of the deficit. Specifically, the following conditions will be considered:

I. Visual impairment
    i. Cataract, Grade 1-3
    ii. Glaucoma, Grade 1
    iii. Double vision, Grade 2
    iv. Blindness, Grade 1-4
    v. Crossed eye, Grade 1

II. Hearing impairment
    i. Loss of hearing, Grade 1-4

III. Vestibular Dysfunction
    i. Vertigo, Grade 1

IV. Neuropathy
    i. Sensory neuropathy, Grade 1

ii. Balance, Grades 1-4
iii. Tremors, Grade 1
iv. Weakness in leg, Grade 1-2
v. Weakness in arm, Grade 1

[Note: grades refer to CTCAE grades available for each condition in CCSS.]

The *prevalence* of neurosensory impairments (i.e., at least one condition [i.e., ≥grade 1]) will be examined in each sensory organ system (e.g., survivors with at least one vision condition) and in any of the four sensory organ systems (i.e., survivors with at least one neurosensory condition) in non-mutually exclusive categories. For example, a participant with both vision and hearing impairments will contribute to the categories of "vision impairment (yes/no)", "hearing impairment (yes/no)" and "any impairment (yes/no)".

The *patterns of neurosensory comorbidities* will be examined by considering the number of sensory organ systems affected (i.e., none, 1 domain, 2 domains). For example, a participant with vision impairment will contribute only to the category "1 sensory impairment" whereas a participant with both vision and hearing impairments will contribute only to the category "2 sensory domains". A similar approach will be taken for survivors with impairments in 3 or 4 sensory organ systems. If appropriate, categories will be collapsed based on the observed distribution in the sample. The specific combinations of neurosensory comorbidities will also be explored (e.g., vision + hearing, hearing + vestibular, etc.).

Of note, most neurosensory impairments in CCSS are coded as grade 1-2 and only few conditions are coded as grade 3-4. Therefore, all the analysis will consider any condition ≥grade 1 as indicative of neurosensory impairment.

While previous studies examined neurosensory deficits in isolation, the use of patterns of neurosensory morbidities will enable us to address the novel question of this study regarding the impact of multiple/different neurosensory deficits on functional outcomes.

Outcomes:

For aim 2, the primary interest is the impact of neurosensory deficits on cognitive functioning. Therefore, all secondary outcomes will be collected at the same time point as the CCSS-NCQ.

Neurocognitive Outcomes:

CCSS-NCQ: Childhood Cancer Survivor Study Neurocognitive Questionnaire will be used to measure neurocognitive function. Four scales will be examined: task efficiency, memory, emotional regulation, and organization. Scores >1.3 SD below normative mean will represent impairment.

- Original: Follow-up 2 (J1-25), Follow-up 5 (Q1-33; or long version of Follow-up 6 [G1-33]) and Follow-up 7 (P1-33)
- Expansion: Follow-up 5 (Q1-33) and Follow-up 7 (P1-33)

Health-Related Quality of Life:

SF-36: Health-related quality of life will be measured using the SF-36 Medical Outcomes Survey Short Form - 36. Eight subscales will be examined: physical function, role-physical, bodily pain, general health, vitality, social function, role-emotional, mental health. T-scores <40 will represent reduced HRQoL.

- Original: Follow-up 2 (E1-F14), Follow-up 5 (O1-P3; or long version of Follow-up 6 [E1-F3]) and Follow-up 7 (N1-O3)
- Expansion: Follow-up 5 (O1-P3) and Follow-up 7 (N1-O3)

Emotional Distress:

BSI-18: Psychological distress will be measured using the Brief Symptom Inventory-18. Three subscales will be considered: anxiety, depression, somatization. T-scores ≥63 will represent emotional distress.

- Original: Follow-up 2 (G1-18), Follow-up 5 (L1-18) and Follow-up 7 (L1-18)
- Expansion: Follow-up 5 (L1-18) and Follow-up 7 (L1-18)

Social Attainment:

Marital Status:

- History of marriage (married; living as married; widowed; divorced; separated) vs. single never married
- Original: Follow-up 2 (2), Follow-up 5 (M2) and Follow-up 7 (A10)
- Expansion: Follow-up-5 (M2) and Follow-up 7 (A10)

Independent Living

- Yes (live with spouse/partner; live alone; live with roommates) vs. No
- Original: Follow-up 2 (3), Follow-up-5 (M1) and Follow-up 7 (A9)
- Expansion: Follow-up-5 (M1) and Follow-up 7 (A9)

Employment Status

- Full-time (working full time; student; caring for family) vs. other
- Original: Follow-up 2 (4), Follow-up-5 (A5) and Follow-up 7 (A7)
- Expansion: Follow-up-5 (A5) and Follow-up 7 (A7)

Education

- College graduate (college graduate; post graduate level) vs. high school graduate (completed high school; training after high school; some college) vs. less than high school (1-8 years; 9-12 years but did not graduate)
- Original: Follow-up 2 (1), Follow-up-5 (A4) and Follow-up 7 (A7)
- Expansion: Follow-up-5 (A4) and Follow-up 7 (A7)

Health Insurance:

- Yes (yes; Canadian resident) vs. No
- Original: Follow-up 2 (M1), Follow-up-5 (A10) and Follow-up 7 (A16)
- Expansion: Follow-up-5 (A10) and Follow-up 7 (A16)

Deaths due to unintentional causes:

Deaths due to unintentional causes (including motor vehicle accidents, falls, and accidental poisonings) will be evaluated using the National Death Index (NDI).

Covariates:

- Age at survey completion
- Age at diagnosis
- Sex
- Race/ethnicity (White/non-Hispanic, Black/non-Hispanic, Hispanic, others)
- Diagnosis
    - Leukemias
    - CNS
    - Bone

        - Soft tissue sarcoma
        - Hodgkin
        - Non-Hodgkin
        - Kidney
        - Neuroblastoma
        - Other
    - **Chemotherapy** - (MRAF)
        - We will consider cumulative dose and dichotomous variables yes/no as well as dose categories and, as available and appropriate
            - Corticosteroids
            - Alkylating agents
            - Platinum agents
            - Plant alkaloids
            - Anthracyclines
            - Cytarabine
            - Methotrexate
            - Cyclophosphamide
    - **Radiation** – (MRAF)
        - Will code as four mutually exclusive categories:
            - No radiation
            - Cranial radiation < 30Gy
            - Cranial radiation ≥ 30Gy
            - Non-cranial radiation
        - We will also consider the impact of location of radiation to the brain:
            - Posterior fossa
            - Frontal lobe
            - Temporal lobe
            - Parieto-occipital lobe
    - Chronic health conditions (any chronic condition graded 3 or 4 according to CTCAE, except for neurosensory impairments)

Analytic Approach:

Descriptive statistics will be generated and compared between survivor and sibling cohorts (Table 1). Chi-square tests and t-tests will be used to compare survivors and siblings on categorical and continuous variables, respectively.

Aim 1: This set of analyses will consider neurosensory deficits at the most recent follow-up as outcomes of interest. Because most neurosensory deficits in CCSS are coded as grade 1-2, condition ≥grade 1 will be considered indicative of neurosensory deficits.

First, we will examine the *prevalence* of neurosensory deficits in each individual neurosensory domain (i.e., vision impairment yes vs. no; hearing impairment yes vs. no; etc.) and any neurosensory domain (yes vs. no) in non-mutually exclusive categories. Binomial regression models will be used to evaluate prevalence ratios comparing survivors and siblings (Table 2).

The *patterns of multisensory morbidities* will be examined by considering the number of sensory organ systems affected (i.e., none, 1 domain, 2 domains). The specific combinations of neurosensory comorbidities will also be explored (e.g., vision + hearing, hearing + vestibular, etc.). Categories may be collapsed based on the observed distribution in the sample. Multinomial regression models will be used to evaluate prevalence ratios comparing survivors and siblings, adjusted for age at survey completion, sex, race/ethnicity. Prevalence ratios and 95% CI will be reported (Table 2).

Aim 2: This set of analyses will consider neurocognitive functioning (CCSS-NCQ) at the most recent follow-up as the outcome of interest. All secondary outcomes at the same time point as neurocognitive functioning. The predictor of interest will be the patterns of morbidities with date of onset prior to the outcomes.

Separate multinomial regression models will be employed to examine associations between the patterns of neurosensory comorbidities across the four organ systems (predictors) and neurocognitive problems (4 outcomes, CCSS-NCQ domains; Table 3), health-related quality of life (8 outcomes, SF-36 domains; Table 4), emotional distress (3 outcomes, BSI-18 domains; Table 5), and social attainment (5 outcomes, marital status, independent living, employment status, education, health insurance; only for survivors aged 25+; Table 6). In the approach focused on impairment types, survivors with impairment in a specific sensory organ system will be compared to survivors without impairment on that sensory organ system (e.g., vision impairment yes vs. no). In the approach focused on neurosensory comorbidities, survivors with 1, 2 or ≥3 sensory organ system affected will be compared with survivors with no sensory organ system affected. Based on specific combinations of impairments that demonstrate sufficient frequency, more specific approaches will be explored to identify specific patterns at elevated risk of poor outcomes (e.g., vision + hearing vs. vision + vertigo). All outcomes will be taken at the same time point, and separate models will be used for each outcome. These models will be adjusted for age at survey completion, sex, race/ethnicity, neurotoxic therapies (CRT, cytarabine and methotrexate), and any grade 3-4 chronic health conditions (excluding neurosensory conditions).

Although different conditions may have a different impact on functioning, this analysis assumes that conditions with similar grade have similar severity and impact based on the CTCAE grading system. This approach is appropriate for neurocognitive outcomes of primary interest, as impairments on the CCSS-NCQ scales reflect broad problems in daily living rather than deficits of specific neurocognitive processes.

Table 1. Demographic and clinical factors of adult survivors of childhood cancer and sibling controls.

	Survivors	Siblings	*p* value
Age at diagnosis (years)			
Age at assessment (years)			
Sex			
Male			
Female			
Race			
White, non-Hispanic			
White, Hispanic			
Black			
Other			
Marital status			
Single/never married			
Ever married			
Independent living			
Yes			
No			
Employment status			
Full-time			
Part-time/unemployed			
Educational attainment			
≤ High school			
Some college, training			
College graduate			
Health Insurance			
Yes/Canadian			
No			
Diagnosis			
Leukemia			
CNS tumor			
Osteosarcoma			
Soft tissue sarcoma			
Hodgkin lymphoma			
non-Hodgkin lymphoma			
Wilms tumor			
Neuroblastoma			
Other			
Chemotherapy			
any			
corticosteroids			
alkylating agents			
platinum agents			
plant alkaloids			
cytarabine			
anthracyclines			
methotrexate			
cyclophosphamide			
Radiation			
None			

CRT <30 Gy	
CRT ≥30 Gy	
Non-CRT	
Radiation location	
Posterior fossa	
Frontal lobe	
Temporal lobe	
Parieto-occipital lobe	

Abbreviations: CNS, central nervous system; CRT, cranial radiation therapy; CSI, craniospinal irradiation

Table 2. Prevalence of neurosensory deficits among adult survivors of childhood cancer and sibling controls.

	Survivors (N =)	**Controls (N =)**	
Sensory organ system(s) affected	**n (%)**	**n (%)**	**PR (95% CI)**
Neurosensory impairments (yes vs. no) [a]			
Any			
Vision			
Hearing			
Vestibular			
Neuropathy			
Patterns of neurosensory comorbidities [b]			
None			
1 sensory domain			
2 sensory domains			
3+ sensory domains			

[a] Each sensory organ system is considered affected if participants have at least one condition (≥grade 1) in that organ system. Categories of neurosensory deficits are not mutually exclusive; for example, a participant with both vision and hearing impairments will contribute to the cells “vision”, “hearing” and “any”.

[b] Each sensory organ system is considered affected if participants have at least one condition (≥grade 1) in that organ system. Categories are mutually exclusive; for example, a survivor with both vision and hearing impairments will contribute only to the cell corresponding to “2 sensory domains”.

Table 3. Associations between neurosensory deficits and neurocognitive outcomes.

	Task Efficiency	Emotional Regulation	Organization	Memory
	OR (95% CI)	**OR (95% CI)**	**OR (95% CI)**	**OR (95% CI)**
Neurosensory impairments (yes vs. no) [a]				
Any				
Vision				
Hearing				
Vestibular				
Neuropathy				
Patterns of neurosensory comorbidities [b]				
None	Ref.	Ref.	Ref.	Ref.
1 sensory domain				
2 sensory domains				
3+ sensory domains				

Abbreviations: OR, odds ratio; CI, confidence interval.

T-scores >1.3 SD below normative mean indicate neurocognitive impairment.

Multivariable models adjusted for age at survey completion, sex, race/ethnicity, neurotoxic therapies (CRT, cytarabine and methotrexate), and any grade 3-4 chronic health conditions (excluding neurosensory conditions).

Table 4. Associations between neurosensory deficits and health-related quality of life.

	Physical function	Role physical	Bodily pain	General health	Vitality	Social function	Role emotional	Mental health
	OR (95% CI)	OR (95% CI)	OR (95% CI)	OR (95% CI)	OR (95% CI)	OR (95% CI)	OR (95% CI)	OR (95% CI)
Neurosensory impairments (yes vs. no) [a]								
Any								
Vision								
Hearing								
Vestibular								
Neuropathy								
Patterns of neurosensory comorbidities [b]								
None	Ref.	Ref.	Ref.	Ref.	Ref.	Ref.	Ref.	Ref.
1 sensory domain								
2 sensory domains								
3+ sensory domains								

Abbreviations: OR, odds ratio; CI, confidence interval.

T-scores of <40 indicate impaired quality of life.

Multivariable models adjusted for age at survey completion, sex, race/ethnicity, neurotoxic therapies (CRT, cytarabine and methotrexate), and any grade 3-4 chronic health conditions (excluding neurosensory conditions).

Table 5. Associations between neurosensory deficits and emotional distress.

	Anxiety	Depression	Somatization
	OR (95% CI)	**OR (95% CI)**	**OR (95% CI)**
Neurosensory impairments (yes vs. no) [a]			
Any			
Vision			
Hearing			
Vestibular			
Neuropathy			
Patterns of neurosensory comorbidities [b]			
None	Ref.	Ref.	Ref.
1 sensory domain			
2 sensory domains			
3+ sensory domains			

Abbreviations: OR, odds ratio; CI, confidence interval.
T-scores ≥63 indicate significant emotional distress symptoms.
Multivariable models adjusted for age at survey completion, sex, race/ethnicity, neurotoxic therapies (CRT, cytarabine and methotrexate), and any grade 3-4 chronic health conditions (excluding neurosensory conditions).

Table 6. Associations between neurosensory deficits and social attainment (only survivors aged 25+).

	Marital status	Independent living	Employment status	Education	Health Insurance
	OR (95% CI)	**OR (95% CI)**	**OR (95% CI)**	**OR (95% CI)**	**OR (95% CI)**
Neurosensory impairments (yes vs. no) [a]					
Any					
Vision					
Hearing					
Vestibular					
Neuropathy					
Patterns of neurosensory comorbidities [b]					
None	Ref.	Ref.	Ref.	Ref.	Ref.
1 sensory domain					
2 sensory domains					
3+ sensory domains					

Abbreviations: OR, odds ratio; CI, confidence interval.

Multivariable models adjusted for age at survey completion, sex, race/ethnicity, neurotoxic therapies (CRT, cytarabine and methotrexate), and grade 3-4 chronic health conditions (excluding neurosensory conditions).

REFERENCES:

1. Fast Stats: An interactive tool for access to SEER cancer statistics. Surveillance Research Program NCI, 2018
2. Robison LL, Hudson MM: Survivors of childhood and adolescent cancer: life-long risks and responsibilities. Nat Rev Cancer 14:61-70, 2014
3. Ness KK, Hudson MM, Jones KE, et al: Effect of temporal changes in therapeutic exposure on self-reported health status in Childhood Cancer Survivors. Ann Intern Med 166:89-98, 2017
4. Giordano G, Costa LG: Developmental neurotoxicity: some old and new issues. ISRN Toxicol 2012:814795, 2012
5. Jariyakosol S, Hirunwiwatkul P, Lerdlum S, et al: Prevalence and Associated Factors of Neurovascular Contact in Patients With Hemifacial Spasm. Asia Pac J Ophthalmol (Phila) 4:212-5, 2015
6. Bass JK, Hua CH, Huang J, et al: Hearing Loss in Patients Who Received Cranial Radiation Therapy for Childhood Cancer. Journal of Clinical Oncology 34:1248-1255, 2016
7. Goldsby RE, Liu Q, Nathan PC, et al: Late-occurring neurologic sequelae in adult survivors of childhood acute lymphoblastic leukemia: a report from the Childhood Cancer Survivor Study. Journal of Clinical Oncology 28:324-331, 2010
8. Whelan KF, Stratton K, Kawashima T, et al: Ocular late effects in childhood and adolescent cancer survivors: a report from the Childhood Cancer Survivor Study. Pediatric Blood & Cancer 54:103-9, 2010
9. Saha A, Salley CG, Saigal P, et al: Late effects in survivors of childhood CNS tumors treated on Head Start I and II protocols. Pediatr Blood Cancer 61:1644-1652, 2014
10. Gunn ME, Lahdesmaki T, Malila N, et al: Late morbidity in long-term survivors of childhood brain tumors: a nationwide registry-based study in Finland. Neuro Oncol 17:747-56, 2015
11. Essig S, Li Q, Chen Y, et al: Risk of late effects of treatment in children newly diagnosed with standard-risk acute lymphoblastic leukaemia: a report from the Childhood Cancer Survivor Study cohort. Lancet Oncol 15:841-51, 2014
12. Alloin AL, Barlogis V, Auquier P, et al: Prevalence and risk factors of cataract after chemotherapy with or without central nervous system irradiation for childhood acute lymphoblastic leukaemia: an LEA study. Br J Haematol 164:94-100, 2014
13. Wilson C, Gawade P, Ness K: Impairments that Influence Physical Function among Survivors of Childhood Cancer. Children 2:1-36, 2015
14. Chodick G, Sigurdson AJ, Kleinerman RA, et al: The Risk of Cataract among Survivors of Childhood and Adolescent Cancer: A Report from the Childhood Cancer Survivor Study. Radiation Research 185:366-374, 2016
15. Chadha RK, Subramanian A: The effect of visual impairment on quality of life of children aged 3-16 years. Br J Ophthalmol 95:642-5, 2011
16. Gerber NU, Zehnder D, Zuzak TJ, et al: Outcome in children with brain tumours diagnosed in the first year of life: long-term complications and quality of life. Arch Dis Child 93:582-9, 2008
17. Aarsen FK, Paquier PF, Arts WF, et al: Cognitive deficits and predictors 3 years after diagnosis of a pilocytic astrocytoma in childhood. Journal of Clinical Oncology 27:3526-32, 2009
18. Laffond C, Dellatolas G, Alapetite C, et al: Quality-of-life, mood and executive functioning after childhood craniopharyngioma treated with surgery and proton beam therapy. Brain Inj 26:270-81, 2012

19. Schulte F, Kunin-Batson AS, Olson-Bullis BA, et al: Social attainment in survivors of pediatric central nervous system tumors: a systematic review and meta-analysis from the Children's Oncology Group. Journal of Cancer Survivorship 13:921-931, 2019
20. Chia EM, Wang JJ, Rochtchina E, et al: Impact of bilateral visual impairment on health-related quality of life: the Blue Mountains Eye Study. Invest Ophthalmol Vis Sci 45:71-6, 2004
21. Salive ME, Guralnik J, Glynn RJ, et al: Association of visual impairment with mobility and physical function. J Am Geriatr Soc 42:287-92, 1994
22. Ness KK, Morris EB, Nolan VG, et al: Physical performance limitations among adult survivors of childhood brain tumors. Cancer 116:3034-44, 2010
23. de Blank PM, Fisher MJ, Lu L, et al: Impact of vision loss among survivors of childhood central nervous system astroglial tumors. Cancer 122:730-9, 2016
24. Alessi D, Dama E, Barr R, et al: Health-related quality of life of long-term childhood cancer survivors: a population-based study from the Childhood Cancer Registry of Piedmont, Italy. European Journal of Cancer 43:2545-52, 2007
25. Friedman DN, Chou JF, Francis JH, et al: Vision-Targeted Health-Related Quality of Life in Adult Survivors of Retinoblastoma. JAMA Ophthalmology 136:637, 2018
26. Belson PJ, Eastwood J-A, Brecht M-L, et al: A Review of Literature on Health-Related Quality of Life of Retinoblastoma Survivors. Journal of Pediatric Oncology Nursing 37:116-127, 2020
27. Kushner BH, Budnick A, Kramer K, et al: Ototoxicity from high-dose use of platinum compounds in patients with neuroblastoma. Cancer 107:417-422, 2006
28. Bertolini P, Lassalle M, Mercier G, et al: Platinum compound-related ototoxicity in children: long-term follow-up reveals continuous worsening of hearing loss. J Pediatr Hematol Oncol 26:649-55, 2004
29. Knight KRG, Kraemer DF, Neuwelt EA: Ototoxicity in children receiving platinum chemotherapy: underestimating a commonly occurring toxicity that may influence academic and social development. Journal of Clinical Oncology 23:8588-8596, 2005
30. Ruggiero A, Trombatore G, Triarico S, et al: Platinum compounds in children with cancer: toxicity and clinical management. Anticancer Drugs 24:1007-19, 2013
31. Kushalnagar P, Topolski TD, Schick B, et al: Mode of communication, perceived level of understanding, and perceived quality of life in youth who are deaf or hard of hearing. J Deaf Stud Deaf Educ 16:512-23, 2011
32. Bess FH, Dodd-Murphy J, Parker RA: Children with minimal sensorineural hearing loss: prevalence, educational performance, and functional status. Ear Hear 19:339-54, 1998
33. Wake M, Hughes EK, Collins CM, et al: Parent-reported health-related quality of life in children with congenital hearing loss: a population study. Ambul Pediatr 4:411-7, 2004
34. Einarsson E-J, Petersen H, Wiebe T, et al: Severe difficulties with word recognition in noise after platinum chemotherapy in childhood, and improvements with open-fitting hearing-aids. International Journal of Audiology 50:642-651, 2011
35. Liberman PHP, Schultz C, Goffi-Gomez MVS, et al: Speech recognition and frequency of hearing loss in patients treated for cancer in childhood. Pediatric Blood & Cancer 60:1709-1713, 2013
36. Heitzer AM, Villagran AM, Raghubar K, et al: Effect of sensorineural hearing loss on neurocognitive and adaptive functioning in survivors of pediatric embryonal brain tumor. Journal of Neuro-Oncology 146:147-156, 2020
37. Olivier TW, Bass JK, Ashford JM, et al: Cognitive Implications of Ototoxicity in Pediatric Patients With Embryonal Brain Tumors. Journal of Clinical Oncology 37:1566-1575, 2019

38. Orgel E, O'Neil SH, Kayser K, et al: Effect of Sensorineural Hearing Loss on Neurocognitive Functioning in Pediatric Brain Tumor Survivors. Pediatr Blood Cancer 63:527-34, 2016
39. Moxon-Emre I, Dahl C, Ramaswamy V, et al: Hearing loss and intellectual outcome in children treated for embryonal brain tumors: Implications for young children treated with radiation sparing approaches. Cancer Medicine, 2021
40. Gurney JG, Tersak JM, Ness KK, et al: Hearing loss, quality of life, and academic problems in long-term neuroblastoma survivors: a report from the Children's Oncology Group. Pediatrics 120:e1229-36, 2007
41. Brinkman TM, Bass JK, Li Z, et al: Treatment-induced hearing loss and adult social outcomes in survivors of childhood CNS and non-CNS solid tumors: Results from the St. Jude Lifetime Cohort Study. Cancer 121:4053-61, 2015
42. Khan A, Mubdi N, Budnick A, et al: The experience of hearing loss in adult survivors of childhood and young adult cancer: A qualitative study. Cancer 126:1776-1783, 2020
43. Breglio AM, Rusheen AE, Shide ED, et al: Cisplatin is retained in the cochlea indefinitely following chemotherapy. Nature Communications 8, 2017
44. Ding D, Jiang H, Zhang J, et al: Cisplatin-induced vestibular hair cell lesion-less damage at high doses. J Otol 13:115-121, 2018
45. Kobayashi H, Ohashi N, Watanabe Y, et al: Clinical features of cisplatin vestibulotoxicity and hearing loss. ORL J Otorhinolaryngol Relat Spec 49:67-72, 1987
46. Buchman CA, Joy J, Hodges A, et al: Vestibular effects of cochlear implantation. Laryngoscope 114:1-22, 2004
47. Cushing SL, Gordon KA, Rutka JA, et al: Vestibular end-organ dysfunction in children with sensorineural hearing loss and cochlear implants: an expanded cohort and etiologic assessment. Otol Neurotol 34:422-8, 2013
48. Licameli G, Zhou G, Kenna MA: Disturbance of vestibular function attributable to cochlear implantation in children. Laryngoscope 119:740-5, 2009
49. Cushing SL, Papsin BC, Rutka JA, et al: Vestibular end-organ and balance deficits after meningitis and cochlear implantation in children correlate poorly with functional outcome. Otol Neurotol 30:488-95, 2009
50. Camet ML, Hayashi SS, Sinks BC, et al: Determining the prevalence of vestibular screening failures in pediatric cancer patients whose therapies include radiation to the head/neck and platin-based therapies: A pilot study. Pediatric Blood & Cancer 65:e26992, 2018
51. Sokolov M, Gordon KA, Polonenko M, et al: Vestibular and balance function is often impaired in children with profound unilateral sensorineural hearing loss. Hear Res, 2018
52. Piscione PJ, Bouffet E, Mabbott DJ, et al: Physical functioning in pediatric survivors of childhood posterior fossa brain tumors. Neuro Oncol 16:147-55, 2014
53. Varedi M, Lu L, Phillips NS, et al: Balance impairment in survivors of pediatric brain cancers: risk factors and associated physical limitations. Journal of Cancer Survivorship 15:311-324, 2021
54. Muir SW, Berg K, Chesworth B, et al: Quantifying the magnitude of risk for balance impairment on falls in community-dwelling older adults: a systematic review and meta-analysis. J Clin Epidemiol 63:389-406, 2010
55. Ganz DA, Bao Y, Shekelle PG, et al: Will my patient fall? JAMA 297:77-86, 2007
56. Hill KD, Goldie PA, Baker PA, et al: Retest reliability of the temporal and distance characteristics of hemiplegic gait using a footswitch system. Archives of Physical Medicine and Rehabilitation 75:577-83, 1994
57. Brown CJ, Flood KL: Mobility limitation in the older patient: a clinical review. JAMA 310:1168-77, 2013

58. Morita S, Suzuki M, Iizuka K: A comparison of the short-term outcome in patients with acute low-tone sensorineural hearing loss. ORL J Otorhinolaryngol Relat Spec 72:295-9, 2010
59. Sharma A, Dorman MF, Kral A: The influence of a sensitive period on central auditory development in children with unilateral and bilateral cochlear implants. Hear Res 203:134-43, 2005
60. Dancer J, Burl NT, Waters S: Effects of unilateral hearing loss on teacher responses to the SIFTER. Screening Instrument for Targeting Educational Risk. Am Ann Deaf 140:291-4, 1995
61. Windebank AJ, Grisold W: Chemotherapy-induced neuropathy. J Peripher Nerv Syst 13:27-46, 2008
62. Legha SS: Vincristine neurotoxicity. Pathophysiology and management. Med Toxicol 1:421-7, 1986
63. Quasthoff S, Hartung HP: Chemotherapy-induced peripheral neuropathy. J Neurol 249:9-17, 2002
64. Jain P, Gulati S, Seth R, et al: Vincristine-induced neuropathy in childhood ALL (acute lymphoblastic leukemia) survivors: prevalence and electrophysiological characteristics. J Child Neurol 29:932-7, 2014
65. Ramchandren S, Leonard M, Mody RJ, et al: Peripheral neuropathy in survivors of childhood acute lymphoblastic leukemia. J Peripher Nerv Syst 14:184-9, 2009
66. Gomber S, Dewan P, Chhonker D: Vincristine induced neurotoxicity in cancer patients. Indian J Pediatr 77:97-100, 2010
67. Mohrmann C, Armer J, Hayashi RJ: Challenges Evaluating Chemotherapy-Induced Peripheral Neuropathy in Childhood Cancer Survivors. J Pediatr Oncol Nurs 34:106-114, 2017
68. Ness KK, Hudson MM, Pui CH, et al: Neuromuscular impairments in adult survivors of childhood acute lymphoblastic leukemia: associations with physical performance and chemotherapy doses. Cancer 118:828-38, 2012
69. Ness KK, Jones KE, Smith WA, et al: Chemotherapy-related neuropathic symptoms and functional impairment in adult survivors of extracranial solid tumors of childhood: results from the St. Jude Lifetime Cohort Study. Archives of Physical Medicine and Rehabilitation 94:1451-7, 2013
70. Rodwin RL, Chen Y, Yasui Y, et al: Longitudinal Evaluation of Neuromuscular Dysfunction in Long-term Survivors of Childhood Cancer: A Report from the Childhood Cancer Survivor Study. Cancer Epidemiology, Biomarkers and Prevention 30:1536-1545, 2021
71. Anderson DM, Rennie KM, Ziegler RS, et al: Medical and neurocognitive late effects among survivors of childhood central nervous system tumors. Cancer 92:2709-19, 2001
72. Packer RJ, Gurney JG, Punyko JA, et al: Long-term neurologic and neurosensory sequelae in adult survivors of a childhood brain tumor: childhood cancer survivor study. Journal of Clinical Oncology 21:3255-61, 2003
73. Schultz KA, Ness KK, Whitton J, et al: Behavioral and social outcomes in adolescent survivors of childhood cancer: a report from the childhood cancer survivor study. Journal of Clinical Oncology 25:3649-56, 2007
74. Ellenberg L, Liu Q, Gioia G, et al: Neurocognitive status in long-term survivors of childhood CNS malignancies: a report from the Childhood Cancer Survivor Study. Neuropsychology 23:705-717, 2009
75. Tonning Olsson I, Brinkman TM, Wang M, et al: Neurocognitive and psychosocial outcomes in adult survivors of childhood soft-tissue sarcoma: A report from the St. Jude Lifetime Cohort. Cancer 126:1576-1584, 2020

76. Armstrong NM, Wang H, E J-Y, et al: Patterns of Prevalence of Multiple Sensory Impairments Among Community-dwelling Older Adults. The Journals of Gerontology: Series A 77:2123-2132, 2022
77. Brenowitz WD, Kaup AR, Lin FR, et al: Multiple Sensory Impairment Is Associated With Increased Risk of Dementia Among Black and White Older Adults. The Journals of Gerontology: Series A 74:890-896, 2019
78. Liljas AEM, Jones A, Cadar D, et al: Association of Multisensory Impairment With Quality of Life and Depression in English Older Adults. JAMA Otolaryngol Head Neck Surg 146:278-285, 2020
79. Geenen MM, Cardous-Ubbink MC, Kremer LC, et al: Medical assessment of adverse health outcomes in long-term survivors of childhood cancer. JAMA 297:2705-2715, 2007
80. Lubas MM, Mandrell BN, Ness KK, et al: Short sleep duration and physical and psychological health outcomes among adult survivors of childhood cancer. Pediatric Blood & Cancer 68:e28988, 2021
81. Williams AM, Cheung YT, Hyun G, et al: Childhood neurotoxicity and brain resilience to adverse events during adulthood. Annals of Neurology 89:534-545, 2021
82. Horan MR, Srivastava DK, Bhakta N, et al: Determinants of health-related quality-of-life in adult survivors of childhood cancer: integrating personal and societal values through a health utility approach. EClinicalMedicine 58:101921, 2023
83. Green KA, McGwin G, Owsley C: Associations Between Visual, Hearing, and Dual Sensory Impairments and History of Motor Vehicle Collision Involvement of Older Drivers. Journal of the American Geriatrics Society 61:252-257, 2013
84. Ogliari G, Ryg J, Qureshi N, et al: Subjective vision and hearing impairment and falls among community-dwelling adults: a prospective study in the Survey of Health, Ageing and Retirement in Europe (SHARE). European Geriatric Medicine 12:1031-1043, 2021
85. Camidge DR, Stockton DL, Frame S, et al: Hospital admissions and deaths relating to deliberate self-harm and accidents within 5 years of a cancer diagnosis: a national study in Scotland, UK. British Journal of Cancer 96:752-757, 2007
86. Geenen MM, Cardous-Ubbink MC, Kremer LC, et al: Medical assessment of adverse health outcomes in long-term survivors of childhood cancer. JAMA 297:2705-15, 2007