Longitudinal changes in functional independence in aging adult survivors of pediatric brain tumors

WORKING GROUPS:
Primary: Psychology
Secondary: Chronic Disease

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BACKGROUND AND RATIONALE:

Brain and central nervous system (CNS) tumors are the most common solid tumors in infants and children 0-14 years old, with an incidence of 5.26 per 100,000 in the United States and a current five-year survival rate of approximately 72.6%.[1] While the majority of pediatric patients become long term survivors,[2,3] this group is the most functionally impaired among any pediatric neoplasms and are more likely to have multiple chronic health conditions.[4] Effects of tumor location within the CNS and CNS-directed therapies include increased risk for late mortality, subsequent neoplasms, endocrinopathies, musculoskeletal abnormalities, sensory and neurologic deficits, neurocognitive impairment, and physical performance limitations, among others.[5-10]

As survivors of CNS tumors are now aging into adulthood, the inability of many to achieve independence is becoming apparent. Independence can be characterized by activities (self-care, independent living), social engagement (partnership/marriage), and economic autonomy (education, employment). We recently examined indicators of functional independence in approximately 300 adult survivors of childhood CNS tumors who are part of the St. Jude Lifetime Cohort Study (SJLIFE).[11] Three unique classes of independence were identified (independent, moderately independent, non-independent) and 60% of survivors were classified as either moderately independent or non-independent. In multivariable models, craniospinal irradiation and younger age at diagnosis were associated with risk of nonindependence versus independence. Beyond impaired IQ, limitations in aerobic capacity, flexibility and adaptive physical function were associated with nonindependence versus independence. Nonindependent survivors reported reduced physical but not mental health-related quality of life compared with independent survivors. However, it remains unclear how independence changes as survivors age. Long-term survivors of CNS tumors continue to be at-risk for late onset neurological morbidities[7,8] and these may contribute to worsened functional independence over time.

The original Childhood Cancer Survivor Study (CCSS) cohort includes over 1,800 adult survivors of childhood CNS tumors.[6] In this study we propose to develop latent classes of functional and social independence using the six observed indicators: independent living; employment/unable to attend school or work because of an impairment or health problem; marital status, assistance with

personal care needs such as eating, bathing, dressing or getting around your home; assistance with routine needs such as everyday chores, doing necessary business, shopping or getting around for other purposes; and currently holding a driver's license. We will also examine change in class membership over time as well as examine treatment exposures and late health morbidities associated with change in class membership over time. Understanding risk factors for and patterns of functional independence in survivors may inform intervention strategies and supportive care measures for survivors going forward.

SPECIFIC AIMS:

Aim 1: To identify/confirm latent classes of functional independence in adult survivors of pediatric brain tumors.

Hypothesis: Three previously established latent classes of functional independence identified in the SJLIFE cohort will be validated in the CCSS cohort.

Aim 2: To identify change in class membership over time.

Hypothesis: The majority of survivors will remain in the same class or will move to a less functionally independent class over time (as they age).

Aim 3: To determine the impact of treatment exposures and chronic conditions associated with changes in class membership over time.

Hypothesis: Risk for persistent non-independence and worsening independence will be greatest in survivors who received craniospinal irradiation and survivors with the highest cumulative prevalence and severity of chronic health conditions, particularly new onset conditions.

Aim 4: To examine the association between declining independence with health-related quality of life and emotional distress.

Hypothesis: Survivors who have worsening independence over time (e.g., move from moderately independent to non-independent) will report poorer health related quality of life and greater symptoms of emotional distress than survivors who remain independent over time.

Exploratory Aim: To examine baseline classes of functional independence in the expansion cohort and compare these to baseline classes of functional independence in the original cohort.

Hypotheseis: The prevalence of survivors identified as non-independent will be lower in the expansion cohort compared to the original cohort.

ANALYSIS FRAMEWORK:

Study population: Adult survivors in the original CCSS cohort, diagnosed with a primary brain tumor who completed baseline, FU4, and/or FU 5 (baseline and at least one follow-up survey). Adult survivors in the expansion cohort, diagnosed with a primary brain tumor, who completed a baseline survey.

Exclusion criteria: Genetic syndromes associated with cognitive impairment unrelated to primary cancer diagnosis, e.g. Klinefelter or Turner.

Primary outcome: Classes of functional and social independence

Indicators:

1) Independent living (yes/no) B A9 E A9 (Yes – Own/Rent, No – Live with Parents) F4 M1 F5 M1(Yes – Live with spouse/partner/roommates/siblings/alone, No – live with parents, relatives)
2) Impairment/Health Problem Prevent Work/School (yes/no) B N11 E O18 F4 N24 F5 N27
3) Marital Status (yes/no) B L1 E M2, F4 M2 F5 M2 (Yes – married/living with partner/widowed/divorced'/separated, No – single)
4) Assistance with personal care needs (yes/no) B N10 E O16 F4 N22 F5 N25
5) Assistance with routine needs (yes/no) B N11 EO17 F4 N23 F5 N26
6) Current driver's license (yes/no) B N13 E O19 F4 N25 F5 N28

Treatment exposures:

- Diagnosis
  - Astrocytoma
  - Medulloblastoma
  - Ependymoma
  - Craniopharyngioma
  - Other

- Radiation Exposure
  - Maximum target dose (maxTD) to 4 regions: frontal, temporal, posterior fossa, parieto-occipital regions
  - Craniospinal Irradiation (CSI) total dose

- Chemotherapy:
  - Alkylating agents (cyclophosphamide equivalent dose (mg/m2)) (mean, IQR)
  - Cisplatin cumulative dose (mg/m2) (mean, IQR)
  - Carboplatin cumulative dose (mg/m2) (mean, IQR)
  - Lomustine cumulative dose (mg/m2) (mean, IQR)
  - Vincristine cumulative dose (mg/m2) (mean, IQR)

- Surgical resection
  - No
  - Yes

- Extraventricular shunt
  - No
  - Yes

Chronic health conditions (CHC) and SMN:

1) Overall CHC: Using CTCAE grading, survivors will be classified as having:
   a) no CHC
   b) any grade 2-4 CHC
   c) any grade 3-4 CHC

d) >1 grade 3-4 CHC

2) Specific CHC: Any grade 2-4 CHC in the following categories will be considered:
   a) endocrine
   b) cardiac
   c) pulmonary
   d) neurologic
   e) hearing
   f) vision
   g) speech

3) Any Subsequent Malignant Neoplasm

We will consider conditions that were present at baseline as well as new onset conditions (date of onset reported after baseline but before the survey from which functional independence is gleaned for each analysis). We will also examine the prevalence of Grade 2 conditions to determine the appropriateness of including those in our multivariable models.

Covariates

- Age at diagnosis (years, continuous)
- Age at evaluation (years, continuous)
- Race/ethnicity (White/non-Hispanic vs. other)
- Sex
- Disease relapse/subsequent malignant neoplasms
- Genetic syndromes related to cancer, e.g. Neurofibromatosis or Tuberous sclerosis

Health-related Quality of Life (HRQOL) will be assessed using SF-36

- Physical function
- Role limitations due to physical health problems
- Bodily pain
- General health
- Vitality
- Social functioning
- Role limitations due to emotional problems
- Emotional well-being

T-scores <40 on will be considered to represent reduced HRQoL. We will examine each subscale independently.

Emotional distress

- Psychological distress (anxiety, depression and somatization) will be measured with the BSI-18. T-scores $\geq$63 will be considered to represent significant emotional distress symptoms and classified as “yes” otherwise this will be classified as “no”. We will examine each subscale independently.). B J16-25, 26, 27, 29-35, E K1-18, F4 L1-18, F5 L1-18

Statistical Approach

For Aim 1, latent class analysis using the five observed indicators of independence will be used to identify classes of independence at baseline. We identified three classes in the SJLIFE analysis

(non-independent, moderately independent, independent) and will look to confirm these 3 groups in CCSS.

For Aim 2, we will repeat the latent class analysis as described for Aim 1 using five observed indicators measured at FU4 or FU5. If both are available we will use the most recent data (providing the longest interval of follow-up). We will examine the proportion of survivors who report 1) stable independence [stable independent vs. stable non-independent] this will be defined as staying in the same groups at both assessment time points, 2) improved independence, defined as a) moving from non-independent to moderately independent and b) moving from moderately independent to independent, and 3) worsened independence, defined as a) moving from independent to moderately independent or non-independent and b) moving from moderately independent to non-independent.

For Aim 3, we will utilize multivariable log binomial models (or modified Poisson regression) to examine treatment exposures and chronic health conditions (including new onset conditions) associated with stable non-independence and worsened dependence compared to stable independence. If there are enough events we also will examine exposures associated with improved independence. Prevalence Ratios (PR) and 95% confidence intervals (95% CIs) will be calculated.

For Aim 4, we will utilize multivariable log binomial models (or modified Poisson regression) to examine associations between stable non-independence and worsening independence (vs. stable independence) and binary measures of reduced health related quality of life (T-scores <40) and symptoms of emotional distress (T-scores $\geq$63). Prevalence Ratios (PR) and 95% confidence intervals (95% CIs) will be calculated.

List of Tables

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Demographic and Treatment Characteristics of the Cohorts

Characteristic	Baseline	Expansion
Diagnosis		
Astrocytoma		
Medulloblastoma		
Ependymoma		
Craniopharyngioma		
Other		
Age at Diagnosis (N,%)		
<5years		
5-9.9years		
10-14.9years		
≥15years		
Age at Most Recent Evaluation (N,%)		
<20 years		
20 – 29.0 years		
30 – 39.9 years		
≥40 years		
Race/Ethnicity (N,%)		
Non-Hispanic White		
Non-Hispanic Black		
Hispanic		
Other		
Sex (N,%)		
Male		
Female		
NF Status (N,%)		
Neurofibromatosis type 1 (NF1) negative		
Neurofibromatosis type 1 (NF1) positive		
Surgical Resection		
Yes		
No		
Chemotherapy Exposure		
Alkylating agents (cyclophosphamide equivalent dose (mg/m2)) (mean, IQR)		
Cisplatin cumulative dose (mg/m2) (mean, IQR)		
Carboplatin cumulative dose (mg/m2) (mean, IQR)		
Lomustine cumulative dose (mg/m2) (mean, IQR)		
Vincristine cumulative dose (mg/m2) (mean, IQR)		
Radiation exposure		
None		
Maximum dose to 4 regions (frontal, posterior fossa, parieto-occipital)		
CST total dose		
Extraventricular Shunt		
Yes		
No		

Indicators of Functional Independence at Baseline - Original Cohort						
	Living Independently	Full Time Employment	Married	Assistance with Personal Care Needs	Assistance with Routine Needs	Active Drivers License
	% Yes	% Yes, No, Part Time	% Yes	% Yes	% Yes	% Yes
Class 1: Independent						
%in class						
Class 2: Moderately Independent						
%in class						
Class 3: Non-Independent						
%in class						

Indicators of Functional Independence at Baseline – Expansion Cohort					

	Living Independently	Full Time Employment	Married	Assistance with Personal Care Needs	Assistance with Routine Needs	Active Drivers License
	% Yes	% Yes, No, Part Time	% Yes	% Yes	% Yes	% Yes
Class 1: Independent						
%in class						
Class 2: Moderately Independent						
%in class						
Class 3: Non-Independent						
%in class						

Diagnosis and Treatment Characteristics by Classes of Independence – Original Cohort	Class 1: Independent		Class 2: Moderately Independent		Class 3: Non-Independent
Characteristic	%in class		%in class		%in class
Sex					
Age					
Age at diagnosis					
Time since diagnosis					
Diagnosis					
Astrocytoma					
Medulloblastoma					
Ependymoma					
Craniopharyngioma					
Other					
Surgical Resection					
Yes					
No					
Chemotherapy Exposure					
Alkylating agents (cyclophosphamide equivalent dose (mg/m2)) (mean, IQR)					
Cisplatin cumulative dose (mg/m2) (mean, IQR)					
Carboplatin cumulative dose (mg/m2) (mean, IQR)					
Lomustine cumulative dose (mg/m2) (mean, IQR)					
Vincristine cumulative dose (mg/m2) (mean, IQR)					
Radiation exposure					
None					
Maximum dose to 4 regions (frontal, posterior fossa, parieto-occipital)					
CST total dose					
Extraventricular Shunt					
Yes					
No					

Diagnosis and Treatment Characteristics by Classes of Independence – Expansion Cohort	Class 1: Independent		Class 2: Moderately Independent		Class 3: Non-Independent
Characteristic	%in class		%in class		%in class
Sex					
Age					
Age at diagnosis					
Time since diagnosis					
Diagnosis					
Astrocytoma					
Medulloblastoma					
Ependymoma					
Craniopharyngioma					
Other					
Surgical Resection					
Yes					
No					
Chemotherapy Exposure					
Alkylating agents (cyclophosphamide equivalent dose (mg/m2)) (mean, IQR)					
Cisplatin cumulative dose (mg/m2) (mean, IQR)					
Carboplatin cumulative dose (mg/m2) (mean, IQR)					
Lomustine cumulative dose (mg/m2) (mean, IQR)					
Vincristine cumulative dose (mg/m2) (mean, IQR)					
Radiation exposure					
None					
Maximum dose to 4 regions (frontal, posterior fossa, parieto-occipital)					
CST total dose					
Extraventricular Shunt					
Yes					
No					

Classes of Functional Independence at Follow Up (FU4 or FU5) – Original Cohort						
	Living Independently	Full Time Employment	Married	Assistance with Personal Care Needs	Assistance with Routine Needs	Active Drivers License
	% Yes	% Yes, No, Part Time	% Yes	% Yes	% Yes	% Yes
Class 1: Stable Independence						
% stable independent						
% stable non-independent						
Class 2: Improved Independence						
%in class						
Class 3: Worsened Independence						
%in class						

Prevalence of Cronic Health Conditions - Original Cohort												
	No CHC	Any grade 2-4	Any grade 3-4	>1 Grade 3-4	Any Grade 2-4 Endocrine CHC	Any Grade 2-4 Cardiac CHC	Any Grade 2-4 Pulmonary CHC	Any Grade 2-4 Neurological CHC	Any Grade 2-4 Vision CHC	Any Grade 2-4 Hearing CHC	Any Grade 2-4 Speech CHC	Any SMN
Characteristic		HR [95% CI]	HR [95% CI]	HR [95% CI]	HR [95% CI]	HR [95% CI]	HR [95% CI]	HR [95% CI]	HR [95% CI]	HR [95% CI]	HR [95% CI]	
Diagnosis												
Astrocytoma												
Medulloblastoma												
Ependymoma												
Craniopharyngioma												
Other												
Surgical Resection												
Yes												
No												
Chemotherapy Exposure												
Alkylating agents (cyclophosphamide equivalent dose (mg/m2)) (mean, IQR)												
Cisplatin cumulative dose (mg/m2) (mean, IQR)												
Carboplatin cumulative dose (mg/m2) (mean, IQR)												
Lomustine cumulative dose (mg/m2) (mean, IQR)												
Vincristine cumulative dose (mg/m2) (mean, IQR)												

Radiation exposure												
None												
Maximum dose to 4 regions (frontal, posterior fossa, parieto-occipital)												
CST total dose												
Extraventricular Shunt												
Yes												
No												

Prevalence of Cronic Health Conditions - Expansion Cohort												
	No CHC	Any grade 2-4	Any grade 3-4	>1 Grade 3-4	Any Grade 2-4 Endocrine CHC	Any Grade 2-4 Cardiac CHC	Any Grade 2-4 Pulmonary CHC	Any Grade 2-4 Neurological CHC	Any Grade 2-4 Vision CHC	Any Grade 2-4 Hearing CHC	Any Grade 2-4 Speech CHC	Any SMN
Characteristic		HR [95% CI]	HR [95% CI]	HR [95% CI]	HR [95% CI]	HR [95% CI]	HR [95% CI]	HR [95% CI]	HR [95% CI]	HR [95% CI]	HR [95% CI]	
Diagnosis												
Astrocytoma												
Medulloblastoma												
Ependymoma												
Craniopharyngioma												
Other												
Surgical Resection												
Yes												
No												
Chemotherapy Exposure												
Alkylating agents (cyclophosphamide equivalent dose (mg/m2)) (mean, IQR)												
Cisplatin cumulative dose (mg/m2) (mean, IQR)												
Carboplatin cumulative dose (mg/m2) (mean, IQR)												
Lomustine cumulative dose (mg/m2) (mean, IQR)												
Vincristine cumulative dose (mg/m2) (mean, IQR)												

Radiation exposure												
None												
Maximum dose to 4 regions (frontal, posterior fossa, parieto-occipital)												
CST total dose												
Extraventricular Shunt												
Yes												
No												

* adjusted for sex, race, age at diagnosis, disease relapse/second malignant neoplasms, NF1/TS status				
Class Change and Treatment Exposures/Chronic Health Conditions – Original Cohort				
Characteristic	Stable Independent	Stable Non-Independent	Improved Independence	Worsened Independence
Diagnosis	OR [95%CI]	OR [95%CI]	OR [95%CI]	OR [95%CI]
Astrocytoma				
Medulloblastoma				
Ependymoma				
Craniopharyngioma				
Other				
Surgical Resection				
Yes				
No				
Chemotherapy Exposure				
Alkylating agents (cyclophosphamide equivalent dose (mg/m2)) (mean, IQR)				
Cisplatin cumulative dose (mg/m2) (mean, IQR)				
Carboplatin cumulative dose (mg/m2) (mean, IQR)				
Lomustine cumulative dose (mg/m2) (mean, IQR)				
Vincristine cumulative dose (mg/m2) (mean, IQR)				
Radiation exposure				
None				
Maximum dose to 4 regions (frontal, posterior fossa, parieto-occipital)				
CST total dose				
Extraventricular Shunt				
Yes				
No				
CHC				
No CHC				
Any grade 2-4				
Any grade 3-4				
>1 Grade 3-4				
Any Grade 2-4 Endocrine CHC				
Any Grade 2-4 Cardiac CHC				
Any Grade 2-4 Pulmonary CHC				
Any Grade 2-4 Neurological CHC				
Any Grade 2-4 Vision CHC				

Any Grade 2-4 Hearing CHC				
Any Grade 2-4 Speech CHC				
Any SMN				

Associations Between Independence and HRQOL/Emotional Distress Original Cohort				
	Stable Independent	Stable Non-Independent	Improved Independence	Worsened Independence
	OR [95%CI]	OR [95%CI]	OR [95%CI]	OR [95%CI]
Health Related Quality of Life				
Physical Component Summary Scores				
Mental Component Summary Scores				
Emotional Distress				