1. STUDY TITLE: The Impact of Vision Loss Among Childhood Survivors of Central Nervous System Astroglial Tumors

2. WORKING GROUP AND INVESTIGATORS:
   2.1. Working Group: Psychology
   2.2. Investigators:

Peter de Blank	peter.deblank@uhhospitals.org
Kevin Krull	kevin.krull@stjude.org
Chuck Sklar	sklarc@mskcc.org
Wendy Leisenring	wleisenr@fhcrc.org
Marilyn Stovall	mstovall@mdanderson.org
Les Robison	les.robison@stjude.org
Greg Armstrong	greg.armstrong@stjude.org
Michael Fisher	fisherm@email.chop.edu

3. BACKGROUND AND RATIONALE

Astroglial tumors are the most common brain tumor in children.[1] Depending on their location, these tumors can cause vision loss by direct infiltration of the visual pathways (as optic pathway gliomas) or indirect compression or damage of visual circuits. Fortunately, low grade astroglial tumors are associated with prolonged patient survival,[2] even in cases where surgical resection is not practical,[3] and only a portion of those tumors that threaten vision will become symptomatic.[4] Therefore, treatment of astroglial tumors that threaten vision is often focused on preserving vision. Vision loss due to astroglial tumors frequently occurs at a young age,[5] and is often permanent and uncorrectable with corrective lenses. Radiation and chemotherapy have been used to help preserve vision and halt growth of astroglial tumors. However, radiation therapy of CNS tumors can result in endocrine dysfunction, stroke, secondary malignant neoplasm and neurocognitive deficits in young children.[6, 7] Chemotherapy with carboplatin and vincristine is better tolerated but exposes children to cytopenias, peripheral neuropathies, infection and hypersensitivity reactions.[8] To better advise patients with progressive astroglial tumors that threaten vision regarding the risks and benefits of therapy, we must first understand the long-term effect of childhood vision loss.

Studies investigating the impact of tumor-associated vision loss are missing in the medical literature, and existing studies of all-cause vision loss typically focus on adult populations. In two related studies about adults from the 1958 British birth cohort, Rahi and colleagues found that all-cause visual impairment among adults was associated with increased odds of unemployment, lower socioeconomic status and worse mental health.[9] Likewise, impaired vision-related quality of life (VRQoL) was independently associated with the inability to work and not being married.[10] In these studies, nearly 1/5 of the total burden of visual impairment is disproportionately found in the 1/1000 participants who were blind. However, these studies also find that vision loss is not associated with decreased participation in social organizations, increased risk of unintentional injury, or likelihood of having children.

The impact of all-cause blindness in children has not been well defined.[11, 12] While VRQoL is decreased in children with visual impairment compared to age-matched

controls,[13] there is wide variability in this measure suggesting that a portion of visually impaired children experience only minor effects on VRQoL. Other measures of the impact of childhood vision loss are inferred from studies of vision loss in the general population (both childhood- and adult-onset). In the British birth cohort, Rahi notes that only 7.1% of adults who report severe vision loss (of childhood- or adult-onset) have impaired VRQoL. He suggests that impaired VRQoL may be less frequent in this population in part due to adaptation in the portion of subjects who experienced childhood vision loss.[10] The impact of vision loss may vary with age. In a study from the 1995 National Health Interview Survey on Disability, Swanson demonstrates that the greatest effect of visual impairment on activities of daily living and instrumental activities of daily living was seen in younger subjects.[14] However, studies of the effect of amblyopia demonstrate that vision loss at a young age is associated with decreased academic performance[15] and worse psychosocial distress in adults.[16]

The impact of vision loss in children with low-grade gliomas has not been studied. It is possible that these children, who suffer from a greater number of "blind years" and have significant neurologic comorbidities, may be disproportionately affected in quality of life and educational, economic and social measures. Alternatively, they may have more ready access to social supports that help them adapt to their visual impairments. Vision loss due to CNS tumors represents a unique group of childhood visual impairments with unique comorbidities (including neurofibromatosis type 1 and treatment) and timing of onset that may be significantly different from congenitally blind children or vision loss due to other causes. In this proposal, we focus on vision loss associated with low grade gliomas because visual acuity loss is a frequent indication for treatment of these tumors.[17] It is therefore imperative to understand the subjective (psychological) and objective (socioeconomic) impact of vision loss in patients with optic pathway gliomas and to explore the change in these effects over time in order to better advise patients and their families about the risks and benefits of therapy.

The population of CNS survivors in the CCSS population is the ideal cohort in which to study this question. The size of the CCSS cohort ensures that adequate numbers of survivors of astroglial tumors with and without vision loss (236 and 997, respectively, in unpublished data from the 2008 Follow-Up Survey (Elizabeth Wells)) are available. These investigations will review a sub-cohort who experienced vision loss by 2003, but this group will still represent one of the largest collections of astroglial survivors yet assessed. In addition, the CCSS has detailed information on outcomes as well as potentially important confounding variables. The current proposal is designed to describe the psychological and socioeconomic effects of vision loss associated with low-grade gliomas among survivors of childhood cancer. We will examine how the impact of vision loss differs between childhood- and adult-onset, and explore potential factors that influence this difference. To our knowledge, this study represents the first effort to focus directly on the impact of vision loss in low-grade gliomas and the data generated will inform treatment decisions of current patients and guide early intervention efforts to reduce the impact of vision loss.

4. SPECIFIC AIMS/OBJECTIVES/RESEARCH HYPOTHESES:

4.1. Primary Aims:

4.1.1. Evaluate the cumulative incidence of vision loss among survivors of astroglial tumors

4.1.2 Compare psychologic and socioeconomic outcomes among survivors of astroglial tumors with and without vision loss.

4.2. Secondary Aims:

4.2.1. Explore the effect of age of vision impairment on psychological and socioeconomic outcomes among childhood survivors of astrocytomas with vision loss.

4.3. Primary Hypothesis:

4.3.1. The cumulative incidence of vision loss will continue to rise as years from diagnosis increases in survivors of astroglial tumors.

4.3.1. In a model adjusting for age at diagnosis, age at interview, gender, cranial radiation, and medical comorbidities, vision loss will be associated with increased risk of lower health-related quality of life, life satisfaction, employment, annual income and educational level.

4.4. Secondary Hypotheses:

4.4.1. In a model controlling for age at diagnosis, age at interview, gender, cranial radiation, and medical comorbidities, older age of vision loss will be independently associated with increased risk of lower income, rate of employment, and health-related quality of life among survivors of astroglial tumors with vision loss.

ANALYSIS FRAMEWORK:

5.1 Primary Outcome Variables:

5.1.1. Psychological

5.1.1.1. SF-36: Health-related quality of life will be measured with the Medical Outcomes Survey Short Form-36 (SF-36). The SF-36 has two summary scales (physical component summary and mental component summary) that are presented at T scores with a mean score of 50 and a standard deviation of 10. Scores will be dichotomized with T scores less than 40 identified as impaired.

5.1.1.2. BSI-18: Psychological distress will be measured with the Brief Symptom Inventory-18 (BSI-18). Subscales of depression, anxiety and somatization, as well as the summary scale (Global Distress Index) will be dichotomized with impairment defined as a performance falling at or below the 10^{th} percentile based on standardized norms. Only the Global Distress Index will be considered for multivariate analysis in order to reduce the number of comparisons tested.

5.1.1.3. Cantril Ladder of Life: Life satisfaction will be measured with the Cantril Ladder of Life (present), which will be dichotomized as ≥ 7 or <7.

5.1.1.4. CCSS NCQ: Task Efficiency, Emotional Regulation, Organization, Memory. Factor scores will be dichotomized based on whether the

performance is considered impaired or not (yes/no), with impairment defined as a performance falling ≤ 10^{th} percentile compared to the sibling group.

5.1.2. Socioeconomic

5.1.2.1. Married: Marital status will be dichotomized from question 2 of the 2003 follow-up. Married (yes) will be defined as responses that include "married," "widowed," "divorced," and "separated or no longer living as married."

5.1.2.2. Independent living: Independent living will be dichotomized from question 3 of the 2003 follow-up. Living Independently (yes) will be defined as responses that include "live with spouse/partner" or "live alone"

5.1.2.3. Employment: Employment will be dichotomized from question 4 of the 2003 follow-up. Employed (yes) will be defined as responses that include "working full-time" and "working part-time."

5.1.2.4. Income: Income will be dichotomized from question S3 in the 2003 follow-up questionnaire. Income <$20,000 (yes) will be defined as responses that include "less than $19,999" or "none."

5.1.2.5. Education: Educational attainment will be dichotomized from question 1 of the 2003 follow-up. "< College" (yes) will be defined as responses that include "1-8 years (grade school)," "9-12 years (high school)," "completed high school/GED," "Training after high school, other than college."

5.2 . Primary Predictors:

5.2.1. Vision loss: vision loss will be defined categorically (bilateral vision loss, unilateral vision loss, no vision loss) from questions D8 and D9 of the 2007 Follow-Up Survey for Aim 4.1.1. For statistical aims 4.1.2 and 4.2.1, vision loss will be defined as having occurred before 2004 to correspond with primary outcome variables derived from the 2007 Follow Up Survey.

5.3. Covariates

5.3.1. Age at tumor diagnosis: Age at diagnosis will be defined continuously in years.

5.3.2. Age at interview: Age at interview will be defined from the 2003 Follow Up Questionnaire and will be defined categorically as 20-29years, 30-39 years, 40-49years, and ≥50years.

5.3.3. Gender

5.3.4. History of radiation therapy: Distribution of total CNS radiation dose will be examined among the cohort and defined categorically (for example, no cranial radiation, cranial radiation ≤30Gy, cranial radiation >30Gy).

5.3.5. Age of onset of vision loss: defined continuously from question C8 and C9 of the 2007 Follow-up Survey. Because no pre-existing data exists to support an *a priori* dichotomization of this variable, definition of age categories will be exploratory and depend on the distribution of ages in the population (above and below the mean age of vision loss onset).

5.3.6. Medical Comorbidity: dichotomized as yes/no, defined by the presence of any grade 3 or 4 medical conditions occurring before 2004 (excluding vision questions D8-D18) on the 2007 follow-up.

5.4. Related to the specific hypotheses, the following analyses will be conducted:

5.4.1. Frequency distributions will be examined to categorize relevant outcome variables and covariates according to reasonable groupings and consistent with previous CCSS manuscripts to determine whether above categories define a reasonable distribution.

5.4.2 The cumulative incidence of vision loss in survivors of astroglial tumors will be graphed (1) vs. years since diagnosis and (2) vs. age. Secondary plots will show the cumulative incidence of unilateral vision loss and bilateral vision loss vs. years since diagnosis.

5.4.3. Descriptive statistics will be reported for all predictors, outcomes and covariates. (See Table 1).

5.4.4. Comparisons of continuously valued outcome measures will be performed with a one-way ANOVA between categories of visual function (Table 2).

5.4.5. Multivariable logistic regression analyses will be conducted for each binary outcome variable (SF-36, BSI-18, Cantril Ladder of Life, CCSS NCQ, proportion married, proportion living independently, proportion employed, proportion with income $\geq$ \$20,000, proportion with education $\geq$ college as described in 5.1 above) using vision loss as the primary predictor controlling for covariates as indicated above to create adjusted odds ratios for associations between outcomes and vision loss (Table 3).

5.4.6. In the population with vision loss, multivariable logistic regression analyses will be conducted for each outcome variable (SF-36, BSI-18, Cantril Ladder of Life, CCSS NCQ, proportion married, proportion living independently, proportion employed, proportion with income $\geq$ \$20,000, proportion with education $\geq$ college as described in 5.1 above) using age of onset of vision loss as the primary predictor controlling for covariates as indicated above to create adjusted odds ratios for outcomes with age of onset of vision loss (Table 4).

5.5. Subject population:

5.5.1. CCSS survivor cohort for the 2007 Follow-up Survey who also responded to the Follow Up 2003 survey.

5.5.1.1. Inclusion criteria: CCSS survivors of astroglial tumors who completed the psychological or socioeconomic questions from the

Follow Up 2003 survey and have vision data available from the 2007 Follow Up Survey.

5.5.1.2. Exclusion criteria: Survivors with second malignant neoplasms of the CNS that are not astroglial in origin will be excluded.

5.5.1.3. Exclusion criteria: Statistical analysis (Aims 4.2.1 and 4.2.1) will be performed on subjects with vision loss before or during the 2003 Follow Up Survey.

6. TABLES

Table 1. Description of the cohort of survivors of childhood astroglial tumors

Characteristic	Survivors	
	No.	%
Age at Interview, years		
20-29		
30-39		
40-49		
>/=50		
Sex		
Male		
Female		
Age at diagnosis, years		
</=4		
5-9		
>/=10		
Treatment		
Surgery		
Chemotherapy		
Radiation		
Vision Loss		
None		
Unilateral		
Bilateral		
Age at first vision loss, years		
</=18		
>18		

Table 2. Univariate comparison of psychological and socioeconomic outcomes among survivors of childhood astroglial tumors with and without vision loss.

	Vision Status			
	No vision loss N=	Unilateral Vision Loss N=	Bilateral Vision loss N=	P value
Psychological Outcomes				
Health-Related Quality of Life (SF-36)				
Physical Component				
Mental Component				
Psychological Distress (BSI-18)				
Global Distress Index				
Depression				
Anxiety				
Somatization				
Life Satisfaction (Cantril Ladder of Life) <7				
Neurocognitive (CCSS-NCQ)				
Task Efficiency				
Emotional Regulation				
Organization				
Memory				
Socioeconomic Outcomes				
% Married				
% Living Independently				
% Employed				
Income ≤ $20,000				
Education ≥ College				

Table 3. Multivariable analysis of psychological and socioeconomic outcomes among survivors of childhood astroglial tumors

	Psychological Status								Socioeconomic Status				
	SF-36 Physical	SF-36 Mental	BSI-18 Global Distress Index	Cantril Ladder of Life	Task Efficiency	Emotion Regul-ation	Organ-ization	Memory	Not married	Living alone	Not employed	Income ≤ $20,000	Educ-ation ≥ College
Vision Status													
Normal	Ref.	Ref.	Ref.	Ref.	Ref.	Ref.	Ref.	Ref.	Ref.	Ref.	Ref.	Ref.	Ref.
Unilateral Vision Loss													
Bilateral Vision Loss													
Age at Diagnosis													
Age (years)													
Age at Interview, years													
20-29	Ref.	Ref.	Ref.	Ref.	Ref.	Ref.	Ref.	Ref.	Ref.	Ref.	Ref.	Ref.	Ref.
30-39													
40-49													
≥50													
Sex													
Male	Ref.	Ref.	Ref.	Ref.	Ref.	Ref.	Ref.	Ref.	Ref.	Ref.	Ref.	Ref.	Ref.
Female													
Cranial Radiation													
None	Ref.	Ref.	Ref.	Ref.	Ref.	Ref.	Ref.	Ref.	Ref.	Ref.	Ref.	Ref.	Ref.
≤30Gy													
>30Gy													
Medical Comorbidity (Grade 3 or 4)													
No	Ref.	Ref.	Ref.	Ref.	Ref.	Ref.	Ref.	Ref.	Ref.	Ref.	Ref.	Ref.	Ref.
Yes													

Table 4. Multivariable analysis of psychological and socioeconomic outcomes among survivors of childhood astroglial tumors with vision loss, evaluating impact of age at vision loss

	Psychological Status								Socioeconomic Status				
	SF-36 Physical	SF-36 Mental	BSI-18 Global Distress Index	Cantril Ladder of Life	Task Efficiency	Emotion Regul-ation	Organ-ization	Memory	Not married	Living alone	Not employed	Income ≤ $20,000	Educ-ation ≥ College
Vision Status													
Unilateral Vision Loss	Ref.	Ref.	Ref.	Ref.	Ref.	Ref.	Ref.	Ref.	Ref.	Ref.	Ref.	Ref.	Ref.
Bilateral Vision Loss													
Age at Diagnosis													
Age (years)													
Age at Interview, years													
20-29	Ref.	Ref.	Ref.	Ref.	Ref.	Ref.	Ref.	Ref.	Ref.	Ref.	Ref.	Ref.	Ref.
30-39													
40-49													
≥50													
Sex													
Male	Ref.	Ref.	Ref.	Ref.	Ref.	Ref.	Ref.	Ref.	Ref.	Ref.	Ref.	Ref.	Ref.
Female													
Cranial Radiation													
None	Ref.	Ref.	Ref.	Ref.	Ref.	Ref.	Ref.	Ref.	Ref.	Ref.	Ref.	Ref.	Ref.
≤30Gy													
>30Gy													
Medical Comorbidity (Grade 3 or 4)													
No	Ref.	Ref.	Ref.	Ref.	Ref.	Ref.	Ref.	Ref.	Ref.	Ref.	Ref.	Ref.	Ref.
Yes													
Age of Onset of Vision Loss, years													
Age (years)													

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