Childhood Cancer Survivor Study Analysis Concept Proposal

Date: December 2013

1. Title: Longitudinal Evaluation of Health Status in Survivors of Pediatric Astrocytoma: A Report from the Childhood Cancer Survivor Study (CCSS).

2. Primary Working Group: Cancer Control
Secondary Oversight: Chronic Disease and Psychology

Investigators:

Karen Effinger	effinger@stanford.edu
Neyssa Marina	nmarina@stanford.edu
Paul Fisher	pfisher@stanford.edu
Kiri Ness	kiri.ness@stjude.org
Gregory Armstrong	greg.armstrong@stjude.org
Marilyn Stovall	mstovall@mdanderson.org
Wendy Leisenring	wleisenr@fhcrc.org
Les Robison	les.robison@stjude.org
Kevin Oeffinger	oeffingk@mskcc.org
Kevin Krull	kevin.krull@stjude.org
Paul Nathan	paul.nathan@sickkids.ca

3. Background and Rationale

Astrocytoma are the most common pediatric solid tumor with an incidence of 15.4 cases per million children aged 0 to 19 years and a five-year survival rate of approximately 80% for astrocytomas and 60% for other gliomas.[1] Unfortunately, survivors often suffer from treatment-related cognitive, neurologic, endocrine, and sensory impairment.[2-11] In a study of 60 survivors of low-grade astrocytoma treated with surgical resection alone, 85% had at least one late effect of therapy and 28% had three or more.[10] Although this tumor is common and the number of survivors continues to expand, little is known about health status outcomes (physical and psychosocial functioning) in these survivors.

Previous studies reporting health status tend to focus on survivors of all pediatric brain tumors[12-16] or are small, cross-sectional evaluations of astrocytoma survivors focused on one or two components of health status.[7, 10, 11, 17, 18] These studies showed mixed results, although one larger study of brain tumor survivors, which included 282 pediatric astrocytoma survivors, reported astrocytoma survivors had clinically relevant deficiencies in ambulation, sensation, and overall health.[16] In this study, older age at the time of assessment was associated with worse outcomes.[16] A cross-sectional evaluation of pediatric brain tumor survivors in the Childhood Cancer Survivor Study (CCSS) revealed poor health status across all domains;[19, 20] however, these studies did

not evaluate survivors based on the type of brain tumor.

There are no comprehensive studies of health status in astrocytoma survivors and no longitudinal evaluations. The current proposal aims to compare longitudinal changes in health status of astrocytoma survivors to that of sibling controls and to examine the influence of chronic medical conditions and participation outcomes (educational attainment, employment status, marital status, and income) on health status. With multiple time points, we will be able to determine if survivor health status outcomes worsen over time at an accelerated rate compared to sibling controls. Additionally, by examining the influence of chronic medical conditions, participation outcomes, and treatment data, we will evaluate other factors that influence poor health status. This knowledge will aid in the treatment of long-term survivors, serve as guidance in the development of early interventions to prevent poor health status in current adult survivors, and be used as a baseline for future studies to determine if changes in therapy aimed at decreasing late medical effects also improve health status.

4. Specific Aims

4.1 Aim 1: To evaluate the change in prevalence of adverse health status outcomes (general health, mental health, functional impairment, activity limitation, cancer-related pain, and cancer-related anxiety) as pediatric astrocytoma survivors age and compare the trajectory for non-cancer-related outcomes in survivors to the trajectory in sibling controls.

4.1.1 Hypothesis: As pediatric astrocytoma survivors age, they will develop more adverse health status outcomes. This increase in adverse outcomes will be greater in survivors compared to siblings.

4.2 Aim 2: To evaluate the influence of chronic medical conditions (grade 3 or 4 based upon Common Terminology Criteria for Adverse Events [CTCAE], version 3) and participation outcomes (educational attainment, employment status, marital status, and income) on the difference in health status trajectory as survivors age compared to siblings.

4.2.1 Hypothesis: The number of chronic medical conditions and psychosocial status will influence the change in health status (i.e., increased number of serious medical conditions and poor psychosocial status will be associated with adverse health status).

4.3 Aim 3: To identify treatment factors associated with adverse health status as pediatric astrocytoma survivors age.

4.3.1 Hypothesis: Treatment factors (e.g., younger age at diagnosis, higher radiation dose, supratentorial radiation location, multimodality treatment with surgery+radiation+chemotherapy, and earlier decade of treatment) will be associated with adverse health status that worsens with aging.

5. Analysis Framework

5.1 Study Population

5.1.1 Astrocytoma survivors

5.1.1.1 Consented for medical record abstraction
5.1.1.2 Completed at least one of the baseline, 2003, or 2007 questionnaires
5.1.1.3 Questionnaires included only if survivor was alive at completion

5.1.2 Siblings

5.1.2.1 Completed at least one of the baseline, 2003, or 2007 questionnaires
5.1.1.3 Questionnaires included only if sibling was alive at completion

5.2 Outcome Variables

5.2.1 Domains of Health Status

5.2.1.1 General Health (BL N15; FU2003 E1; FU2007 L19)
5.2.1.2 Mental Health (BL J16-35; FU2003 G1-18; FU2007 L1-18)
5.2.1.3 Functional Impairment (BL N10-N12; FU2003 E12, E15, E16; FU2007 N22-N24)
5.2.1.4 Activity Limitations (BL N14 b,c,e; FU2003 E4-E6, E11; FU2007 N26 b,c,e)
5.2.1.5 Anxiety (Survivors Only: BL J37; FU2003 G20; FU2007 L20)
5.2.1.6 Pain (Survivors Only: BL J36 ;FU2003 G19; FU2007 L21)

5.2.2 Definition of Outcomes

Outcomes will be dichotomized to define “adversely” affected individuals as follows:

5.2.2.1 General health: Answer of fair or poor vs. good, very good or excellent
5.2.2.2 Mental health: T-score of 63 or higher vs. score of less than 63 on the any of subscales of the brief symptom inventory (BSI)-18.
5.2.2.3 Functional impairment: Answer of yes vs. no to any of the three questions listed in 5.2.1.3 above
5.2.2.4 Activity limitation: Answer of limited for more than three months over the past two years or limited a lot (in 2003 survey) vs. limited for 3 months or less/not limited at all or limited a little/not limited at all (in 2003 survey) to any of the questions listed in 5.2.1.4 above

5.2.2.5 Anxiety: Answer of very many, a lot, or medium amount of extreme anxiety/fears vs. no or small amount of anxiety/fears

5.2.2.6 Pain: Answer of very bad, a lot, or medium amount of pain vs. no or small amount of pain or (in 2007) severe, very severe, moderate amount of pain vs. mild, very mild, or none

5.3 Covariates

5.3.1 Exploratory Variables

5.3.1.1 Age at questionnaire (continuous and categorical: <18, 18-29, 30-39, ≥40yrs)

5.3.1.2 Survivor vs. sibling status

5.3.1.3 Interaction between age and survivor vs. sibling status

5.3.1.4 BMI

5.3.1.5 Chronic Conditions

Grade 3-4 chronic conditions present at time of questionnaire completion will be evaluated based on the Common Terminology Criteria for Adverse Events 3.0 as previously described.[33]

5.3.1.5.1 Neurological Disorders

5.3.1.5.2 Sensory (Hearing, Visual, Speech)

5.3.1.5.3 Malignancy (Subsequent malignant neoplasm, recurrent astrocytoma)

5.3.1.5.4 Endocrine Disorders

5.3.1.5.5 Cardiovascular Disorders

5.3.1.5.6 Pulmonary Disorders

5.3.1.5.7 Gastrointestinal Disorders

5.3.1.5.8 Renal Disorders

5.3.1.5.9 Musculoskeletal Disorders

5.3.1.5.10 Hematologic Disorders

5.3.1.5.11 Infectious Complications

5.3.1.6 Participation Outcomes

5.3.1.6.1 Educational attainment (BL O1; FU2003 1; FU2007 A3)
College graduate vs. non-college graduate

5.3.1.6.2 Employment status (BL O5-6; FU2003 4, FU2007 A4)
Currently employed vs. unemployed

5.3.1.6.3 Marital status (BL L2, FU2003 2, FU2007 M2)
Married vs. not married

5.3.1.6.4 Annual Household Income (BL Q8, FU2003 S1, FU2007 A6)
≥$20,000 vs. <$20,000

5.3.2 Potential Confounders and Effect Modifiers

5.3.2.1 Gender

5.3.2.2 Race/Ethnicity

5.3.3 Covariates for Secondary Survivor-Only Analysis

5.3.3.1 Age at diagnosis
5.3.3.2 Time from diagnosis to questionnaire completion
5.3.3.3 Treatment decade (1970-1970 vs. 1980-1986)
5.3.3.4 Surgical resection (resection vs. biopsy only)
5.3.3.5 Chemotherapy for primary disease (yes/no)
5.3.3.6 Radiation for primary disease (yes/no; none, >0 to <50 Gy, ≥50Gy; whole brain vs. localized radiation; location: posterior fossa [Region 1], temporal [Region 2], frontal [Region 3], parieto-occipital [Region 4]; right vs. left hemisphere)
5.3.3.7 Multimodality treatment (surgery alone, surgery+radiation, surgery+chemotherapy, chemotherapy+radiation, surgery+radiation+chemotherapy)

5.4 Analysis

A correlation matrix will be used to determine if significant correlation exists between any pair of health status outcomes. If strong correlations exist, measures will be employed to reduce the dimensionality of the data. Chi-squared tests will be used to determine if outcome differences exist between proxy-completed and survivor-completed questionnaires. If proxy-completed outcomes differ significantly, further statistical evaluations will be performed on survivor-completed data only. Additionally, chi-squared tests will be used to assess the difference between those who responded to the 2003 and/or 2007 and those who did not respond in order to determine the extent our results may be biased attrition or death.

Models will include data from all three questionnaires and use current age as the measure of time. Model diagnostics will be used to evaluate the appropriate functional form required for the time variable in the model (i.e., linear, more flexible spline, or categorical factors). Multiple logistic regression models and generalized estimating equation (GEE) methods stratified by sex will be used to evaluate the effect of aging and compare survivors and siblings with respect to prevalence of adverse outcome for each domain. A binomial distribution with a log link will be assumed in order to directly estimate relative rates, since odds ratios from logistic regression models will not reasonably represent relative risks due to the high prevalence of poor health outcomes. GEEs will include repeated statements to account for within participant and possible within family correlation. All regressions will include an indicator for race and age. Models comparing survivors and siblings will include indicators for survivor/sibling status and the product of survivor/sibling status and age. Number of chronic conditions, BMI, and participation outcomes will be determined from each questionnaire and values from each questionnaire will be included in the GEE models as time-varying covariates. Chronic conditions by organ system will be evaluated to determine the type of conditions with the largest influence on health status.

In the secondary analysis, treatment effects will be evaluated using univariate and multivariate GEEs. Univariate analyses will be performed to determine if adjustment will be made for treatment era, age at diagnosis, or time from diagnosis to questionnaire. Missing data will be imputed using multiple imputation techniques. Multivariate models will also adjust for the number of chronic conditions, BMI, and participation outcomes.

6. Special Consideration

Karen Effinger will perform the statistical analyses with assistance available from Dr. Kristin Sainani, Clinical Assistant Professor, Department of Health Research and Policy at Stanford University. Statistical methodology, programs and analytic results will be reviewed and approved by the CCSS Statistical Center.

References:

1. Howlader N NA, Krapcho M, Neyman N, et al (eds). SEER Cancer Statistics Review, 1975-2009 (Vintage 2009 Populations). Based on November 2011 SEER data submission, posted to the SEER web site, April 2012. ed. Bethesda, MD: National Cancer Institute.

2. Armstrong GT, Conklin HM, Huang S, Srivastava D, Sanford R, Ellison DW, et al. Survival and long-term health and cognitive outcomes after low-grade glioma. *Neuro Oncol*. 2011;13(2):223-234.

3. Benesch M, Lackner H, Sovinz P, Suppan E, Schwinger W, Eder HG, et al. Late sequela after treatment of childhood low-grade gliomas: a retrospective analysis of 69 long-term survivors treated between 1983 and 2003. *J Neurooncol*. 2006;78(2):199-205.

4. Kortmann RD, Timmermann B, Taylor RE, Scarzello G, Plasswilm L, Paulsen F, et al. Current and future strategies in radiotherapy of childhood low-grade glioma of the brain. Part II: Treatment-related late toxicity. *Strahlenther Onkol*. 2003;179(9):585-597.

5. Terashima K, Chow K, Jones J, Ahern C, Jo E, Ellezam B, et al. Long-term outcome of centrally located low-grade glioma in children. *Cancer*. 2013;119(14):2630-2638.

6. Chadderton RD, West CG, Schuller S, Quirke DC, Gattamaneni R, Taylor R. Radiotherapy in the treatment of low-grade astrocytomas. II. The physical and cognitive sequelae. *Childs Nerv Syst*. 1995;11(8):443-448.

7. Aarsen FK, Paquier PF, Reddingius RE, Streng IC, Arts WF, Evera-Preesman M, et al. Functional outcome after low-grade astrocytoma treatment in childhood. *Cancer*. 2006;106(2):396-402.

8. Merchant TE, Conklin HM, Wu S, Lustig RH, Xiong X. Late effects of conformal radiation therapy for pediatric patients with low-grade glioma: prospective evaluation of cognitive, endocrine, and hearing deficits. *J Clin Oncol*. 2009;27(22):3691-3697.

9. Ris MD, Beebe DW. Neurodevelopmental outcomes of children with low-grade gliomas. *Dev Disabil Res Rev*. 2008;14(3):196-202.

10. Turner CD, Chordas CA, Liptak CC, Rey-Casserly C, Delaney BL, Ullrich NJ, et al. Medical, psychological, cognitive and educational late-effects in pediatric low-

grade glioma survivors treated with surgery only. *Pediatr Blood Cancer*. 2009;53(3):417-423.

11. Zuzak TJ, Poretti A, Drexel B, Zehnder D, Boltshauser E, Grotzer MA. Outcome of children with low-grade cerebellar astrocytoma: long-term complications and quality of life. *Childs Nerv Syst*. 2008;24(12):1447-1455.

12. Brinkman TM, Li Z, Neglia JP, Gajjar A, Klosky JL, Allgood R, et al. Restricted access to the environment and quality of life in adult survivors of childhood brain tumors. *J Neurooncol*. 2013;111(2):195-203.

13. Cardarelli C, Cereda C, Masiero L, Viscardi E, Faggin R, Laverda A, et al. Evaluation of health status and health-related quality of life in a cohort of Italian children following treatment for a primary brain tumor. *Pediatr Blood Cancer*. 2006;46(5):637-644.

14. Kulkarni AV, Piscione J, Shams I, Bouffet E. Long-term quality of life in children treated for posterior fossa brain tumors. *J Neurosurg Pediatr*. 2013.

15. Mostow EN, Byrne J, Connelly RR, Mulvihill JJ. Quality of life in long-term survivors of CNS tumors of childhood and adolescence. *J Clin Oncol*. 1991;9(4):592-599.

16. Boman KK, Hoven E, Anclair M, Lannering B, Gustafsson G. Health and persistent functional late effects in adult survivors of childhood CNS tumours: a population-based cohort study. *Eur J Cancer*. 2009;45(14):2552-2561.

17. Musial-Bright L, Panteli L, Hernaiz Driever P. Pediatric low-grade glioma survivors experience high quality of life. *Childs Nerv Syst*. 2011;27(11):1895-1902.

18. Sands SA, Zhou T, O'Neil SH, Patel SK, Allen J, McGuire Cullen P, et al. Long-term follow-up of children treated for high-grade gliomas: children's oncology group L991 final study report. *J Clin Oncol*. 2012;30(9):943-949.

19. Armstrong GT, Liu Q, Yasui Y, Huang S, Ness KK, Leisenring W, et al. Long-term outcomes among adult survivors of childhood central nervous system malignancies in the Childhood Cancer Survivor Study. *J Natl Cancer Inst*. 2009;101(13):946-958.

20. Hudson MM, Mertens AC, Yasui Y, Hobbie W, Chen H, Gurney JG, et al. Health status of adult long-term survivors of childhood cancer: a report from the Childhood Cancer Survivor Study. *JAMA*. 2003;290(12):1583-1592.

Example Tables and Figures

Table 1: Demographic characteristics of long-term astrocytoma lymphoma survivors and sibling controls

	Astrocytoma Survivor				Sibling Control		
	All	**Male**	**Female**		**All**	**Male**	**Female**
	N (%) N=	**N (%)** N=	**N (%)** N=		**N (%)** N=	**N (%)** N=	**N (%)** N=
Gender							
Male		N/A	N/A			N/A	N/A
Female		N/A	N/A			N/A	N/A
Race/Ethnicity (Baseline)							
Non-Hispanic White							
Non-Hispanic Black							
Hispanic							
Other							
Unknown							
Age at baseline questionnaire							
< 18 years							
18-29 years							
30-39 years							
≥ 40 years							
Age at 2003 questionnaire							
< 18 years							
18-29 years							
30-39 years							
≥ 40 years							
Age at 2007 questionnaire							
< 18 years							
18-29 years							
30-39 years							
≥ 40 years							
Body Mass Index (Baseline)							
Median							
Range							
Body Mass Index (2003)							
Median							
Range							
Body Mass Index (2007)							
Median							
Range							

Table 2: Treatment Factors

	Astrocytoma Survivor	
	Male	**Female**
	N (%) N=	**N (%)** N=
Age at diagnosis (y)		
Mean (SD)		
Range		
Treatment Era		
1970-1979		
1980-1986		
Surgical Resection		
Biopsy only		
Resection		
Chemotherapy		
Received		
None		
Radiation		
None		
>0 to <50 Gy		
≥50 Gy		
Multimodality Therapy		
Surgery only		
Chemotherapy only		
Radiation only		
Surgery+radiation		
Surgery+chemotherapy		
Radiation+chemotherapy		
Surgery+radiation+chemo		

Table 3: Participation outcomes by age at questionnaire response

	<18 years		**18-29 years**		**30-39 years**		**≥40 years**	
	Survivor	**Sibling**	**Survivor**	**Sibling**	**Survivor**	**Sibling**	**Survivor**	**Sibling**
	N (%) N=	**N (%)** N=	**N (%)** N=	**N (%)** N=	**N (%)** N=	**N (%)** N=	**N (%)** N=	**N (%)** N=
Educational Attainment								
College graduate								
Non-college graduate								
Employment Status								
Employed								
Unemployed								
Marital Status								
Married								
Not married								
Annual Household Income								
< $20,000								
≥$20,000								

Figure 1: Chronic conditions present in astrocytoma survivors and sibling controls by age

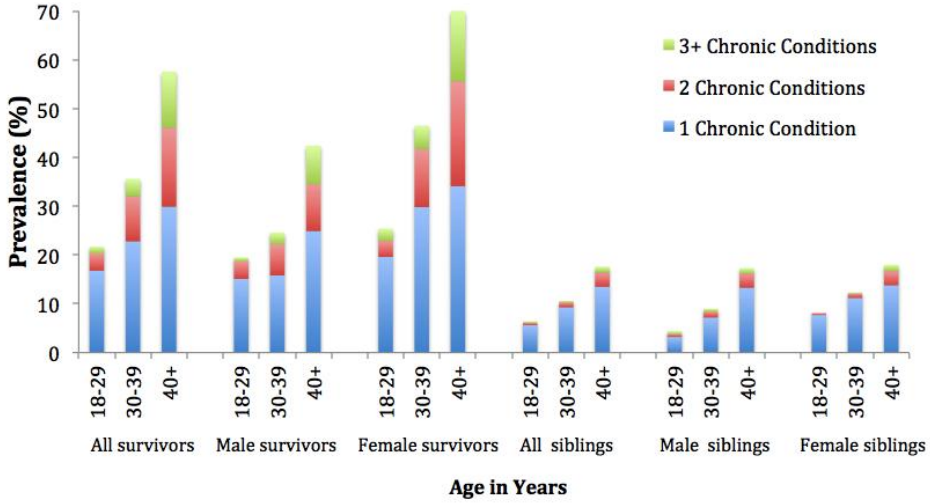

Table 4. Adverse health status outcomes in astrocytoma survivors and siblings in relation to survivor status

	General Health		Functional Impairment		Activity Limitation		Mental Health	
	OR (95% CI)		OR (95% CI)		OR (95% CI)		OR (95% CI)	
	Males	Females	Males	Females	Males	Females	Males	Females
Overall Survivor vs. Sibling								
Survivor vs. Sibling by age								
<18 years								
18-29 years								
30-39 years								
≥ 40 years								

Table 5. Adverse health status outcomes in astrocytoma survivors and siblings in relation to demographic characteristics

Variables	General Health		Functional Impairment		Activity Limitation	
	OR (95% CI)		OR (95% CI)		OR (95% CI)	
	Males	Females	Males	Females	Males	Females
Age						
< 18 years						
18-29 years						
30-39 years						
≥ 40 years						
Race						
Non-Hispanic Caucasian						
Other						
BMI						
Number of Chronic Conditions						
0 Chronic Conditions						
1 Chronic Condition						
2+ Chronic Conditions						
Participation Outcomes						
Non-college graduate						
Unemployed						
Not married						
Income <$20,000						

Table 5. Adverse health status outcomes in astrocytoma survivors and siblings in relation to demographic characteristics (cont)

Variables	Mental Health		Cancer-related Pain		Cancer-related Anxiety	
	OR (95% CI)		OR (95% CI)		OR (95% CI)	
	Males	Females	Males	Females	Males	Females
Age						
<18 years						
18-29 years						
30-39 years						
≥ 40 years						
Race						
Non-Hispanic Caucasian						
Other						
BMI						
Number of Chronic Conditions						
0 Chronic Conditions						
1 Chronic Condition						
2+ Chronic Conditions						
Participation Outcomes						
Non-college graduate						
Unemployed						
Not married						
Income <$20,000						

Table 5: Treatment-related risk factors for adverse health status outcomes in astrocytoma survivors

Variables	General Health		Functional Impairment		Activity Limitation	
	OR (95% CI)		OR (95% CI)		OR (95% CI)	
	Males	Females	Males	Females	Males	Females
Age at diagnosis (y)						
0-4						
5-9						
10-14						
15-21						
Treatment Era						
1970-1979						
1980-1986						
Surgical Resection						
Biopsy only						
Resection						
Chemotherapy						
Received						
None						
Radiation						
None						
>0 to <50 Gy						
≥50 Gy						
Multimodality Therapy						
Surgery only						
Chemotherapy only						
Radiation only						
Surgery+radiation						
Surgery+chemo						
Radiation+chemo						
Surgery+rad+chemo						

Table 5: Treatment-related risk factors for adverse health status outcomes in astrocytoma survivors (cont)

Variables	Mental Health		Cancer-related Pain		Cancer-related Anxiety	
	OR (95% CI)		OR (95% CI)		OR (95% CI)	
	Males	Females	Males	Females	Males	Females
Age at diagnosis (y)						
0-4						
5-9						
10-14						
15-21						
Treatment Era						
1970-1979						
1980-1986						
Surgical Resection						
Biopsy only						
Resection						
Chemotherapy						
Received						
None						
Radiation						
None						
>0 to <50 Gy						
≥50 Gy						
Multimodality Therapy						
Surgery only						
Chemotherapy only						
Radiation only						
Surgery+radiation						
Surgery+chemo						
Radiation+chemo						
Surgery+rad+chemo						

Abbreviations: OR, odds ratio. CI, confidence interval

Figure 2 (Example): Probability of moderate to severe health status outcomes in astrocytoma survivors and sibling controls by age