

Childhood Cancer Survivor Study Analysis Concept Proposal

1. **Title:** Health and Functional Status of Long Term Adult Medulloblastoma/PNET Survivors: A Report from the Childhood Cancer Survivor Study

2. **Working Group and Investigators:**

2.1 This proposed publication will be within the Chronic Disease Working Group.

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3. **Background and Rationale:**

Central nervous system (CNS) tumors are the second most common form of childhood malignancy¹. Previous studies have documented that survivors of CNS tumors are among those at highest risk for cognitive dysfunction², lower levels of academic attainment³, neurological dysfunction⁴, stroke⁵ and endocrine dysfunction⁶ when compared to other childhood cancer survivors. Fertility rates among these survivors were lower than their siblings as were the frequency of intimate relationships^{7, 8, 9, 10}. Within the CCSS, even the earliest assessments documented these findings. As the CCSS cohort has aged, more recent manuscripts have documented an even higher incidence of second malignancies¹¹, late mortality and chronic health conditions among survivors of CNS tumors than previously described¹².

Medulloblastoma is the most common malignant CNS tumor¹, and survival rates for children with medulloblastoma have increased from 40 to over 80% over the past 30 years¹³. The addition of chemotherapy to surgical resection and radiation is largely responsible for the improved outcomes. The now adult survivors of childhood medulloblastoma are facing issues of adulthood that include managing chronic health conditions, living independently, engaging in intimate relationships, family planning and preparing for the future. These issues are likely of even greater concern among these survivors because the majority were treated with radiation therapy. Previous studies have presented data on CNS tumor survivors in aggregate but have not focused on the subset of survivors with medulloblastoma/PNET.

We propose to complete an analysis of the updated 2007 questionnaires of medulloblastoma/PNET survivors and their siblings to address chronic medical conditions, cognitive function, employment status, perceived health status, and anxiety. We will also measure the level of concern regarding future health and fertility. These results should provide data to address the challenges and concerns of long-term survivors of childhood medulloblastoma. This will likely be the last cohort of survivors who were treated systematically with 3600 cGy of craniospinal radiation. Comprehensively characterizing long term outcomes in this cohort will provide critical background information against which to compare survivors treated with more contemporary regimens that reduced craniospinal dose to 2340 cGy and utilize chemotherapy for standard risk patients.

4. Specific Aims:

4.1. Primary Aim:

- To summarize the late occurring chronic medical conditions, health status, and psycho-social functioning of childhood medulloblastoma/PNET survivors and compare their experience with a sibling cohort. Specifically, we will focus on the following outcomes: neurological conditions, memory impairment, hearing/vision/speech, cardiac disease, respiratory conditions, fertility, perceived health status, emotional distress and health related anxiety. Educational history, employment status, income level, marital status and current living situation will also be reported to provide a description of the survivors' function/performance.

4.2 Secondary Aim:

- To assess the association of the following treatment factors with the neurological, cognitive/memory and fertility outcomes, if the data distribution allows:
 - o Treatment type: Surgery + Radiation (n=137), Surgery + Radiation + Chemotherapy (n=195) for primary therapy

4.3 Hypotheses for each outcome:

4.3.1 Neurological conditions

4.3.1.1 Hearing loss, cataracts, and speech defects will be higher among medulloblastoma survivors than among sibling controls and highest among survivors with a history of cranial radiation with chemotherapy. Increasing radiation doses to the temporal lobe will be associated with the greatest hearing loss.

4.3.1.1.1 Preliminary data distribution are ~8% < 30 Gy, 50% 30-49 Gy, and 42% > 50Gy

4.3.1.1.2 If outcomes in the three groups are too sparse, the data will be dichotomizes at 50 Gy

4.3.2 Cognitive/memory impairment

4.3.2.1 Problems with learning or memory will be more prevalent among survivors than among sibling controls.

4.3.3 Cardiac disease

- 4.3.3.1 Late cardiac disease will be higher among survivors than among sibling controls.
- 4.3.4 Respiratory disease
 - 4.3.4.1 Late respiratory disease will be higher among survivors than among sibling controls.
- 4.3.5 Fertility
 - 4.3.5.1 Lower rates of fertility will occur among survivors than among sibling controls.
 - 4.3.5.2 Survivors who were treated with both chemotherapy and radiation will have lower fertility rates than those treated with radiation alone.
- 4.3.6 Perceived health status and health related anxiety
 - 4.3.6.1 Lower levels of health status and higher levels of anxiety will be present among survivors when compared to sibling controls.
- 4.3.7 Emotional distress
 - 4.3.7.1 Higher levels of emotional distress will be present among survivors when compared to sibling controls.
- 4.3.8 Education
 - 4.3.8.1 Level of academic attainment will be lower among survivors than among sibling controls.
- 4.3.9 Employment/income
 - 4.3.9.1 Survivors who were treated with radiation will be less likely to work full-time and will have lower levels of personal income than sibling controls.
- 4.3.10 Marital status and current living arrangement
 - 4.3.10.1 Survivors will be less likely to marry and less likely to live independently when compared to sibling controls.

5. Analysis Framework:

- 5.1. Primary Outcomes for Analysis (outcome for each subject will be determined from the aggregate data from all available questionnaires):
 - 5.1.1. Neurological conditions
 - 5.1.1.1. Follow-up 2007, Sections D and K2-14
 - 5.1.1.1.1. D4 – tinnitus
 - 5.1.1.1.2. D5 – vertigo
 - 5.1.1.1.3. D10 – cataract
 - 5.1.1.1.4. K2 – epilepsy
 - 5.1.1.1.5. K5 – Problems with balance/equilibrium
 - 5.1.1.1.6. K11-13 – address paralysis
 - 5.1.1.2. Follow-up 2000, Section 12
 - 5.1.1.2.1. 12G and H – epilepsy/seizures
 - 5.1.1.3. Baseline, Sections C and J
 - 5.1.2. Cognitive/memory impairment

- 5.1.2.1. Follow-up 2007, Section K1
 - 5.1.3. Cardiac disease (BMJ 2009;339:b4606. doi:10.1136/bmj.b4606)
 - 5.1.1.1. Follow-up 2007, Section G
 - 5.1.1.1.1. G1, 2, 7+8, 9 (CHF, MI, valve disease, pericarditis)
 - 5.1.1.2. Follow-up 2000, Section 10
 - 5.1.1.2.1. 10d, e, i+j, k
 - 5.1.1.3. Baseline, Section F
 - 5.1.2. Respiratory disease (Cancer. 2002 Dec 1;95(11):2431-41.)
 - 5.1.2.1. Follow-up 2007, Section H (lung fibrosis, recurrent pneumonia, chronic cough)
 - 5.1.2.1.1. H2, 4, 6
 - 5.1.2.2. Follow-up 2000, Section 11
 - 5.1.2.2.1. 11 l, j, h
 - 5.1.2.3. Baseline, Section G
 - 5.1.3. Fertility – defined as ever been pregnant (JCO 27:2677,2009; JCO28:332,2010)
 - 5.1.3.1. Follow-up 2007, Section Q
 - 5.1.3.2. Follow-up 2003, Section N
 - 5.1.3.3. Follow-up 2000, Section 8
 - 5.1.3.4. Baseline, Section M
 - 5.1.3.5. Pregnancy questionnaire
 - 5.1.4. Perceived health status and health related anxiety
 - 5.1.4.1. Follow-up 2007, Sections L19-20 and O1-2
 - 5.1.4.2. Baseline, Sections J and R
 - 5.1.5. Emotional distress
 - 5.1.5.1. Follow-up 2003, Section G
 - 5.1.6. Education (will decide on definition for coding responses from multiple questionnaires – likely taking the last response for 5.1.6 – 5.1.8)
 - 5.1.6.1. Follow-up 2007, Section A3
 - 5.1.6.2. Follow-up 2003, Item 1
 - 5.1.6.3. Follow-up 2000, Item 1
 - 5.1.6.4. Baseline, Section O1
 - 5.1.7. Employment/Income
 - 5.1.7.1. Follow-up 2007, Section A4-A8
 - 5.1.7.2. Follow-up 2003, Items 4 and S1-S3
 - 5.1.8. Marital status and current living arrangement
 - 5.1.8.1. Follow-up 2007, Section M
 - 5.1.8.2. Follow-up 2003, Items 2 and 3
 - 5.1.8.3. Follow-up 2000, Items 2 (marital status only)
 - 5.1.8.4. Baseline, Sections L and A9
- 5.2. Covariates
- 5.2.1. Age at diagnosis
 - 5.2.2. Age at time of questionnaire
 - 5.2.3. Sex
 - 5.2.4. Treatment type (Surgery + XRT, Surgery + XRT + Chemo)
 - 5.2.5. Will request the XRT data on the chest for cardiac and lung exposure. That would be chest wall dosing like the Mertens paper in 2002.
- 5.3. Planned Analyses

Descriptive characteristics for all outcomes and covariates will be summarized separately for cancer survivors and sibling controls. Where necessary, frequency distributions will be examined to aid in forming reasonable groupings for categorical variables that will be used in statistical modeling.

The type of statistical model utilized for comparison of survivors to controls for each outcome will depend upon the structure of the outcome measure. For outcomes for which CCSS collects data on age of onset and which were ascertained on at least the baseline questionnaire (neurologic problems, cardiac disease, respiratory disease), Cox regression models of time-to-first-onset will be used. Event times will be censored at time of loss-to-follow-up or death. For sibling control subjects, their entry into the at-risk group will be at age 5, the youngest age a survivor can enter the cohort. Hazard ratios for the outcome event in cancer survivors versus sibling controls will be estimated, along with the accompanying 95% confidence intervals. Robust estimation procedures will be utilized to account for any dependence among observations on subjects from the same family. Cumulative incidence curves may also be presented as graphical summaries for these outcome measures.

One notable exception to the analysis of medical outcomes is the cognitive impairment/memory measure. This item was only asked on the 2007 questionnaire. Consequently we do not have appropriate follow-up on the whole cohort of 5 year medulloblastoma/PNET survivors that would be necessary to do a Cox regression analysis. This outcome will instead be evaluated as a dichotomous Y/N outcome in a cross-sectional analysis that is limited to subjects who responded to the cognitive impairment questions on the FU2007 questionnaire.

The remaining outcome measures are interval, ordinal or nominal scale observations. Most of these measures have longitudinal data collected at multiple time points. In order to utilize all available observations, these outcomes will be analyzed using Generalized Estimating Equation modeling. Outcome measures will first be dichotomized [e.g. living arrangement (7 categories) condensed into living independently Y/N], and the GEE model will estimate the relative risk parameter and 95% confidence interval for cancer survivors versus siblings. Either a log-binomial or a Poisson implementation of the relative risk estimation can be used for the relative risk estimation.

All of the above regression analyses for the primary aim will be carried out with the goal of evaluating the comparison of survivors to siblings, with appropriate adjustment for the demographic covariates, age, gender and race.

The analyses relating to the secondary study aim will utilize data from the cancer survivor cohort only. The same types of modeling approaches described above will be used to evaluate the impact of categories of cancer treatment exposures on the neurological, cognitive/memory and fertility outcomes. Univariate analyses will be conducted first, and additional covariates for which $p \leq 0.20$ in univariate analyses will then be evaluated in multivariable models. (Note: certain outcomes may have core adjustment

factors that the literature suggests should always be included; in those situations a core factor may be included in the model regardless of the univariate result.)

5.4. Subject population:

5.4.1. CCSS participants

5.4.1.1. Inclusion Criteria

5.4.1.1.1. Medulloblastoma/PNET survivors

5.4.1.1.2. Sibling controls

All subjects who completed at least the baseline questionnaire will be included in the full analysis data set, and will be utilized for most outcome analyses. For a subset of the outcomes that were only ascertained on specific questionnaires, only those subjects who responded to the relevant questionnaire will be utilized, and analyses will be carried out in a cross-sectional fashion.

5.5. Tables

Table 1. Descriptives of Study Population (Survivors of Medullo/PNET)

	Survivor		Sibling	
	N	%	N	%
Sex				
Female				
Male				
Age at Diagnosis				
0-4 years				
5-9 years				
10-14 years				
> 14 years				
Radiation therapy				
None				
Cranial				
Craniospinal				
Spinal				
Chemotherapy (yes)				

Table 2. Chronic Conditions of Medulloblastoma/PNET survivors, in comparison to siblings.

	Number	%	Number of Siblings	%	RR/OR	95% CI	p-value
Hearing/Vision Speech							
List issues							
Seizures							
Migraines							
Ataxia							
Problems with learning or memory							
Cardiac Disease							
List issues							
Respiratory Disease							
List issues							
Fertility							
Ever had children or currently pregnant							

Table 3. Issues Related to Function and Daily Living of Survivors of Medulloblastoma/PNET

	Number of Survivors	%	Number of Siblings	%	RR/OR	95% CI	p-value
Rating of current health status							
List distribution of responses							
Emotional distress (previous paper used raw scores and t-scores)							
GSI							
Depression							
Somatic distress							
Anxiety							
Anxieties/fears regarding treatment							
List distribution of responses							
Concern about future health							
List distribution of responses							
Concern about having children							
List distribution of responses							
Education							
No high school or GED							
High school diploma or GED							
Some college, no bachelor's degree							
Bachelor's degree or higher							
Employment status							
Full-time							
Part-time							
Unemployed							
Income							
List distribution							
Marital status							
List distribution							
Living situation							
List distribution							

**Will footnote adjustments for age, sex, etc.

Table 4. Will create table to illustrate impact of treatment variables key outcomes

- Fertility
- Neuro
- Cognitive

6.0 References

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