Childhood Cancer Survivor Study
Analysis Concept Proposal

Title: Long-Term Outcomes of Childhood Central Nervous System Tumor Survivors: A Report from the Childhood Cancer Survivor Study

Working Group and Investigators:

This proposed publication will be within the Neuropsychologic/Neurologic Working Group

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Background and Rationale:

Central nervous system (CNS) tumors are the most common solid tumors of childhood and second only to the leukemias in regard to overall incidence among children. Unfortunately, as the improvements in survival of CNS tumors has lagged behind that of acute lymphoblastic leukemia, CNS tumors are now the leading cause of cancer death among children. In addition, those who survive a CNS malignancy are at significant risk for a broad array of late effects simply based on the central nature of the lesion. Traditional treatment for most CNS tumors includes surgical resection, and for the majority of tumors, some form of radiation therapy, each of which carries additional risk for poor long-term outcome. More recently, the use of multi-modal therapy that includes chemotherapy, in tumors with known chemotherapy sensitivity, in addition to surgery and radiation was initiated in an attempt to reduce long-term morbidity.

Each treatment modality poses such significant risks for the long-term survivor that the risks of effective therapy must be carefully balanced with the benefits that may be achieved. True understanding of these risks and benefits can only occur if the cumulative experience of CNS tumor survivors is accurately quantified and summarized. Because of the large number of participants with CNS tumors within the Childhood Cancer Survior Study cohort the CCSS is powered to report one of the broadest experiences of CNS tumor survivorship to date.

The CCSS Steering Committee, in February 2004, set forth an objective to evaluate survivorship issues for each primary cancer diagnosis. This concept proposal will address key issues among survivors of CNS tumors across a wide scope of outcome measures including: mortality, recurrence, second malignant neoplasms (SMN), chronic medical conditions, health status, education, marriage, insurance, and employment.

It has been previously reported by the CCSS that the all-cause mortality rate for all participants in the cohort was 11.4% at twenty years and that children with CNS tumors have the poorest overall survival with a cumulative mortality rate of 16.8% at 20 years[1]. Further information regarding the mortality rate among the different diagnostic categories of CNS tumors captured by the CCSS (Astrocytoma, PNET, Ependymoma) and by treatment type (surgery alone, surgery + CNS radiation, surgery + CNS radiation + chemotherapy) will be a significant contribution to the literature. We hope to build on previously established knowledge of second malignant neoplasm (SMN) and other outcomes among survivors in CCSS with CNS tumors as summarized in the aims and hypotheses of this concept.

Additional detail of how this concept will build on data previously reported by the CCSS is provided in Appendix 1.

Specific Aims:

Primary Aim:

-To update and summarize the survival experience of a large population of patients diagnosed with a CNS tumor during childhood and to compare their survival experience with a sibling cohort across nine major outcomes including: mortality, late recurrence, development of second malignant neoplasms, medical complications, health status, education, employment, marriage, and insurance status.

-To assess the effect of five key variables upon the major outcomes:

1) Primary CNS tumor diagnosis: Astrocytoma (1610 = 383 high-grade + 294 low-grade + 992 astrocytoma NOS), PNET (541), Ependymoma (186)

2) Treatment type: Surgery alone (414), surgery + radiation (682), surgery + radiation + chemotherapy (446)

3) Total maximal radiation dose: none, <30Gy, 30-49Gy, >/=50Gy

4) Location of maximal radiation dose: none, frontal cortex, temporal cortex, parietal/occipital cortex, posterior fossa, spine

5) Craniospinal radiation: Yes or No

Hypotheses for each outcome:

Mortality

-Late mortality rate will be higher for PNET and Ependymoma compared to astrocytoma due to increased late recurrence

-Late mortality will be increased in patients with CNS tumors who receive radiotherapy compared to those who do not

Recurrence

-Late recurrence rate of primary tumor will be higher in patients with PNETs and Ependymomas than in patients with Astrocytomas

-Late recurrence rate will be higher in survivors with high grade astrocytomas than in those with low grade astrocytomas

Second Malignant Neoplasms

-SMNs within the CNS will occur more often in patients who receive radiotherapy and if the number of events is sufficient to support the analysis, a dose effect will be demonstrated

-Leukemia as a SMN will occur more often in patients who receive chemotherapy

Education

-Level of education attained and use of special education services will be associated with the use of radiation and a dose effect will be evident

-Level of education attained and use of special education services will be associated with craniospinal radiation and focal radiation of the cortex

Employment

-Patients with CNS radiation will be less likely to have ever gotten a job and will have lower personal income

Insurance

-Patients treated with craniospinal radiation are less likely to be insured than survivors treated with focal radiation alone, or with no radiation

Marriage

-Survivors of PNET in this era (craniospinal radiation) will be less likely to marry as compared to survivors of Ependymoma (focal radiation) due to the therapy they received

Health Status

-Poor health status is associated with use of radiation, total dose and location

Additional Hypotheses:

-Patients with PNET will have lower Educational attainment, will be less likely to be employed, and lower rates of marriage than survivors of Ependymoma due to high does of craniospinal radiation used during this era (3600 cGy)

-An inverse dose response relationship will exist between rates of fecundity and fertility and dose of CNS radiation (much of which may be reported in Dr.Green's forthcoming manuscript).

Please reference Appendix 1 for full detail on how these aims/hypotheses build on previous investigations

Analysis Framework:

A. Outcomes of interest:
   1. Survival rates/Mortality
   2. Late Recurrence of Primary Malignancy
      a. Baseline: section K
      b. Follow-up 1: question 17
      c. Follow-up 2: section R
   3. Second Malignant Neoplasms:
      a. Baseline: section K
      b. Follow-up 1: question 17
      c. Follow-up 2: section R
   4. Medical Complications:
      a. Baseline: sections C,D,E,F,G,H,I,J
   5. Education: a. Baseline: section O, questions 1-4
      b. Follow-up 1: question 1
      c. Follow-up 2: question 1
   6. Employment:
      a. Baseline section O, questions 5-11, section Q, questions 8 & 9
      b. Follow-up 2: Question 4-6
   7. Insurance:
      a. Baseline: section Q, questions 1-6
      b Follow-up1: question 16
      c. Follow-up 2: section M
   8. Marriage:
      a. Baseline: section L
      b. Follow-up 1: question 2
      c. Follow-up 2: questions 2 & 3
   9. Health Status

Radiation Cutoffs dates: For all outcomes, total radiation received will be calculated from the time of diagnosis to five years from the time of the original diagnosis.

B. Population

1)All participants in the CCSS diagnosed with a CNS malignancy. (Certain analyses will be limited to Astrocytoma, PNET, and Ependymoma only as only these subgroups have sufficient size to allow meaningful statistical analysis.)

2) Entire sibling cohort will be used as controls

C. Explanatory Variables:

1. Type of treatment: surgery alone, surgery + RT, surgery + RT+chemo
2. Diagnosis: Astrocytoma (1610 = 383 high-grade + 294 low-grade + 992 astrocytoma NOS), PNET (541), Ependymoma (186)
3. Age at diagnosis
4. Gender
5. Cumulative doses of chemo therapy, specifically alkylator score
6. Location of maximal radiation dose (none, Frontal cortex, temporal cortex, parietal/occipital cortex, posterior fossa, spine)
7. Cumulative doses of radiation (none, <30Gy, 30-49Gy, >/=50Gy)
8. Craniospinal radiation: Yes/no

D. Analysis Plan:

1. Descriptive/summary Statistics

a. characteristics of CNS tumor survivors and siblings will be described using absolute numbers, means (SD) and/or medians (range) (Table 1)

2. Mortality

a. Cumulative mortality probability and standardized mortality rates for CCSS participants have been previously published. We propose further investigation into this population by reporting cumulative mortality rates among participants with primary CNS tumors by :

i.) Primary CNS tumor diagnosis
ii) Type of Treatment

compared to the expected survival in the age and gender matched U.S. population using the Kaplan-Meier method.

b. Report specific causes of death for patients with primary CNS tumors (Table 2) and cause-specific (SMN, Cardiac, Pulmonary, External, Other) SMRs and 95% CI by primary CNS tumor diagnosis and treatment type (Table 3).

c. Hazard ratios/Relative risks comparing survival between different treatment groups using Cox/Poisson regression models adjusted for age at diagnosis, sex, and race (Table 4).

3. Recurrence and SMN

Cumulative incidence, and standardized incidence ratios (SIR), of recurrence of primary malignancy and of SMN will be calculated treating death prior to recurrence or SMN as a competing risk event (2 analyses: by diagnosis, then by treatment group, Table 5). This analysis will further previous analyses of this data by breaking down events by major CNS tumors by diagnosis (Astrocytoma, PNET, Ependymoma) and by major treatment type (surgery alone, surgery + radiation, surgery+ radiation + chemotherapy) and radiation dose(none, <30Gy, 30-49Gy, >/=50Gy). For additional detail on how this analysis and other analyses will add to previous data published by CCSS please see Appendix 1.

Hazard ratios for these outcomes, comparing different groups will be calculated using Cox Proportional Hazards/Poisson regression model adjusted for age at diagnosis, gender, race, alkylator, platinum and epipodophyllotoxin exposure, and radiation dose(Table 6).

4. Chronic Health Conditions.

The incidence and severity of chronic medical complications will be determined by using the methodology established by Oeffinger in the recent report on this information. A single table of incidence by medical outcome, in the form used in the Appendix of the Oeffinger report will be helpful to determine areas or condition that require closer attention. Primary comparison will be between CNS tumor survivors and their siblings. Comparison between different treatment types for the CNS tumor population may be warranted for a limited number of chronic medical conditions. Cardiac and Endocrine outcomes have been previously reported and will not be reported here unless updates from Follow-up #2 reveal new trends or changes in these outcomes. A table reporting the three main outcomes reported in the Oeffinger paper should be provided. (Table 8)

5. Socioeconomic/ Demographic.

Comparisons of educational levels, employment status, insurance status, and marital status between CNS tumor survivors and siblings will be carried out. Comparisons will be made via univariate and multivariate logistic regression utilizing robust generalized variance estimates to account for intra-family correlation between survivors and siblings. Where appropriate polytomous logistic regression will be employed. Multivariate comparisons will be adjusted for age at time of interview, gender, and ethnicity. These comparisons will be limited to subjects over the age of 25 at the time of interview.

Among survivors, similar univariate and adjusted comparisons will be made between CNS tumor survivors who received radiation compared to those who did not (may want to consider looking at all treatment groups but this is the most important analysis). Multivariate analyses will be adjusted for age at time of interview, gender, ethnicity, cumulative chemo dosing, and history of surgery.

7. Health Status.

Health status of CNS tumor survivors will be established using the methodology described by Hudson et. al., (Hudson CCSS 2003) for comparison of survivors with siblings and with-in group comparisons of CNS tumor survivors by diagnosis and treatment type. Multivariate logistic regression should adjust for age at interview, gender, race, education, household income, health insurance as per the Hudson analysis.

Table 1. Characteristics of the Study Population					
	CNS Tumor Survivors		**Siblings**		p-value
	N	%	N	%	
Tumor Type					
Astrocytoma			n/a	n/a	
Medulloblastoma			n/a	n/a	
Gender					
Male					
Female					
Age at Diagnosis					
0-3					
4-9					
10-14					
15+					
Treatment Type					
Surgery alone					
Surgery + RT					
Surgery + Chemo					
Surg + RT + Chemo					
Highest level of Education					
Grade School					
High School					
Technical School					
College					
Post graduate					
Not indicated					
Marital status					
Married or Living as married					
Not married					
Not indicated					
Employment status					
Working full time					
Not working full time					

Table 2. Specific Causes of Death among participants with primary CNS tumors	
Specific Cause of Death	**# of Patients**
Recurrence	
Treatment Related Consequences	
Subsequent neoplasm	
Brain	
Bone	
Etc	
Cardiac	
Pulmonary	
Other sequeale	
Non-treatment related causes of death	
External causes	
Motor vehicle accident	
Homicide	
Suicide	
Medical conditions	

Table 3. Cause specific SMRs by Diagnosis and Treatment										
	Subsequent Cancer		**Cardiac**		**Pulmonary**		**External Causes**		**Other Deaths**	
	SMR	95% CI	SMR	95% CI	SMR	95% CI	SMR	95% CI	SMR	95% CI
All Cases										
Diagnosis										
Astrocytoma										
Medulloblastoma										
Ependymoma										
Germinoma										
Non-GGCTs										
Treatment Type										
Surgery alone										
surgery + RT										
Surgery + chem										
Surgery + Rt + chemo										

Table 4. Summary of regression model for deaths not from Recurrence								
	SMN		Cardiac		Pulmonary		Other	
	RR	95% CI	RR	95% CI	RR	95% CI	RR	95% CI
Sex								
Male								
Female								
Age at Dx								
Years since Dx								
5-9y								
10-14y								
15-19y								
>20 y								
CNS Radiation								
Whole brain/CSI								
Focal only								
None								
Alkylating Score								
epipodophillotoxin score								

Table 5. SMN Occurrence Based on Original Diagnosis and Treatment Type						
	Primary CNS Tumor			Treatment Type		
SMN	Glial	PNET	Ependymoma	Surgery alone	Surg + RT	Surgery + RT + Chemo
Leukemia						
CNS Tumor						
HD						
NHL						
Nueroblastoma						
ST Sarcoma						
Bone Cancer						

Table 6. Multivariate Analysis of RF's for SMN by CNS tumor Diagnosis										
	Astrocytoma		Medulloblatoma		Ependymoma		Geminoma		sPNET	
Sex										
Male										
Female										
Age at Dx										
0-3y										
4-9y										
10-14y										
>15y										
CNS Radiation										
Whole brain/CSI										
Focal only										
None										
Alkylating Score										
epipodophillotoxin score										

Table 7. Relative risks and 95% CI for chronic health conditions in CNS tumor Survivors compared to Siblings						
	Grade 1-4		**Grade 3 or 4**		**>2 conditions**	
	RR	**95%CI**	**RR**	**95% CI**	**RR**	**95%CI**
Siblings						
All CNS Survivors						
Primary Dx						
Astrocytoma						
Medulloblastoma						
Ependymoma						
Germinoma						
Non-GGCTs						
Treatment Type						
Surgery alone						
surgery + RT						
Surgery + chem						
Surgery + Rt + chemo						

Tables for all additional outcomes will follow a general format consistent with the templates below:

	Outcome Measure of Interest			
Primary Diagnosis				
Astrocytoma				
PNET				
Ependymoma				

	Outcome Measure of Interest			
Treatment Type				
Surgery alone				
Surgery + RT				
Surgery + RT + Chemo				

References

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4. Mitby PA, Robison LL, Whitton JA, et al: Utilization of special education services and educational attainment among long-term survivors of childhood cancer: a report from the Childhood Cancer Survivor Study. Cancer 97:1115-26, 2003
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8. Hudson MM, Mertens AC, Yasui Y, et al: Health status of adult long-term survivors of childhood cancer: a report from the Childhood Cancer Survivor Study. Jama 290:1583-92, 2003

Appendix

	Previously Reported on CNS Tumors	Additional Analyses Planned for this Report on CNS Tumors
Outcome Measure		
Mortality[1]	-377 deaths among Primary CNS tumor pts. -Cumulative mortality = 16.8% at 20 years -Specific causes of death among all participants (list) -Yearly mortality rate for death due to recurrence for all CNS tumors = .91% -Cause specific SMRs for all CNS tumors as a single group -Poisson regression model for deaths not from recurrence among all participants	-Cumulative mortality by major CNS diagnosis* -Cumulative mortality by major treatment category^ -Specific causes of death among CNS tumors -Yearly mortality rate for Death by recurrence by specific CNS tumor diagnosis* and also by treatment category^ -Cause specific SMRs for CNS tumors by major CNS diagnosis* and by major treatment category^ -Poisson regression model for deaths not due to recurrence among all CNS tumors
Recurrence	-Publication pending	-Number of cases of recurrence of primary tumor among CNS tumor survivors -Cumulative incidence of recurrence among CNS tumor survivors - Multivariate analysis of RFs for recurrence among CNS tumors
Second Malignant[2] Neoplasm	-24 cases of SMN among CNS primary tumors patients at baseline study -Cumulative incidence of SMN = 3.2% at 20 years -Standardized incidence ratios (SIR) of SMNs among all participants -Multivariate analysis of RFs for SMN among CNS tumors	-Update number of cases of SMN among CNS tumor survivors, from follow-up #2 and break down by major CNS tumors by diagnosis* and by major treatment category^ -Cumulative incidence of SMN among CNS tumor survivors -SIRs of all types of SMNs among primary CNS tumors - Multivariate analysis of RFs for SMN among CNS tumors, however, with more

		detailed exposure data (should include radiation variables, not included in original report)
Chronic Medical[3] Conditions	-complete reports on cardiac, endocrine, and neurologic outcomes for patients with CNS tumors	-Evaluate respiratory, urinary, digestive, and surgical outcome measures for significant findings -Follow-up cardiac, neurologic and endocrine from F/U survey 1 & 2
Education[4]	-CNS tumor patients less likely to complete high school compared to sibs (OR = 2.7) -more likely to use special education services (OR = 18.8)	-Evaluate high school and college completion and use of special education services by both major treatment group and by primary diagnosis (this may be a good opportunity to highlight our very large medulloblatoma group)
Employment[5]	-"Ever had a job" and "Employment in the last year" reported in bone tumors only	-report "ever had a job", "job in last year", "ever not gotten a job because of medical history" and "personal income last year" in CNS tumors as compared to sibs and then among CNS tumors by treatment group.
Insurance[6]	-"Currently have health insurance" and "had difficulty obtaining health insurance" reported in all survivors vs. siblings -Multivariate analysis shows cranial radiation risk factor for lack of insurance	-Report findings for health/life insurance among CNS tumors (total, and by treatment type) -Consider multivariate model with insurance status as outcome adjusting with factors consistent with report by Parks
Marraige[7]	-CNS tumor less likely to be married and more likely to be divorced than US population (descriptive data only)	-Likelihood of marriage and divorce in CNS tumor compared to sibs -Likelihood of marriage and divorce among CNS tumors assessed by treatment group and by diagnosis (again, an opportunity to highlight medulloblastoma patients)
Health Status[8]	CNS tumors at increased risk for adverse health status compared with Leukemia survivors, and at higher risk than any other primary diagnosis when compared to sibs (OR = 3.5) for poor general health and functional impairment, and mental health	-Report percentage of participants with CNS tumors who have adverse health status (6 domains) by primary CNS tumor diagnosis and also by treatment type -Multivariate regression for all 6 domains of health status among primary CNS tumors controlling for demographic and social factors as per Hudson and including variables for the major

		treatment domains and for radiation dose and location

* = Major CNS Diagnostic categories (# of pts at baseline): Astrocytoma (1610 = 383 high-grade + 294 low-grade + 992 astrocytoma NOS), PNET (541), Ependymoma (186)
^ = Major treatment categories: Surgery alone (414), surgery + radiation (682) + surgery+ radiation + chemotherapy (446)
© = maximum total radiation dose (none, <30Gy, 30-49Gy, >/=50Gy)
♠ = location of maximal radiation dose (none, Frontal cortex, temporal cortex, parietal/occipital cortex, posterior fossa, spine)