Analysis Concept

STUDY TITLE: Prevalence of gonadal failure and infertility in survivors of childhood brain tumors: a report from the Childhood Cancer Survivor Study

WORKING GROUP: Chronic disease

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BACKGROUND AND RATIONALE

While outcomes for pediatric cancers have improved, high rates of morbidity remain in the long term.[1-3] Survivors of pediatric central nervous system (CNS) malignancies are at increased risk of late effects from therapy, including neurocognitive impairment, obesity and panhypopituitarism, when compared with their peers in the general population.[1,4-9] Previous proposals through the Childhood Cancer Survivor Study (CCSS) have evaluated fertility outcomes (**Table 1**).[10-13] However, these studies have often included all survivors of childhood cancer including leukemias, extra cranial solid tumors and CNS tumors.

Therapy for pediatric CNS malignancies carry a unique risk for gonadal impairment as treatment can affect both central gonadotropin secretion via intracranial radiation and cause primary ovarian or testicular dysfunction via alkylator chemotherapy.[14-16] The dose response relationship for the risk of ovarian failure from stray radiation including either the CNS or gonads is well established.[17] Furthermore, radiation to the CNS impacts the hypothalamic-pituitary axis in patients treated for other malignancies.[18] In the last two decades, we have improved understanding regarding specific impact of cranial radiation therapy used for treatment of CNS tumors. In one early review of 32 post-pubertal patients treated for CNS tumors in childhood, radiation doses of $\geq$40-70Gy to the CNS region in 14 of 23 (61%) resulted in laboratory of hypogonadism.[19] More recently, radiation sparing approaches to therapy have been adopted for very young children with CNS tumors to preserve neurocognitive function.[20-22] These protocols include high dose alkylator therapy, which may be followed by radiation therapy at the time of relapse. While avoiding radiation in very young children seems to improve intellectual function,[21] other late effects of this intensive therapeutic approach are not as well understood. Primary ovarian failure is reported in this group of cancer survivors;[23-25] however, these studies lacked more in-depth analyses that accounted for both alkylator and CNS radiation exposure.

Although it is well known that many treatment factors affect endocrine function, including gonadal function in survivors of pediatric CNS tumors, it is not clear whether the age at the time of treatment changes risk of gonadal failure. The average age of onset of puberty in the United States is 8-13 years in females and 9-14 years in males.[26] Prior to puberty, the hypothalamic-pituitary-gonadal (HPG) axis is dormant and activation at puberty occurs in response to gonadal hormone secretion resulting in growth, physical maturation, and fertility. Some early work by Shalet et al in pediatric cancer survivors suggested a higher incidence of gonadal failure in those children treated prior to puberty.[27-29] These

reports with limited numbers were not specific to CNS tumors and not necessarily reflective of current therapy. More recently, Meacham et al and van Dorp et al have both reviewed reproductive function in pediatric cancer survivors and found that within female survivors, older age at time of treatment conferred a greater risk of gonadal failure as a result of the age-related decline in ovarian reserve.[30,31] In contrast, others (albeit in small numbers with limited analysis) have hypothesized that oncologic treatment given to pre-pubertal children may result in a decreased risk of gonadal failure compared with pubertal children who received the same treatment.[15] The impact of radiation therapy and alkylator exposure to the HPG axis in relation to age has not yet been formally evaluated in a large cohort of CNS tumor survivors.

While previous CCSS proposals and non-CCSS research have described gonadal failure and fertility outcomes, to our knowledge, there are no dedicated analyses of gonadal failure and infertility outcomes within survivors of pediatric CNS tumors within such a large cohort. The CCSS cohort provides a unique opportunity to examine the effects of therapy for childhood CNS tumors on reported gonadal failure and fertility. In addition, in prior proposals, the data for survivors of CNS tumors are described together with those of other solid tumors and leukemia. Furthermore, a unique group within CNS tumor survivors are those treated with radiation sparing means as per infant CNS tumors protocols and it will be important to describe endocrine outcomes in this group separately within CNS tumors survivors. Building on the work by Moustoufi-Moab et al,[32] from the original subcohort, this proposal will aim to address these gaps and describe gonadal function and infertility outcomes in a disease-focused group of CNS tumor survivors treated from 1970 to 1999. The large size of the CCSS e cohort (N= ?) will also provide greater power (increased CNS tumors survivors by one third) with which to examine individual treatment groups including less studied radiation sparing approaches for very young children[33] and the impact of pubertal status at the time of treatment on gonadal function in survivors. Furthermore, we will explore the association between treatment factors and age of treatment with gonadal failure and infertility using age cut-offs that represent typical stages of HPG axis maturation.

Supplemental Table 1: CCSS analyses of fertility or gonadal function

Proposal#	Concept Title	Approval Year	Citation	Relationship to current proposal
03-07	Fertility rates in long-term survivors.	2003	Green DM, et al. J Clin Oncol. 2009. PMID: 19364965 (female) Green DM, et al. J Clin Oncol. 2010. PMID: 19949008 (male)	These studies do not include gonadal failure or relationship to treatment; limited to baseline cohort.
09-11	Fertility Rates in Long-Term Survivors of Acute Lymphoblastic Leukemia.	2009	Green DM, et al. Fertil Steril. 2011 PMID: 21376314	Does not include survivors of CNS tumors; limited to baseline cohort
10-24	Male Infertility and fertility preservation in childhood and adolescent cancer survivors diagnosed from 1970-1986: A report from the Childhood Cancer Survivor Study.	2010	Wasilewski-Masker K, et al. J Cancer Surviv. 2014. PMID: 24711092	Baseline cohort males only, does not include current therapeutic approaches including radiation sparing treatment
11-04	Infertility and the use of fertility treatments in female survivors of childhood cancer.	2011	Barton SE, et al. Lancet Oncol. 2013. PMID: 23856401	Baseline cohort females only
14-05	Fertility following Contemporary Chemotherapy in Childhood Cancer Survivors.	2014	Chow EJ, et al. Lancet Oncol. 2016. PMID: 27020005	Entire CCSS population but specifically excluded those exposed to cranial & gonadal radiation
14-02	Chronic endocrine disorders in adult survivors of childhood cancer: A Report from the Childhood Cancer Survivor Study.	2014	Mostoufi-Moab S, et al. J Clin Oncol. 2016. PMID: 27382091	Description of gonadal failure. Does not include expansion cohort
15-05	Cyclophosphamide Equivalent Dosing and Male Health Late Effects – Infertility, Erectile Dysfunction, Sexual Function and Testosterone Replacement Therapy in Survivors diagnosed from 1970-1986: A report from the Childhood Cancer Survivor Study.	2015	Gilleland Marchak J, et al. Cancer. 2018. PMID: 29663341	Specific evaluation of cyclophosphamide treatment and impact on gonadal function in men; limited to baseline cohort only.
17-13	Infertility, assisted reproductive technology utilization and pregnancy outcomes in childhood cancer survivor population: a CCSS and SART CORS data linkage study	2017	Not yet published	

AIMS AND HYPOTHESES

Aim 1. To describe the prevalence of and risk factors associated with gonadal failure (defined collectively as patient reported gonadal failure, early menopause, premature ovarian failure, primary

amenorrhea, or report of using estrogen or testosterone replacement therapy) in survivors of childhood CNS tumors by tumor type (medulloblastoma, ependymoma and gliomas) compared with siblings. *Hypothesis*: Gonadal failure (as defined) will be more commonly reported in survivors of childhood CNS tumors than in sibling comparators and will vary by CNS tumor diagnosis. Furthermore, gonadal failure will be more commonly reported in those subjects who are older (>8 years of age) at the time of diagnosis, who received higher cumulative cyclophosphamide equivalent doses or in those who received ≥30 Gy of CNS radiation therapy.

Aim 2. To describe the prevalence of and risk factors associated with infertility (based on patient report for those women who attempted to become pregnant for one year or more, without success or men whose partners have attempted to conceive a child for one year or more without success or those women with ovarian failure who may not have attempted pregnancy) in survivors of childhood CNS tumors by tumor type (medulloblastoma, ependymoma and gliomas) compared with siblings. *Hypothesis:* Infertility will be more common in survivors of childhood CNS tumors than in siblings and will vary by CNS tumor diagnosis. Furthermore, gonadal failure will be more commonly reported in those subjects who were older (>8 years of age) at the time of diagnosis, who received higher cumulative cyclophosphamide equivalent doses or in those who received ≥30 Gy of CNS radiation therapy.

ANALYSIS FRAMEWORK

Surveys: Baseline surveys and all CCSS Follow-up questionnaires for original and expansion cohorts. **Study Population:** This study will include all survivors (aged 15-44 at time of survey) within the CCSS database treated for CNS tumors in childhood (prior to age 21) with a history of medulloblastoma, ependymoma or glioma (N=4029 with treatment data). Survivors will include those treated by any means (including surgery only, chemotherapy, radiation therapy, and/or combination therapy). Siblings of the same age range and who are not surgically sterile will be considered as a comparison group. Analyses will be performed for each sex separately.

Outcomes of Interest

1. Gonadal dysfunction *(as measured on the baseline and follow up questionnaires)* This includes self-reported gonadal dysfunction including ovarian failure or testicular hypofunction and reported post ablative ovarian failure or testicular hypofunction. Information from questionnaires will be used together with the *medications* (use of estrogen, progesterone, testosterone supplementation) to describe reported gonadal failure. We will define gonadal failure as any of: premature menopause, premature ovarian failure, report of primary amenorrhea (no natural menstrual period), use of estrogen, progesterone, testosterone, report of amenorrhea, removal of both ovaries or both testicles similar to prior CCSS analyses[32] and based on the chronic conditions dataset.

2. Infertility, which will be described based on the *baseline and follow-up* CCSS questionnaires (specifically, attempted pregnancy without success). Similar to prior CCSS analyses[10] , this variable will be described together with information from the *medications* section (specifically use of fertility medications if available, for example, clomiphene). Infertility will be defined as those women who attempted to become pregnant for one year or more, without success (*Follow up questionnaire*: N5: was there ever a period in life when you or partner tried for one year or more to become pregnant without success) or men whose have attempted to conceive a child for one year or more without success or those women with ovarian failure who may not have attempted pregnancy. Within the CCSS questionnaires, this will include any of: attempt at pregnancy for more than 1 year without success, treatment with fertility medications (clomid, progesterone), fertility procedure, removal of both ovaries or both testicles. Report of pregnancy will be evaluated using *follow-up CCSS questionnaires* defined using time to first pregnancy.

Covariates: Demographics (race, sex, education, marital status), age at diagnosis, tumor type (medulloblastoma, ependymoma or glioma), cancer treatment (chemotherapy, radiation therapy or combination of both), Contributing psychosocial and other factors (marriage, education), medical care (hormonal systems, gonadal function, surgical procedures, pregnancy history, medications, menstrual history)

Covariates – Questionnaire Specific Items:

1. Demographics
   - Age at follow-up
   - Sex
   - Race/Ethnicity
   - Marital Status:

    - Current living arrangement
    - Ever been married or live in partner
    - Current marital status

2. Age at diagnosis
    - Age brackets (<8 years, >=8 years) will be used to explore the association between treatment factors and age of treatment with gonadal failure and infertility using age cut-offs that represent relevant stages of HPG axis maturation.
3. Tumor type
    - Medulloblastoma
    - Ependymoma
    - Glioma
4. Cancer treatment
    - Surgery
        - Biopsy vs resection of primary tumor
    - High risk therapeutic exposures defined based on Children's Oncology Group Long Term Follow Up Guideline[34]. These include total alkylator chemotherapy dose, total cranial radiation dose.
        a. Alkylator exposure: The total exposure to alkylating agents will be quantified as cyclophosphamide equivalent dose and the doses of each individual agent (in total dose per square meter of body surface area) [Alkylators included: busulfan, carmustine, chlorambucil, cyclophosphamide, ifosfamide, lomustine, mechlorethamine, melphalan, procarbazine, thiotepa]. This will be converted to cyclophosphamide equivalent dose[35]. We will then consider categorizing this into low, intermediate and high risk groups per Meacham et al.[30]
        b. Radiation therapy exposure: Reported in Gy and reported as maximum dose to brain segment 2 (surrogate for pituitary/hypothalamus) and maximum dose to testis or ovaries.

Primary statistical analyses:

A priori, analyses will be performed for each sex separately. Descriptive analyses including mean, median and percentages will be analyzed for each primary outcome. Demographic information will be shown as per **Table 2**. Therapy specific toxicity will be described by sex and therapy received (**Table 3**). Prevalence estimates of gonadal failure or infertility will be generated for survivors and siblings, rather than incidence as time to gonadal failure is not available from this dataset. A generalized linear model for the binary outcomes will be evaluate the relationship of covariates described above with gonadal failure or infertility and will be adjusted for age at follow-up survey (**Table 4** *Gonadal Failure, note analysis will be repeated for Infertility Outcome* [**Table 5]**). If the outcomes are rare, logistic regression will be used, otherwise a log-link will be used to model prevalence ratios. Variables in regression analyses will include intracranial radiation therapy, total alkylator dose (in cyclophosphamide equivalent dosing) and age at diagnosis. In addition to the above, when gonadal

failure is analyzed as a primary outcome, initiation of estrogen/androgen replacement OR fertility treatment, whichever is earlier, will be used as outcome of interest. Reported prevalence of gonadal failure and infertility will be compared in age-adjusted models to healthy sibling comparators.

Finally, prevalence estimates as a function of age will be generated to compare risk of gonadal failure and infertility over time between survivors and siblings (**Figures 1 and 2**)

Table 2: Subject Demographics						
	Males N (%)		**Female N (%)**		**Total Population (Survivors) N (%)**	**Total Population (Sibling Comparators) N (%)**
	Subjects	**Sibling Comparison**	**Subjects**	**Sibling Comparison**		
Total						
Age at diagnosis						
<5 years						
5-8 years						
>8 years						
Tumor type						
Medulloblastoma						
Ependymoma						
Glioma						
Therapy received						
Chemotherapy						
Radiation						
Both chemotherapy and radiation						
Neither chemotherapy or radiation therapy						
Medications						
Estrogen or androgen replacement						
Fertility augmentation						
Pregnancy to term*						
Reported gonadal failure						
Reported infertility						
*patient or patient's partner						

Table 3: Therapy Specific Information			
	Males	**Female**	**Total Population of CNS Tumor Survivors**
Alkylator exposure N (%)			
Cyclophosphamide equivalent dose (CED, mean, SD)			
Low (<8/m^2) N (%)			
Moderate (8-12 g/m^2) N (%)			
High (>12 g/m^2) N (%)			
Radiation therapy			
CNS radiation N (%)			
Maximum brain segment 2 dose* (Gy)			
HPA dose* ≥30 Gy N (%)			
HPA dose* < 30 Gy N (%)			
Gonadal radiation N (%)			
Median dose to gonad (Gy)			
Yes			
No			

*****Brain segment 2 dose will be used as surrogate marker of HPA axis dose

Table 4 Logistic regression model evaluating gonadal failure		
	Ovarian Failure OR (95% CI)	**Testicular hormonal failure OR (95%CI)**
Diagnosis		
Medulloblastoma		
Ependymoma		
Glioma		
Age at diagnosis		
<5 years		
5 – 8 years		
>8 years		
Treatment modality		
Chemotherapy		
Radiation therapy		
Both		
Total cyclophosphamide equivalent dose		
Low (<8/m^2)		
Moderate (8-12 g/m^2)		
High (>12 g/m^2)		
None		
Surgical (brain) intervention		
Biopsy		
Resection		
None		
CNS radiation therapy		
HPA dose* ≥30 Gy		
HPA dose* < 30 Gy		
None		
Gonadal radiation therapy		
Yes		
Dose (Gy)		
No		

*****Brain segment 2 dose will be used as surrogate marker of HPA axis dose

Table 5: Logistic regression model evaluating infertility based on age at diagnosis, tumor type and treatment received		
	Infertility, Female CNS tumor survivor, N (%)	**Infertility, Partner of male CNS tumor survivor, N (%)**
Variable List Above (Table 1)		

Proposed Figure 1: Cumulative incidence of self-reported gonadal failure in survivors when compared to siblings over time
Y axis: incidence of gonadal failure, X axis: time. P value reporting statistical difference between incidence in survivors and sibling comparators

Proposed Figure 2: Cumulative incidence of self-reported infertility in survivors when compared to siblings over time
Y axis: incidence of infertility, X axis: time. P value reporting statistical difference between incidence in survivors and sibling comparators

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