CHILDHOOD CANCER SURVIVOR STUDY

Analysis Concept Proposal

February 18, 2013

1. **STUDY TITLE: Subsequent Neoplasms in Survivors of Central Nervous System Tumors**

2. WORKING GROUP AND INVESTIGATORS: This proposed publication will be within the Subsequent Malignancy Working Group with secondary oversight by the Chronic Disease Working Group. Proposed Investigators will include:

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Background:

Treatment outcomes for children diagnosed with medulloblastoma have improved over the past three decades. Prior to the mid- 1980s and use of risk stratification, children older than 3 years of age at diagnosis, with medulloblastoma were treated with 36 Gy Craniospinal radiotherapy (CSI) and an additional boost to the posterior fossa, and had a predicted 5 year progression free survival of 50% to 65% [1]. Over the years, risk stratification was used in attempt to reduce radiation dose, by adding adjuvant chemotherapy, to reduce the undesirable side effects of radiation including neurocognitive and endocrine sequelae. Chemotherapy has been increasingly used and intensified, and is now well accepted as adjuvant therapy for treatment of both average and high risk disease. The St. Jude protocol SJMB96 treated 134 children from 1996-2003 using risk-adapted CSI 23.4Gy for average risk and 36-39 Gy for high risk disease, followed by high dose chemotherapy and stem cell rescue. This resulted in a 5 year event-free survival of 83% (73-93%) in the average risk group, and 70% (55 – 85%) in the high risk group, and overall survival of 85% (75%-94%) and 70% (54%-84%)[2].

In a recently published update of COG 9961, a regimen where 379 children with average risk disease were treated with 23.4 Gy CSI and posterior fossa boost of 32.4 to a total dose of 55.8Gy, a concerning ten year cumulative incidence rate of secondary malignancy of 4.3% (1.9% to 6.5%) was reported, when compared to 1.1% at five years. Patients were treated with chemotherapy comprising of 8 cycles of Cisplatin, Lomustine and Vincristine, as compared with Cisplatin, Cyclophosphamide, and Vincristine(Packer, Gajjar et al.).

This study found 4 cases of second malignant neoplasm (SMN) arose within 5 years of follow up, and 11 cases beyond 5 years of diagnosis, a median timing of diagnosis at 5.6 years (3.1years to 16.8 years). The study raised the concern that use of adjuvant chemotherapy to reduce CSI dose may result in an increased risk for subsequent neoplasm[4]. Furthermore in a recent prospective series from Germany which treated 280 patients with either pre- and post-radiation (RT) chemotherapy, 12 patients developed secondary tumors, including 3 with high grade glioma. Of the 12 patients, two-thirds of patients received the more aggressive sandwich chemotherapy[5].

The etiology of second neoplasms is likely multi-factorial. A previous report in children with primary CNS tumors treated at St. Jude Children's Research Hospital found associated genetic abnormalities in 29% of patients who subsequently developed a second neoplasm[6]. It is well known that radiation therapy predisposes children to subsequent malignant and non-malignant neoplasm, with risk that remains beyond 20 to 30 years post therapy. Furthermore it is increasingly identified that both age of exposure and maximum cranial dosage received are associated with increased cumulative incidence of second neoplasm. From the Childhood Cancer Survivor Study (CCSS), Neglia et al, reported a linear relationship between RT dose and Excess Relative Risk (ERR) for development of subsequent glioma and meningiomas, and the risk of development of glioma is highest in children exposed to RT in less than 5 years of age[7]. Another paper from CCSS indicated that patients who receive RT> 50Gy had a cumulative incidence of a CNS subsequent neoplasm 25 years after diagnosis of 7.1%, compared with 5.2% in those receiving <50 Gy[3].

As we continue to refine our treatment for children diagnosed with medulloblastoma using adjuvant chemotherapy to radiation therapy and surgery, there has been no study that compares the occurrence of subsequent neoplasms from the era when patients received RT alone to current treatment with adjuvant chemotherapy in the recent era. ***This concept proposes to use the subset of survivors of medulloblastoma in CCSS who received RT only (n=140) as a comparison population (Aim 1). The cumulative incidence of subsequent neoplasms from the RT only era (CCSS) and the current era of adjuvant chemotherapy (SJMB studies) will be compared. This concept is a request for release of the CCSS for this St. Jude study.*** In addition, it is important to update and further clarify the characteristics of subsequent neoplasms in our growing population of CNS tumor survivors at St. Jude Children's Research Hospital, and demographic features or treatment factors related to the occurrence of subsequent neoplasm (Aim 2, St. Jude data only). Dr. Tsui is a neuro-oncology fellow leading this St. Jude study under the supervision of Dr. Armstrong.

Aims:

1) To assess whether historical changes in primary therapy for medulloblastoma (addition of chemotherapy, dose reduction of RT) have resulted in an increase in the cumulative incidence of subsequent neoplasms.

2) To estimate the overall cumulative incidence, standardised incidence ratio (SIR) and absolute excess risk of subsequent neoplasms in the large SJ population of CNS tumour survivors and explore demographic and treatment related risk factors for SMN occurrence.

Hypothesis:

1) Patients treated with Craniospinal RT, with addition of chemotherapy for medulloblastoma will not have an increased cumulative incidence of subsequent neoplasms compared to a control population that received 36 Gy Craniospinal RT and no chemotherapy

2) Radiotherapy exposure will be associated with the incidence of subsequent neoplasms

Population:

Aim 1: 5 year survivors enrolled on SJMB096, SJMB03, to be compared with ***140 patients with medulloblastoma who were treated with RT therapy and surgery alone in CCSS***.
Aim 2: 2760 patients enrolled treated in the St. Jude Brain tumour program, 1985-2011.

Outcome of interest:

Aim 1: Subsequent neoplasms (ICDO codes ending in .0-.3) confirmed by pathology report at St. Jude, or at outside institutions, compared to confirmed CCSS subsequent neoplasms.

Aim 2: Cancers eligible for inclusion in these analyses will have International Classification of Disease of Oncology codes: subsequent neoplasms (ICDO codes ending in .0-.3) and subsequent malignant neoplasms (ICDO .3 only)

<u>Analytical Plan: Aim</u> 1

Explanatory Variables

1) Risk group (average risk vs. high risk)

2) Sex

Figure 1: Cumulative Incidence of subsequent neoplasm from time of initial diagnosis by CCSS, and SJMB 96/03, using death as a competing risk among 5 year survivors.

Cumulative incidence estimates for developing subsequent neoplasm will be calculated using Kalbfleisch and Prentice[STAT1] approach where death is treated as a competing risk and any survivor not developing SN is censored at the last follow-up time. Time to developing SN is calculated from the time of entry into cohort (5 years after primary cancer diagnosis) to the time of first occurrence of subsequent neoplasm. Two cumulative incidence figures will be generated to describe 1) CCSS patients compared to SJMB patients 2) Average risk patients SJMB vs. High Risk SJMB. For 1), cumulative incidence functions of the CCSS and SJMB groups will be estimated by the method of Kalbfleisch and Prentice [8]and compared using the method proposed by Gray[9]. Due to very different lengths of follow up between the CCSS and SJMB, the comparison of their incidence functions may not be optimal; therefore, we will also use a Z-test based on the approach decribed by Pintilie[10] to compare the cumulative incidences between the two groups at 5 year and 10 year, respectively, at level α=0.025 to control the type one error rate for the two comparisons. Cumulative incidence tables will be provided to describe the yearly estimated incidence throughout the follow up. Consistent with the CCSS cohort, only 5+ year survivors of SJMB will be included. SJMB patients who expired within 5 years of diagnosis will be described. For 2) cumulative incidence function will be compared using the method proposed by Gray[9].

Table 1:

Data collection for demographic variables listed on the left column of Table 1 amongst the 5 year survivors of CCSS with medulloblastoma /PNET treated with surgery and RT only, and of SJMB96 and 03 treated with average and high risk protocol. Patient numbers and percentages are listed. Statistical analysis will be performed to assess any differences in patient characteristics across groups.

Table 1. Demographics and treatment characteristics of children diagnosed with medulloblastoma / PNET

	CCSS N=140 (%)	**SJMB96/03 Average Risk N = (%)**	**SJMB96/03 High Risk N= (%)**
Gender			
M			
F			
Age at diagnosis			
0-<3			
≥3-<9			
≥9-<15			
≥15			
Ethnicity			
Non-Hispanic White			
Non-Hispanic Black			
Hispanic			
Other			

Location of Tumor
Posterior fossa
Supratentorial
Treatment Era
1970-1979
1980-1989
1990-1999
2000-2009
2010-present
Chemotherapy received (Yes/ No)
Cyclophosphamide
CCNU
Cisplatin
Methotrexate
Vincristine
Radiation therapy (median dose)
Craniospinal
Boost to tumor bed
Follow-up duration
5-<10 years
≥10-<15 years
≥15 years
Recurrence status
No recurrence
Recurrence
SN (no. of pt only)
Age at SN diagnosis (median, range)
Latency
<5 years
≥5-<10 years
≥10 years
Vital status
Alive
Dead

Table 2:

Characteristics of each individual case of SN are listed in a table including age at primary diagnosis, SN pathology diagnosis, time from primary diagnosis to subsequent development of neoplasm, CSI dose, maximum RT dose, chemotherapy exposure and survival status to year 2012. In each stratum cases are listed from the most common pathology to the least.

Table 2. Subsequent neoplasm among patients with Medulloblastoma / PNET , stratified by therapeutic exposure

Case			RT alone (CCSS)				Case			RT + Chemotherapy (SJMB)			
	Age at Dx	Histologic diagnosis	Time to SN	CSI dose	Chemo exposure	Vital Status		Age at Dx	Histologic diagnosis	Time to SN	CSI dose	Chemo exposure	Vital Status

Analysis Plan: Aim 2

Explanatory Variables

1) MRN
2) DOB
3) Sex
4) Ethnicity
5) Date of questionnaire completion
6) Date of death
7) Vital status
8) Date of CNS tumour diagnosis
9) Age at diagnosis
10) Location of tumour
11) Grade / Stage of tumour (localised or metastatic)
12) Surgery (Yes / No)
13) Radiation therapy (Dose)
14) Chemotherapy (Yes / No)
15) Diagnosis of a Familial Cancer syndrome
16) Subsequent Malignancy
17) Site of SN
18) Date of Diagnosis of SN
19) Latency

Table 3:

Data collection for demographic variables listed on the left column amongst all survivors with a primary CNS tumor in the St. Jude cohort without subsequent neoplasm, and 5 year survivors with a primary CNS tumor who are subsequently diagnosed with a neoplasm. Statistical analysis will be performed on each variable for any differences in patient character across groups.

Table 3. Demographics and treatment characteristics of children diagnosed at St. Jude with a primary CNS tumor without and with development of a subsequent neoplasm

	St. Jude 5 year survivors without SN N=	**Children diagnosed with a SN N =**
Gender		
M		
F		
Age at diagnosis		
0-<3		
≥3-<9		
≥9-<15		
≥15		
Ethnicity		
Non-Hispanic White		
Non-Hispanic Black		
Hispanic		
Other		
CNS Tumor Type		
Astrocytic tumor		
Glioma		
Medulloblastoma / PNET		
Ependymoma		
Other CNS tumor		
Treatment Era		
1970-1979		
1980-1989		
1990-1999		
2000-2009		
2010-present		
Primary treatment		
Surgery only		
Surgery + RT		
Surgery + chemo		
Surgery + RT + chemo		
Chemotherapy received (if data available)		
Yes		

No
Radiation therapy
Craniospinal
Boost to tumor bed
Primary RT dose
<50Gy
>50Gy
Follow-up duration
<5 years
≥5-<10 years
≥10-<15 years
≥15 years
Progression status
No progression
Single progression
Multiple progression
Age at SN diagnosis
<5 years
≥5-<10 years
≥10-<15 years
≥15-<20 years
≥20-<25 years
≥25 years
Latency
<5 years
≥5-<10 years
≥10 years
Vital status
Alive
Dead

Table 4:

SN cases from the St. Jude 5 year survivors are divided into 2 groups: subsequent malignant neoplasms (SMN; those neoplasms included in SEER), and the neoplasms not included in SEER (largely benign meningiomas and non-melanoma skin cancers). Number of observed events is documented for each category. Number of expected events in the general population will be calculated using SEER age-, sex- and calendar year-specific incidence rates. SIR will be calculated by dividing the number of the observed events by the number of the expected events. Absolute Excess Risk will be obtained by subtracting the expected number from the observed number and dividing the difference by the person-years of follow-up and multiplying it by one thousand. In addition, median time to development of subsequent malignancy for each patient characteristic will be reported.

Table 4. Unadjusted SIRs of subsequent neoplasm stratified by patient characteristics in St. Jude 5 year survivors.

Characteristics	Observed events	Expected events by SEER	SIR (95%CI)	Median no. of years to occurrence
Subsequent neoplasms for which SIRs could be calculated (Overall)				
Sex				
Male				
Female				
Age at diagnosis				
< 5 years				
≥5-<10 years				
≥10 years				
Subsequent Malignancy				
Leukemia				
Lymphoma				
CNS				
Breast				
Bone				
Soft tissue Sarcoma				
Thyroid				
Melanoma				
All other second neoplasms for which SIRs could not be calculated				
Nonmelanoma skin cancer				
Nonmalignant meningiomas				

Table 5:

SMN case numbers by tumor group and respective expected events and SIRs are calculated. Median number of years to occurrence are documented, and statistical analysis for assessing differences in latency will be performed.

Table 5. Unadjusted SIRs of subsequent neoplasm by primary tumor diagnosis in the St. Jude5 year survivors who were diagnosed with a primary CNS tumor.

	Observed SN	Expected events by SEER	SIR (95% CI)	Median no. of years to occurrence
Astrocytoma / Glial tumor				
Medulloblastoma				
Ependymoma				
Other CNS tumors				

Figure 2: Cumulative Incidence rate estimates of subsequent neoplasm by primary diagnosis in survivors diagnosed with a primary CNS tumor

Cumulative incidence rate estimates of subsequent neoplasms for astrocytoma or glial tumor, medulloblastoma, ependymoma, and other CNS tumors will be reported in a similar manner as described for Aim 1 with death as a competing risk. The time to developing the subsequent neoplasm will be obtained from the time of diagnosis of primary CNS tumor to the time of first occurrence of subsequent neoplasm and any survivor not developing the SN will be censored at the last follow-up time.

References:

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