Childhood Cancer Survivor Study

Analysis Concept Proposal

Title: Medulloblastoma and Primitive Neuroectodermal Tumor (PNET) Outcomes Across Three Decades of Diagnosis

Working Group and Investigators:

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

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Background & Rationale:

Medulloblastoma and primitive neuro-ectodermal tumor (PNET) account for over 20% of malignant brain tumors in children[1]. Current treatment strategies consist of maximal surgical resection, followed by the combination of craniospinal irradiation (CSI) and chemotherapy. This multimodal approach has markedly improved survival over the last four decades making medulloblastoma and PNET curable in up to 70-85% of patients[2] depending on multiple factors including age, location, histologic and biological characteristics of the tumor, extent of disease and resection.

Therapy for medulloblastoma and PNET has evolved over the years to the well-accepted multimodal regimens currently used. Historically, while surgery alone resulted only in recurrence and death, the first survivors of medulloblastoma were reported once CSI was introduced

therapeutically in this population with orthovoltage equipment[3]. As early as the 1970's the use of adjuvant radiation therapy (CSI with boost dose RT to the posterior fossa) after surgery resulted in improved survival in patients with medulloblastoma/PNET[4]. The typical radiation doses delivered were 35-36 Gy to the neuraxis (CSI) with an additional 18-20 Gy boost to the posterior fossa (or supratentorial region, in the case of PNET). This postoperative "standard-dose" CSI approach alone resulted in 5-year event free survival (EFS) rates of approximately 60%[5]. During the mid to late 1980's and the 1990's, chemotherapy was incorporated as adjuvant treatment for medulloblastoma/PNET and led to improved disease control. Early reports showed that addition of chemotherapeutic regimens containing CCNU and vincristine to radiotherapy in newly-diagnosed patients with medulloblastoma/PNET offered prolonged survival[6].

Importantly, in the 1990's, patients with medulloblastoma/PNET were risk-stratified based on age, extent of surgical resection and metastatic status at diagnosis[7]. Patients 3 years and older, with a residual disease cross-sectional area of less than 1.5 cm^2 and no evidence of metastatic disease were considered to be average-risk, whereas patients who did not fulfill these criteria were classified as having high-risk disease. The intent was to reduce radiation-related sequelae by reducing the CSI dose from 36 Gy to 23.4 Gy in average-risk patients and to improve survival in high-risk patients by maximizing therapeutic intensity with 36-39.6 Gy CSI and adjuvant chemotherapy. Following encouraging results from pilot studies[4b, 8], 421 patients aged 3-21 years were enrolled in a phase III study of CSI + boost RT, followed by adjuvant chemotherapy for newly-diagnosed average-risk patients with medulloblastoma/PNET (A9961)[2]. Patients were treated with reduced-dose CSI (23.4 Gy) and one of two adjuvant chemotherapy regimens: CCNU, cisplatin, and vincristine; or cyclophosphamide, cisplatin, and vincristine. Five-year EFS and overall survival (OS) for the 379 evaluable patients were 81% and 86% respectively, establishing excellent OS despite CSI dose reduction. Similarly, studies of patients with high-risk disease, who received 36-39.6 Gy CSI with a variety of adjuvant chemotherapy (including dose-intense therapy with stem-cell rescue) reported improved 5-year overall survival for high-risk patients up to 70%[2b]. A summary of the main treatment regimens and their outcomes during that time period is presented in the table below.

Table 1 Comparison of treatment regimens used in patients with average-risk (a) and high-risk (b) medulloblastoma/PNET

a)

Study	**Treatment**	**5-year EFS**	**OS**
CCG 9892[12]	23.4 Gy CSI + weekly VCR; CCNU+CDDP+VCR	79%	85% (3-year)
SJMB 96[3]	23.4 Gy CSI + high-dose Cyclo/CDDP/VCR	83%	85% (5-year)
A 9961[2]	23.4 Gy CSI +weekly VCR; CCNU/Cyclo+CDDP+VCR	81%	86% (5-year)

b)

Study	Treatment	5-year EFS	OS
CCG 921[11]	36 Gy CSI + CCNU/VCR/Prednisone	63%	56% (7-year)
POG 9031[13]	CDDP/VP 16 + 35.2-40 Gy CSI+ Cyclo/VCR Or 35.2-40 Gy CSI + CDDP/VP 16+Cyclo/VCR	66% 70%	73.1% (5-year) 76.1% (5-year)
SJMB 96[3]	36-39.6 Gy CSI + high-dose Cyclo/CDDP/VCR	70%	70% (5-year)

Abbreviations: Cyclo=cyclophosphamide; CDDP=cisplatin; VCR=vincristine; CCNU= lomustine; VP-16= etoposide.

Risk-adapted therapy has succeeded in improving cure rates for patients with high-risk disease and allowed for therapy reduction in patients with average-risk disease (who constitute around 70% of patients with medulloblastoma/PNET), while maintaining good five-year OS and EFS. However, it remains unclear how this therapeutic evolution has affected long-term outcomes (>5 years from diagnosis) including late mortality, late recurrence of the primary tumor, risk for subsequent neoplasms, other chronic health conditions and important sociodemographic outcomes such as marriage and employment. Previous studies using the CCSS original cohort (1970-1986) have shown that survivors of central nervous system tumors are at high risk for late mortality, subsequent neoplasms, chronic health conditions, social and behavioral difficulties as well as neurocognitive impairment[9]. Specifically, in medulloblastoma/PNET survivors, the risk of death was increased 17-fold compared to the US population with the most common causes being disease progression followed by subsequent neoplasms. In addition, several studies suggest that lower dose CSI regimens may lead to less neurocognitive deficits and intellectual preservation in medulloblastoma/PNET survivors[10]. The detrimental effect of higher doses of CSI on IQ and skills like reading and spelling has been found to be particularly true in younger patients (<7 years of age at diagnosis) when compared to patients who received lower doses of CSI[11].

The recent expansion of the CCSS cohort to include survivors across three decades (1970-1999) offers a unique opportunity to explore the impact of temporal changes in therapy on major late-effect outcomes among almost 1000 five-year survivors of medulloblastoma/PNET in a period when pivotal changes in treatment were made. In particular, this provides an opportunity to evaluate whether dose reduction of CSI with use of adjuvant chemotherapy has resulted in reduced rates of subsequent neoplasms, chronic health conditions and late mortality. This study will also examine key indicators of psychosocial functioning such as educational attainment, employment, insurance and marital status, as detailed in the methods section.

Specific Aims & Hypotheses:

Aim 1:

Assess the all-cause and cause-specific late mortality in medulloblastoma/PNET survivors and compare by: 1) treatment era (1970-1979, 1980-1989, 1990-1999) and 2) based on temporal changes in therapy.

Hypotheses:

-Survivors from more recent eras will have reduced incidence of late mortality.
-Survivors with reduced dose CSI will have a reduced incidence of late mortality.

Aim 2:

Determine the cumulative incidence of subsequent neoplasms (both malignant and non-malignant) among medulloblastoma/PNET survivors and compare by: 1) treatment era (1970-1979, 1980-1989, 1990-1999) and 2) based on temporal changes in therapy.

Hypotheses:

-There will be no difference in cumulative incidence of subsequent neoplasms across treatment eras.
-The cumulative incidence of subsequent neoplasms in the CNS will be reduced in survivors who received reduced dose CSI
-The incidence of subsequent malignant neoplasms in medulloblastoma/PNET survivors will be higher than the general population and higher in survivors who received full dose CSI.

Aim 3:

Quantify the occurrence and severity of chronic health conditions among medulloblastoma/PNET survivors and compare by: 1) treatment era (1970-1979, 1980-1989, 1990-1999) and 2) based on temporal changes in therapy

Hypotheses:

-The cumulative incidence and severity of chronic health conditions will be lower in survivors from more recent eras.
-The cumulative incidence and severity of chronic health conditions will be lower in survivors treated with reduced dose CSI.

Aim 4:

Assess psycho-social functioning among medulloblastoma/PNET survivors and compare by: 1) treatment era (1970-1979, 1980-1989, 1990-1999) and, 2) based on temporal changes in therapy.

Hypothesis:

-Survivors with reduced dose CSI will be less likely to receive special education services, be unemployed, and will be more likely to have insurance.

Methods:

A) Population of Interest:

All patients with medulloblastoma/PNET in the CCSS cohort.

For Aim 1 mortality analyses, all eligible subjects may be used (total n=1442; 1970-1979 (n=228), 1980-1989 (n=508), 1990-1999 (n=686)) and for subsequent Aims, the subset of those who completed a baseline survey will be utilized (total n=997; 1970-1979 (n=148), 1980-1989 (n=350), 1990-1999 (n=499)).

B) Outcomes Measures:

Mortality:
-Vital status (alive/dead)
-All cause mortality
-Cause-specific mortality including:
1) Recurrence of primary childhood malignancy
2) External cause (e.g. accidents, injuries, suicide)
3) Nonrecurrence/nonexternal cause (attributable to chronic health conditions):
    a. subsequent neoplasm cause
    b. cardiac cause
    c. pulmonary cause
    d. other

Subsequent neoplasm:
1) Subsequent neoplasms (includes both malignant and benign)
2) Subsequent malignant neoplasms

Overall chronic health conditions:
Using CTCAE grading, chronic health conditions will be identified. Survivors will be classified as having:
1) No chronic condition
2) Any grade 1-5 condition
3) At least one grade 3-5 condition
4) Multiple grade 3-5 conditions

Specific chronic health conditions:
-Endocrine, cardiac, pulmonary, neurological, vision and hearing conditions will be evaluated

Late recurrence of primary malignancy:
-Disease recurrence after five years from diagnosis

Socioeconomic/Demographic:
-Special education resources placement (see questions in original and expansion Baseline)
- Employment, insurance

C) Explanatory variables:

Treatment era:
-The cohort diagnosed between 1970 and 1999 will be divided into 3 treatment eras of 10 years each (1970-1979, 1980-1989, and 1990-1999)
-Patients will be assigned to a given treatment era based on their date of diagnosis.

Treatment type (three mutually exclusive categories):
-Surgery + CSI $\geq$30 Gy, no chemotherapy
-Surgery + CSI $\geq$30 + chemotherapy

-Surgery + CSI <30 Gy + chemotherapy

Specific treatment exposures:
-Chemotherapy exposure:
- -Chemotherapy (yes/no)
- -CCNU (yes/no)
- -Cyclophosphamide (yes/no)
- -Cisplatin (yes/no)
- -Etoposide (yes/no)
- -Vincristine (yes/no)
- -Prednisone (yes/no)
- -Carboplatin (yes/no)
- -Thiotepa (yes/no)
- -Cytarabine (yes/no)
- -Hydroxyurea (yes/no)
- -Procarbazine (yes/no)

-Radiation therapy:
- -CSI dose: <30 Gy vs ≥30 Gy

Demographic characteristics:
- Age at diagnosis, race, ethnicity, sex

Others:
-Current age, length of follow-up

Statistical Approach:

Aim 1:
For Aim 1, all eligible subjects can be used for the mortality outcomes since NDI data is available for this larger cohort. However, since treatment data is not available for all non-participants and some participants in the original cohort and a small subset of the expansion cohort, we will plan to impute treatment data using similar methods to those employed by Armstrong et al. (in press). Descriptive data on demographic and treatment characteristics (surgery, radiation, and chemotherapy) will be summarized using frequencies, means (SD) and/or medians (Table 2). To accomplish the first aim of assessing the all-cause mortality and cause specific late mortality in medulloblastoma/PNET survivors the 15-year (from diagnosis) cumulative mortality incidence will be reported by treatment era and by treatment type accounting for competing risk of death from other causes (Tables 3 and 4, and cumulative incidence figures to be developed). Standardized mortality ratios (SMR) will be calculated and compared across treatment eras and treatment groups (Table 5). Rates from the National Death Index (NDI) will be reported and compared to the expected survival in age, gender and calendar year matched U.S. population. Hazard ratios/Relative risks comparing survival between different treatment eras and treatment groups will be derived using Cox/Poisson regression models using age as the time scale and adjusting for sex, ethnicity, and either age at diagnosis or years from diagnosis (Table 6).

Aim 2: Cumulative incidence of subsequent neoplasm (SN) will be calculated treating death prior to SN as a competing risk. Figures will be provided for cumulative incidence by treatment era and by treatment type. Standardized incidence ratios (SIR) comparing observed subsequent

malignant neoplasms (SMN) to age, gender and calendar year matched expected rates of same cancers in the SEER U.S, database will be reported by treatment era and treatment type (Tables 7 and 8). The SMN categories that will be examined may be modified depending on the number of events available once data is examined. Hazard ratios comparing the occurrence of SN by treatment era and treatment type will be derived using age as the time scale and adjusting for either age at diagnosis or years from diagnosis, with each being evaluated in separate models to assess which is most important (Table 9).

Aim 3: The incidence and severity of chronic health conditions will be determined by using the methodology described previously[12], a comparison will be performed between treatment eras and treatment groups. Cumulative incidence for three major categories (CTCAE grade 1-5, grade 3-5, and multiple grade 3-5 chronic conditions) will be evaluated (figures to be provided) and Cox proportional hazard models will be used to compare any CTCAE grade 1-5, grade 3-5, and multiple grade 3-5 chronic conditions across treatment eras and reported as hazard ratios with 95% confidence intervals (Table 10). We will evaluate whether age or time from diagnosis are the best measures of the time scale for this model. If sibling data is available for the expansion cohort, a model will be fit for which they will also serve as a comparison population. In that model, age will be used as the time scale as siblings do not have a date of diagnosis for reference. Death due to conditions other than those qualifying as a grade 5 fatal chronic condition will be considered as a competing risk event (i.e. death due to recurrence of primary cancer or external causes such as accidents, injuries or suicide). A similar analysis will be performed to correlate the risk of having any grade 1-5, grade 3-5 or multiple grade 3-5 chronic health condition with more specific chemotherapeutic treatment data when available (Table 10). In addition, cumulative incidence of specific grade 1-5 chronic health conditions (Table 11) will be evaluated across the treatment eras and treatment groups (endocrine, cardiac, pulmonary, neurological, vision, hearing). Hazard ratios with 95% confidence intervals for the comparison of each type of outcome across treatment subgroups will be evaluated.

Aim 4: Comparison of special education placement, insurance status, and employment status in medulloblastoma/PNET survivors will be carried out across treatment eras and treatment types (Table 12). Multivariate comparisons will be adjusted for age, gender and ethnicity.

References:

1. Ostrom, Q. T.; Gittleman, H.; Liao, P.; Rouse, C.; Chen, Y.; Dowling, J.; Wolinsky, Y.; Kruchko, C.; Barnholtz-Sloan, J., CBTRUS Statistical Report: Primary Brain and Central Nervous System Tumors Diagnosed in the United States in 2007-2011. *Neuro-oncology* **2014,** *16 Suppl 4*, iv1-iv63.
2. (a) Packer, R. J.; Gajjar, A.; Vezina, G.; Rorke-Adams, L.; Burger, P. C.; Robertson, P. L.; Bayer, L.; LaFond, D.; Donahue, B. R.; Marymont, M. H.; Muraszko, K.; Langston, J.; Sposto, R., Phase III study of craniospinal radiation therapy followed by adjuvant chemotherapy for newly diagnosed average-risk medulloblastoma. *Journal of clinical oncology : official journal of the American Society of Clinical Oncology* **2006,** *24* (25), 4202-8; (b) Gajjar, A.; Chintagumpala, M.; Ashley, D.; Kellie, S.; Kun, L. E.; Merchant, T. E.; Woo, S.; Wheeler, G.; Ahern, V.; Krasin, M. J.; Fouladi, M.; Broniscer, A.; Krance, R.; Hale, G. A.; Stewart, C. F.; Dauser, R.; Sanford, R. A.; Fuller, C.; Lau, C.; Boyett, J. M.; Wallace, D.; Gilbertson, R. J., Risk-adapted craniospinal radiotherapy followed by high-dose chemotherapy and stem-cell rescue in children with newly diagnosed medulloblastoma (St Jude Medulloblastoma-96): long-term results from a prospective, multicentre trial. *The Lancet. Oncology* **2006,** *7* (10), 813-20.
3. Paterson, E.; Farr, R. F., Cerebellar medulloblastoma: treatment by irradiation of the whole central nervous system. *Acta radiologica* **1953,** *39* (4), 323-36.
4. (a) Davis, F. G.; Freels, S.; Grutsch, J.; Barlas, S.; Brem, S., Survival rates in patients with primary malignant brain tumors stratified by patient age and tumor histological type: an analysis based on Surveillance, Epidemiology, and End Results (SEER) data, 1973-1991. *Journal of neurosurgery* **1998,** *88* (1), 1-10; (b) Hughes, E. N.; Shillito, J.; Sallan, S. E.; Loeffler, J. S.; Cassady, J. R.; Tarbell, N. J., Medulloblastoma at the joint center for radiation therapy between 1968 and 1984. The influence of radiation dose on the patterns of failure and survival. *Cancer* **1988,** *61* (10), 1992-8.
5. Jenkin, D.; Goddard, K.; Armstrong, D.; Becker, L.; Berry, M.; Chan, H.; Doherty, M.; Greenberg, M.; Hendrick, B.; Hoffman, H.; et al., Posterior fossa medulloblastoma in childhood: treatment results and a proposal for a new staging system. *International journal of radiation oncology, biology, physics* **1990,** *19* (2), 265-74.
6. (a) Packer, R. J.; Sutton, L. N.; Elterman, R.; Lange, B.; Goldwein, J.; Nicholson, H. S.; Mulne, L.; Boyett, J.; D'Angio, G.; Wechsler-Jentzsch, K.; et al., Outcome for children with medulloblastoma treated with radiation and cisplatin, CCNU, and vincristine chemotherapy. *Journal of neurosurgery* **1994,** *81* (5), 690-8; (b) Tait, D. M.; Thornton-Jones, H.; Bloom, H. J.; Lemerle, J.; Morris-Jones, P., Adjuvant chemotherapy for medulloblastoma: the first multi-centre control trial of the International Society of Paediatric Oncology (SIOP I). *European journal of cancer* **1990,** *26* (4), 464-9.
7. Zeltzer, P. M.; Boyett, J. M.; Finlay, J. L.; Albright, A. L.; Rorke, L. B.; Milstein, J. M.; Allen, J. C.; Stevens, K. R.; Stanley, P.; Li, H.; Wisoff, J. H.; Geyer, J. R.; McGuire-Cullen, P.; Stehbens, J. A.; Shurin, S. B.; Packer, R. J., Metastasis stage, adjuvant treatment, and residual tumor are prognostic factors for medulloblastoma in children: conclusions from the Children's Cancer Group 921 randomized phase III study. *Journal of clinical oncology : official journal of the American Society of Clinical Oncology* **1999,** *17* (3), 832-45.
8. Packer, R. J.; Goldwein, J.; Nicholson, H. S.; Vezina, L. G.; Allen, J. C.; Ris, M. D.; Muraszko, K.; Rorke, L. B.; Wara, W. M.; Cohen, B. H.; Boyett, J. M., Treatment of children with medulloblastomas with reduced-dose craniospinal radiation therapy and adjuvant chemotherapy: A Children's Cancer Group Study. *Journal of clinical oncology : official journal of the American Society of Clinical Oncology* **1999,** *17* (7), 2127-36.
9. (a) Armstrong, G. T.; Liu, Q.; Yasui, Y.; Huang, S.; Ness, K. K.; Leisenring, W.; Hudson, M. M.; Donaldson, S. S.; King, A. A.; Stovall, M.; Krull, K. R.; Robison, L. L.; Packer, R. J., Long-term outcomes among adult survivors of childhood central nervous system malignancies in the Childhood Cancer Survivor Study. *Journal of the National Cancer Institute* **2009,** *101* (13), 946-58; (b) Ellenberg, L.; Liu, Q.; Gioia, G.; Yasui, Y.; Packer, R. J.; Mertens, A.; Donaldson, S. S.; Stovall, M.; Kadan-Lottick, N.; Armstrong, G.; Robison, L. L.; Zeltzer, L. K., Neurocognitive status in long-term survivors of childhood CNS malignancies: a report from

the Childhood Cancer Survivor Study. *Neuropsychology* **2009,** *23* (6), 705-17; (c) Schultz, K. A.; Ness, K. K.; Whitton, J.; Recklitis, C.; Zebrack, B.; Robison, L. L.; Zeltzer, L.; Mertens, A. C., Behavioral and social outcomes in adolescent survivors of childhood cancer: a report from the childhood cancer survivor study. *Journal of clinical oncology : official journal of the American Society of Clinical Oncology* **2007,** *25* (24), 3649-56.

10. (a) Mulhern, R. K.; Kepner, J. L.; Thomas, P. R.; Armstrong, F. D.; Friedman, H. S.; Kun, L. E., Neuropsychologic functioning of survivors of childhood medulloblastoma randomized to receive conventional or reduced-dose craniospinal irradiation: a Pediatric Oncology Group study. *Journal of clinical oncology : official journal of the American Society of Clinical Oncology* **1998,** *16* (5), 1723-8; (b) Ris, M. D.; Packer, R.; Goldwein, J.; Jones-Wallace, D.; Boyett, J. M., Intellectual outcome after reduced-dose radiation therapy plus adjuvant chemotherapy for medulloblastoma: a Children's Cancer Group study. *Journal of clinical oncology : official journal of the American Society of Clinical Oncology* **2001,** *19* (15), 3470-6.

11. Mulhern, R. K.; Palmer, S. L.; Merchant, T. E.; Wallace, D.; Kocak, M.; Brouwers, P.; Krull, K.; Chintagumpala, M.; Stargatt, R.; Ashley, D. M.; Tyc, V. L.; Kun, L.; Boyett, J.; Gajjar, A., Neurocognitive consequences of risk-adapted therapy for childhood medulloblastoma. *Journal of clinical oncology : official journal of the American Society of Clinical Oncology* **2005,** *23* (24), 5511-9.

12. Oeffinger, K. C.; Mertens, A. C.; Sklar, C. A.; Kawashima, T.; Hudson, M. M.; Meadows, A. T.; Friedman, D. L.; Marina, N.; Hobbie, W.; Kadan-Lottick, N. S.; Schwartz, C. L.; Leisenring, W.; Robison, L. L.; Childhood Cancer Survivor, S., Chronic health conditions in adult survivors of childhood cancer. *The New England journal of medicine* **2006,** *355* (15), 1572-82.

13. Green, D. M.; Nolan, V. G.; Goodman, P. J.; Whitton, J. A.; Srivastava, D.; Leisenring, W. M.; Neglia, J. P.; Sklar, C. A.; Kaste, S. C.; Hudson, M. M.; Diller, L. R.; Stovall, M.; Donaldson, S. S.; Robison, L. L., The cyclophosphamide equivalent dose as an approach for quantifying alkylating agent exposure: a report from the Childhood Cancer Survivor Study. *Pediatric blood & cancer* **2014,** *61* (1), 53-67.

Table 2. Diagnosis and Treatment Characteristics of the Study Population							
	Total	**1970-1979**		**1980-1989**		**1990-1999**	
	N	**N**	**%**	**N**	**%**	**N**	**%**
All Survivors							
Sex							
Male							
Female							
Race/Ethnicity							
Non-Hispanic White							
Non-Hispanic Black							
Hispanic							
Other							
Age at Diagnosis							
0-3							
4-7							
8-14							
15-20							
Tumor location							
Posterior fossa							
Supratentorial							
Treatment Type							
Surgery + CSI (≥ 30 Gy), no chemotherapy							

Surgery + CSI (≥ 30 Gy) + chemotherapy							
Surgery + CSI (<30 Gy) + chemotherapy							
Craniospinal Dose							
≥30 Gy							
<30 Gy							
Chemotherapy (Yes/No)							
Carboplatin							
Cisplatin							
Cyclophosphamide							
CCNU							
Vincristine							
Etoposide							
Prednisone							
Procarbazine							
Hydroxyurea							
Cytarabine							
Thiotepa							
Cyclophosphamide equivalent dose (mg/m^2)*							
0							
>0-<4000							
≥4000-<8000							
≥8000							

Cumulative cisplatin dose (mg/m^2)							
0							
>0-<200							
≥200-<400							
≥400							
Cumulative carboplatin dose (mg/m^2)							
0							
>0-<2500							
≥2500-<5000							
≥5000							

*calculated as described previously[13]

Table 3. 15-year cumulative mortality among medulloblastoma/PNET survivors by treatment era			
	1970-1979 **N =**	**1980-1989** **N =**	**1990-1999** **N =**
	Cumulative incidence (95% CI)	**Cumulative incidence (95% CI)**	**Cumulative incidence (95% CI)**
All Cause			
Recurrence/Progression			
External Cause (e.g. accidents, injuries, suicide)			
Non-recurrence/ **Non-external cause**			
Subsequent neoplasm			
Cardiac cause			
Pulmonary Cause			
Other			

Table 4. 15-year cumulative mortality among medulloblastoma/PNET survivors by treatment type			
	Surgery + CSI (≥ 30 Gy), no chemotherapy	**Surgery + CSI (≥ 30 Gy) + chemotherapy**	**Surgery + CSI (<30 Gy) + chemotherapy**
	Cumulative incidence (95% CI)	**Cumulative incidence (95% CI)**	**Cumulative incidence (95% CI)**
All Cause			
Recurrence			
External Cause (e.g. accidents, injuries, suicide)			
Non-recurrence/ Non-external cause			
Subsequent neoplasm			
Cardiac cause			
Pulmonary Cause			
Other			

Table 5. All-cause and cause-specific standard mortality ratios in five-year survivors of childhood medulloblastoma/PNET followed for 15 years																		
	All cause			Health-related Cause			Subsequent Neoplasm			Cardiac Causes			Pulmonary Causes			Other Health-related Causes		
	N	SMR	95% CI	N	SMR	95% CI	N	SMR	95% CI	N	SMR	95% CI	N	SMR	95% CI	N	SMR	95% CI
All survivors																		
Treatment Era																		
1970-1979																		
1980-1989																		
1990-1999																		
Sex																		
Male																		
Female																		
Treatment																		
Surgery + CSI (≥30 Gy), no chemotherapy																		
Surgery + CSI (≥30 Gy)+ chemotherapy																		

Surgery + CSI (<30 Gy), + chemotherapy																		
Year since original diagnosis																		
5-9																		
10-14																		
15+																		

Table 6. Relative rates of mortality based on treatment exposure among five-year survivors of medulloblastoma/PNET *

	All Cause		Recurrence/ Progression		Non-recurrence, Non-external cause	
	RR	95%CI	RR	95%CI	RR	95%CI
Treatment type						
Surgery +CSI (≥30 Gy), no chemotherapy						
Surgery + CSI(≥30 Gy) + chemotherapy						
Surgery + CSI (<30 Gy) + chemotherapy						

*adjusted for sex and age at diagnosis

	Table 7. Standardized incidence ratios of subsequent malignant neoplasms among medulloblastoma/PNET survivors by treatment era									
	Observed	**Expected**	**Overall N=**		**1970-1979 N=**		**1980-1989 N=**		**1990-1999 N=**	
			N of SN	**SIR (95% CI)**	**N of SN**	**SIR (95% CI)**	**N of SN**	**SIR (95% CI)**	**N of SN**	**SIR (95% CI)**
Overall*										
CNS Malignancy										
Astrocytoma										
Malignant meningioma										
Leukemia										
Lymphoma										
Soft Tissue Sarcoma										
Bone Cancer										
Breast Cancer										
Melanoma										
Thyroid Cancer										
SNs for which SIRS could not be calculated										

Non-melanoma skin cancer				-		-		-		-
Non-malignant meningioma				-		-		-		-
Other				-		-		-		-

* SMNs for which SIRs can be calculated

Table 8. Standardized incidence ratios of subsequent malignant neoplasms among medulloblastoma/PNET survivors by treatment type						
	Surgery + CSI (≥ 30 Gy), no chemotherapy N=		**Surgery + CSI (≥ 30 Gy) + chemotherapy N=**		**Surgery + CSI (<30 Gy) + chemotherapy N=**	
	N of SN	**SIR (95% CI)**	**N of SN**	**SIR (95% CI)**	**N of SN**	**SIR (95% CI)**
Overall*						
CNS Malignancy						
Astrocytoma						
Malignant meningioma						
Leukemia						
Lymphoma						
Soft Tissue Sarcoma						
Bone Cancer						
Breast Cancer						
Melanoma						
Thyroid Cancer						
SNs for which SIRS could not be calculated						

Non-melanoma skin cancer		-		-		-
Non-malignant meningioma		-		-		-
Other		-		-		-

* SMNs for which SIRs can be calculated

	Table 9. Hazard ratios of having a subsequent neoplasm in medulloblastoma/PNET survivors across treatment exposures and treatment eras*†									
	Total	**Astrocytoma**	**Malignant meningioma**	**Leukemia**	**Lymphoma**	**Soft tissue sarcoma**	**Bone tumor**	**Breast**	**Thyroid**	**Melanoma**
	N	HR (95%CI)	HR (95%CI)	HR (95%CI)	HR (95%CI)	HR (95%CI)	HR (95%CI)	HR (95%CI)	HR (95%CI)	HR (95%CI)
Treatment type										
Surgery + ≥30 Gy, no chemotherapy		ref	ref	ref	ref	ref	ref	ref	ref	ref
Surgery + ≥30 Gy + chemotherapy										
Surgery + <30 Gy + chemotherapy										
Treatment era										
1970-1979		ref	ref	ref	ref	ref	ref	ref	ref	ref
1980-1989										
1990-1999										

*age as the time scale and adjusted age at diagnosis or years from diagnosis

† all SN types may not be possible to be examined due to numbers

ref=reference

Table 10. Hazard ratios of having chronic health conditions in medulloblastoma /PNET survivors by treatment era, treatment group and chemotherapeutic treatment exposures*			
	Any Grade 1-5	**Any Grade 3-5**	**Multiple Grade 3-5**
	HR (95% CI)	**HR (95% CI)**	**HR (95% CI)**
Treatment era			
1970-1979			
1980-1989			
1990-1999			
Treatment type			
Surgery + CSI (≥ 30 Gy), no chemotherapy			
Surgery + CSI (≥ 30 Gy) + chemotherapy			
Surgery + CSI (<30 Gy) + chemotherapy			
Chemotherapy specifics (yes/no)			
Carboplatin			
Cisplatin			
Cyclophosphamide			
CCNU			
Vincristine			
Etoposide			
Prednisone			
Procarbazine			
Hydroxyurea			
Cytarabine			
Thiotepa			

Cyclophosphamide equivalent dose (mg/m^2)*			
0	reference	reference	reference
>0-<4000			
≥4000-<8000			
≥8000			
Cumulative cisplatin dose (mg/m^2)			
0	reference	reference	reference
>0-<200			
≥200-<400			
≥400			
Cumulative carboplatin dose (mg/m^2)			
0	reference	reference	reference
>0-<2500			
≥2500-<5000			
≥5000			

*age as the time scale and adjusted for age at diagnosis or years since diagnosis

Table 11. Hazard ratios of having an endocrine chronic health condition in medulloblastoma /PNET survivors by treatment era and treatment type*		
	Grade 1-2	**Grade 3-5**
	HR (95% CI)	**HR (95% CI)**
Treatment era		
1970-1979		
1980-1989		
1990-1999		
Treatment type		
Surgery + CSI (≥ 30 Gy), no chemotherapy		
Surgery + CSI (≥ 30 Gy) + chemotherapy		
Surgery + CSI (<30 Gy) + chemotherapy		

* Either age or time since diagnosis as time scale and adjusted for age at diagnosis or the variable not used as time scale.

Note: this table will be reproduced for other specific health conditions including cardiac, pulmonary, neurological, vision and hearing conditions.

Table 12. Sociodemographic outcomes in medulloblastoma/PNET survivors across treatment groups and treatment eras*						
	Placed in special education N =		**Unemployed N =**		**Uninsured N =**	
	RR	95%CI	RR	95%CI	RR	95%CI
Treatment type						
Surgery + ≥30 Gy, no chemotherapy						
Surgery + ≥30 Gy + chemotherapy						
Surgery + <30 Gy + chemotherapy						
Treatment era						
1970-1979						
1980-1989						
1990-1999						

*adjusted for sex, ethnicity, age and age at diagnosis