

## Long-term neurologic health and psychosocial function of adult survivors of childhood medulloblastoma/PNET: a report from the Childhood Cancer Survivor Study

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### Abstract

**Background.** Medulloblastoma is the most common malignant childhood brain tumor, although long-term risks for chronic neurologic health and psychosocial functioning in aging adult survivors are incompletely characterized.

**Methods.** The Childhood Cancer Survivor Study (CCSS) includes 380 five-year survivors of medulloblastoma/primitive neuroectodermal tumor (PNET; median age at follow-up: 30 y, interquartile range 24–36) and sibling comparison ( $n = 4031$ ). Cumulative incidence of neurologic health conditions was reported. Cox regression models provided hazard ratios (HRs) and 95% CIs. Cross-sectional outcomes were assessed using generalized linear models.

**Results.** Compared with siblings, survivors were at increased risk of late-onset hearing loss (HR: 36.0, 95% CI: 23.6–54.9), stroke (HR: 33.9, 95% CI: 17.8–64.7), seizure (HR: 12.8, 95% CI: 9.0–18.1), poor balance (HR: 10.4, 95% CI: 6.7–15.9), tinnitus (HR: 4.8, 95% CI: 3.5–6.8), and cataracts (HR: 31.8, 95% CI: 16.7–60.5). Temporal/frontal lobe radiotherapy of 50 Gy or more increased risk for hearing loss (HR: 1.9, 95% CI: 1.1–1.3), seizure (HR: 2.1, 95% CI: 1.1–3.9), stroke (HR: 3.5, 95% CI: 1.3–9.1), and tinnitus (HR: 2.0, 95% CI: 1.0–3.9). Survivors were less likely than siblings to earn a college degree (relative risk [RR]: 0.49, 95% CI: 0.39–0.60), marry (RR: 0.35, 95% CI: 0.29–0.42), and live independently (RR: 0.58, 95% CI: 0.52–0.66).

**Conclusions.** Adult survivors of childhood medulloblastoma/PNET demonstrate pronounced risk for hearing impairment, stroke, lower educational attainment, and social independence. Interventions to support survivors should be a high priority.

### Key words

late effects | medulloblastoma | neurologic outcomes | psychosocial outcomes

Medulloblastoma and primitive neuroectodermal tumor (PNET) of the CNS are embryonal tumors arising in the infratentorial and supratentorial brain, respectively. This classification was maintained until 2016, when the World Health

Organization retained the term “medulloblastoma” for posterior fossa tumors but replaced the term “PNET” with “embryonal tumors” for other small-cell, hyperchromatic primary CNS tumors.<sup>1</sup> CNS PNET and medulloblastoma comprise

## Importance of the study

The current study estimates the risk for late-onset neurologic and psychosocial outcomes in one of the largest cohorts to date of adult survivors of medulloblastoma/PNET. Chronic neurosensory late effects were common among survivors and continued to increase in incidence with age. In addition, lower levels of educational attainment and social independence were observed relative to siblings. Lessons learned are twofold. For practitioners providing long-term follow-up care of survivors,

lifelong surveillance for conditions such as hearing loss, cataracts, and cerebrovascular disease is needed. Second, given the high burden of morbidity among these survivors, multidisciplinary support in medical, educational, and social settings may be needed. New therapies that have less long-term side effects should be developed, and future studies should evaluate whether modifications of primary therapy intended to reduce risk for late effects have been effective.

approximately 10%–15% of pediatric brain tumors.<sup>2,3</sup> As early as the 1970s, the use of adjuvant craniospinal irradiation (CSI) after surgery resulted in improved survival in patients with medulloblastoma/PNET.<sup>4</sup> The typical radiation doses delivered were 35–36 Gy to the neuraxis (CSI) with an additional boost to the tumor bed. This postoperative “standard dose” CSI approach alone resulted in 5-year event-free survival rates of approximately 60%.<sup>5</sup> More recently, the combination of surgical resection, radiation therapy, and chemotherapy has improved survival to 75%–80% for patients with standard risk medulloblastoma.<sup>6–8</sup> However, these survivors, even at a young age, are at high risk of neurologic late effects,<sup>9–18</sup> which may contribute to poor quality of life. While previous data from the Childhood Cancer Survivor Study (CCSS) have been published in aggregate for all CNS tumor survivors, focused assessment of this important population of medulloblastoma/PNET survivors highlights their specific long-term complications.

Aging survivors of childhood medulloblastoma and CNS PNET now face common adult milestones that include self-management of chronic health conditions, living independently, engaging in intimate relationships, and preparing for the future. It is important to evaluate the impact of late effects on these common adult functions given the standard use of CSI and increasing use of chemotherapy often associated with long-term health risks.<sup>19</sup> The purpose of this study was to estimate risk for neurologic late effects after diagnosis and treatment for medulloblastoma/PNET within the CCSS cohort and to evaluate the personal outcomes and psychosocial function in adulthood.

A randomly selected subset of survivors was asked to identify their siblings. A comparison group of the sibling closest in age to the survivor was recruited to participate. The current analysis compares 380 five-year survivors of medulloblastoma/PNET (Supplementary Fig. 1) from this CCSS cohort with the sibling comparison sample ( $n = 4031$ ). Institutional review boards of all participating centers reviewed and approved the CCSS protocol.

Demographic and health-related outcomes were collected via a self-administered baseline questionnaire. Parents completed the baseline questionnaire if participants were younger than 18 years or if participants older than 18 years were unable to complete the questionnaire themselves.

Updated questionnaires and interviews were subsequently administered (see Supplementary Fig. 1). Questions about specific neurologic conditions and sensory impairments were phrased as, “Have you ever been told by a doctor or other health care professional that you have or have had [condition]?” If the respondent indicated “Yes,” he or she was asked to report the age at first occurrence of the condition. The baseline and 2003 and 2007 follow-up questionnaires also included the Brief Symptom Inventory–18 (BSI-18). The BSI-18 is a set of 18 items designed to assess symptoms of depression, anxiety, and somatic complaints. Participants answer the questions with regard to the past 7 days to describe the extent that they have been distressed by each symptom using a Likert scale ranging from 1 (not at all) to 5 (extremely). In addition to the 3 subscales, responses to all 18 items are summed to provide a global score (Global Severity Index).<sup>22</sup> BSI scores greater than or equal to the 90th percentile on standardized norms were classified as “impaired.” Ratings of general health, cancer-related anxiety, and concerns about future health were reported on 5-point Likert scales, and self-reported memory problems were identified as being present or not.

Subsequent malignant neoplasms (SMNs) included new malignancies collected from the cohort, not including recurrence of the primary childhood malignancy, and were initially ascertained through self- or proxy-report questionnaires and/or death certificates. Cases were subsequently confirmed by pathology report or, when not available, by death certificate or other medical records reviewed by study investigators. Only subsequent malignant neoplasms occurring 5 or more years following the childhood cancer diagnosis were evaluated.

## Methods

### Participants

Participants were drawn from the CCSS, a retrospective cohort with prospective follow-up of children diagnosed and treated for cancer, including CNS tumors, from 1970 to 1986 at 26 collaborating institutions in the United States and Canada. The cohort methodology and study design have been previously described in detail.<sup>20,21</sup> Eligibility for participation in the CCSS included a diagnosis of cancer before age 21 and survival for at least 5 years from

Cancer diagnosis and treatment data including chemotherapy and radiotherapy exposures were abstracted from medical records at treating institutions utilizing standardized CCSS protocols, for survivors who provided authorization.

## Statistical Methods

Demographic data and cancer treatment factors were summarized with descriptive statistics. Neurologic, SMN, and sensory outcomes were analyzed as time-to-event data. Cumulative incidence curves with 95% CIs were used to summarize the pattern of onset for time-to-event outcomes from study entry at 5 years post-cancer diagnosis forward. Death was treated as a competing risk in the cumulative incidence estimations.<sup>23</sup> Cox regression models with age as the time scale were used to estimate cause-specific hazard ratios (HRs) and 95% CIs relative to the sibling comparison population, adjusted for sex. Within the survivor cohort, Cox models evaluated associations between cancer treatment exposures and neurologic outcomes. The treatment exposures considered were: cranial radiation (maximum dose to region), chemotherapy (yes or no), extracranial ventricular shunt, and, for auditory outcomes, platinum agents (yes or no). Sex, age at primary cancer diagnosis, occurrence of an SMN, and recurrence of medulloblastoma/PNET were considered as time-varying covariates. For each outcome, factors that were not statistically significant in the multivariable context were omitted from the final model unless doing so caused a 10% or greater change in the HR estimate for another factor in the model. In cases in which a study participant reported a condition but did not report the age at first occurrence, multiple imputation for the missing event time was performed using a modified version of the technique of Taylor and colleagues.<sup>24</sup> Ten imputed values for each missing age were generated. The models for generating imputed age values included sex, age, and, for cancer survivors, age at cancer diagnosis and type of therapy. Parameter estimates and 95% CIs were obtained using standard formulas for combining analyses across the imputed datasets.<sup>25</sup>

Memory complications and psychosocial outcomes, including BSI, educational status, marital status, independent living, employment status, and income were assessed in cross-sectional analyses. Outcome measures were dichotomized, and generalized linear models were used to estimate relative risks (RRs). A log-link model, rather than a logistic model, was chosen because outcomes were not rare; hence, the odds ratio from a logistic model would not provide a good approximation of RR. The generalized linear model utilized a Poisson error distribution with robust variance estimation.<sup>26</sup> RR estimates were adjusted for age at last follow-up, sex, and race.

## Results

Among 380 five-year survivors of medulloblastoma/PNET, 58% were male, and the median age at last follow-up was

30 years (interquartile range 24–36; [Table 1](#)). Seventy-three percent of survivors were younger than 10 years of age at diagnosis. Among survivors, 94% received CSI, with the majority (74%) receiving greater than 30 Gy. The median dose of CSI was 35 Gy (interquartile range 30–36), and the mean total dose to the tumor bed was 52 Gy (interquartile range 50–54). In this era, few survivors received chemotherapies now accepted as standard therapy for medulloblastoma/PNET, including: cisplatin (24%), CCNU (34%), and cyclophosphamide (21%). See [Table 1](#) for further characteristics of survivors and siblings.

## Chronic Neurosensory and Neurologic Health Conditions

For most neurologic outcomes, the majority of events occurred in the first 5 years postdiagnosis, but substantial numbers of survivors developed new onset of neurologic conditions between 5 and 30 years postdiagnosis ([Table 2](#)). At 30 years after diagnosis, the cumulative incidence of hearing loss was 37.4%; tinnitus, 30.1%; and seizures, 33.8% ([Fig. 1](#)). Problems with balance, coordination, and/or tremors were very common at CCSS cohort entry, and the cumulative incidence rose further to 72.3% by 30 years post-cancer diagnosis ([Fig. 1](#)).

Chronic sensory impairments were more commonly reported among survivors than siblings. A total of 61 survivors reported significant hearing loss (deafness or hearing loss that requires a hearing aid) with onset occurring more than 5 years post-cancer diagnosis (see [Table 2](#)). The age- and sex-adjusted HR for survivors compared with siblings was 36.0 (95% CI: 23.6–54.9). Seizures, tinnitus, and vertigo were more common in survivors than siblings (see [Table 2](#)). Twenty-five survivors reported cataracts more than 5 years after cancer diagnosis (HR: 31.8, 95% CI: 16.7–60.5). Forty (10.5%) survivors reported a history of stroke; 25 suffered the stroke more than 5 years after their original diagnosis (HR: 33.9; 95% CI: 17.8–64.7). Problems with balance, coordination, and/or tremors were also common (HR: 10.4; 95% CI: 6.7–15.9). Temporal/frontal lobe radiotherapy of 50 Gy or more increased risk for hearing loss (HR: 1.9; 95% CI: 1.1–1.3; see [Table 3](#)), seizure (HR: 2.1; 95% CI: 1.1–3.9), stroke (HR: 3.5; 95% CI: 1.3–9.1), and tinnitus (HR: 2.0; 95% CI: 1.0–3.9).

At 30 years postdiagnosis, 70.6% of the survivors were alive ([Supplementary Fig. 2](#)). The cumulative incidence of primary tumor recurrence was 18% (95% CI: 14–22) by 30 years after cancer diagnosis. The 30-year cumulative incidence of a subsequent malignancy was 8% (95% CI: 5–12). Almost half (48%) of subsequent malignancies were thyroid cancers ([Supplementary Table](#)), followed by malignant brain tumors (16%) and sarcomas (16%). Tumor recurrence independently increased risk for seizure (HR: 2.9; 1.4–6.3) and stroke (HR: 3.9; 1.1–14.3).

## Educational Attainment and Social Independence

Among medulloblastoma/PNET survivors, 25% earned a bachelor's degree or higher, compared with 55% of the

**Table 1.** Demographic and treatment characteristics of survivors of medulloblastoma/PNET and sibling comparison population

Characteristics	Survivors (N = 380)		Siblings (N = 4031)	
	N	% <sup>a</sup>	N	% <sup>a</sup>
<b>Sex</b>				
Female	158	42%	2088	52%
Male	222	58%	1943	48%
<b>Race/ethnicity</b>				
White, Non-Hispanic	308	86%	3509	90%
Black, Non-Hispanic	24	7%	112	3%
Hispanic	18	5%	149	4%
Other	10	3%	111	3%
Unknown	20	--	150	--
<b>Age at diagnosis, y</b>				
0–4	127	33%	--	--
5–9	150	40%	--	--
10–14	76	20%	--	--
>14	27	7%	--	--
<b>Radiation therapy (RT)</b>				
None	8	2%	--	--
Cranial	11	3%	--	--
Craniospinal <sup>b</sup>	312	94%	--	--
Unknown <sup>c</sup>	49	--	--	--
<b>Maximum cranial radiation dose</b>				
≥30 Gy	319	96%	--	--
>1 to <30 Gy	5	2%	--	--
No RT	8	2%	--	--
Unknown	48	--	--	--
<b>Maximum spinal radiation dose</b>				
≥30 Gy	245	74%	--	--
>4 to <30 Gy	67	20%	--	--
Scatter exposure from cranial RT only	11	3%	--	--
No RT	8	2%	--	--
Unknown	49	--	--	--
<b>Chemotherapy</b>				
Yes	202	59%	--	--
No	140	41%	--	--
Unknown	38	--	--	--
<b>Cisplatin</b>				
Yes	81	24%	--	--
No	261	76%	--	--
Unknown	38	--	--	--
<b>CCNU</b>				
Yes	116	34%	--	--
No	226	66%	--	--
Unknown	38	--	--	--
<b>Cyclophosphamide</b>				
Yes	71	21%	--	--

No	271	79%	--
Unknown	38	--	--

**Extracranial ventricular shunt**

Yes	136	40%	--
No	207	60%	--
Unknown	37	--	--

<sup>a</sup>Percentages based on survivors for whom data are available.

<sup>b</sup>Median cranial dose = 52 Gy; median spinal dose = 35 Gy.

<sup>c</sup>Forty-eight survivors were missing both the cranial and spinal RT dosimetry data; one survivor had known cranial RT dose, but unknown spinal RT status.

sibling comparison group (RR: 0.49; 95% CI: 0.39–0.60; [Table 4](#)). Fewer than half of the survivors reported working more than 30 hours per week, and almost 90% had personal income less than \$40 000. Compared with siblings, survivors were less likely to report having ever married or lived as being married (RR: 0.35; 95% CI: 0.29–0.42).

### Memory Impairment and General Psychological Distress

Over 60% of survivors reported learning or memory problems, as opposed to only 3% of the sibling comparison group (RR: 19.8; 95% CI: 15.1–25.9; see [Table 4](#)). Among those who reported learning or memory problems, 30% of the survivors and 9% of the siblings reported these problems as disabling. On the BSI-18, survivors were twice as likely to have impaired global function (RR: 2.00; 95% CI: 1.03–3.89) and almost 3 times more likely to report depression (RR: 2.62; 95% CI: 1.55–4.45). There were no significant differences between survivors and siblings on the anxiety and somatization subscales (see [Table 4](#)).

## Discussion

Five-year survival for children with medulloblastoma or PNET has significantly improved over the last 4 decades. However, the use of craniospinal radiotherapy and the more recent addition of chemotherapy to achieve survival still place them at significant risk for long-term, chronic neurologic conditions and impaired psychosocial functioning. The current study estimates risks for these late effects in one of the largest cohorts to date of aging adult survivors of medulloblastoma/PNET.

Based on these results, it is clear that the cumulative incidence of chronic neurologic late effects continues to increase as this population ages. Almost 40% of survivors had significant hearing loss by 30 years posttreatment. Interventions such as amplification devices and cochlear implants are available and may improve hearing,<sup>27</sup> yet many survivors may not continue evaluation for hearing loss after they leave their primary oncology care clinic and establish community-based care during adulthood. Despite the well-established relationships among hearing loss,

**Table 2.** Chronic neurologic health conditions among 5-year survivors of medulloblastoma/PNET

Condition	Timing of Onset of Chronic Health Condition			Hazard Ratio (95% CI) <sup>a</sup>
	Prior to Diagnosis	Diagnosis to 5-Y Postdiagnosis	≥5-Y Postdiagnosis	
Deafness or hearing loss requiring hearing aid	6	48	61	36.0 (23.6–54.9)**
Tinnitus	5	25	36	4.8 (3.5–6.8)**
Vertigo	7	35	17	2.7 (1.7–4.4)**
Problems with balance, coordination, and/or tremors	18	192	22	10.4 (6.7–15.9)**
Seizures	3	57	49	12.8 (9.0–18.1)**
Problems with stuttering or stammering	6	14	5	2.7 (1.1–6.7)*
Cataracts	1	14	25	31.8 (16.7–60.5)**
Stroke	1	15	25	33.9 (17.8–64.7)**

<sup>a</sup>Cox regression models compare survivor versus sibling risks adjusted for sex and accounting for age in the time scale.

\* $P < .05$ .

\*\* $P < .0001$ .

platinum-based therapies, and radiation,<sup>28,29</sup> hearing loss is often known as the “invisible disability,” being frequently ignored.<sup>30</sup> Survivors are also at risk for visual impairments due to cataracts, which were 30 times more likely in the survivor cohort compared with siblings; thus, regular ophthalmologic follow-up is imperative. Both the survivor and providers need to be aware of the survivor’s treatment history to prioritize health screening and open the gateway to interventions.

The risk of stroke was much higher in medulloblastoma/PNET survivors than in siblings. Recent CCSS publications have enumerated first and recurrent stroke risk among all survivors with a history of cranial radiation.<sup>31–33</sup> Additionally, in single-center retrospective studies, approximately 5% of survivors with a history of cranial or cervical radiation had a stroke by 10 years postdiagnosis.<sup>34,35</sup> Among survivors of medulloblastoma or PNET, we found an even higher proportion (11.3%) with a history of stroke, with 59.5% of the strokes occurring more than 5 years postdiagnosis. Previous analysis of data from the Surveillance, Epidemiology, and End Results program for all children treated for CNS malignancies demonstrated an almost 8-fold increased risk of death from cardiovascular or cerebrovascular disease.<sup>36</sup> Thus, increased awareness of this high risk of stroke and considerations for prevention are essential for improved survivorship health.

A substantial number of survivors experienced learning or memory problems in the current study. Multiple investigators have documented the cognitive challenges that brain tumor survivors face.<sup>37–39</sup> The data are also consistent with smaller

studies that documented unemployment among survivors of medulloblastoma.<sup>40</sup> Cognitive ability is a determinant of educational attainment, earning potential, and health outcomes.<sup>41</sup> Based on the findings of the current study, survivors are greatly at risk for poorer after-effects across these outcomes. These findings highlight the challenges of long-term planning for families of these survivors to ensure a support system.

The majority of survivors in this cohort were treated with CSI with a median focal dose of 52 Gy (interquartile range 50–54) and a median CSI dose of 35 Gy (interquartile range 30–36). While this dose remains the standard of care for patients with high-risk medulloblastoma and embryonal tumors, in the past decade, patients with standard-risk medulloblastoma usually have received 23.4 Gy. Further research will be needed to evaluate long-term effects in patients receiving lower-dose CSI. Additionally, while the total dose to the posterior fossa remains 54 to 55.8 Gy, newer and more conformal techniques (eg, intensity modulated radiation therapy, proton beam radiation therapy) now allow for adequate target coverage with a lower dose of radiation to the cochlea and surrounding supratentorial brain.<sup>42,43</sup> Additionally, current chemotherapy dosing includes more dose modifications in response to certain morbidities such as high-frequency hearing loss. The overall impact of these temporal changes in therapy upon the high rates of morbidity we have identified in this manuscript among the first generation of medulloblastoma/PNET survivors will need to be demonstrated.<sup>44</sup>

There are limitations to the current study that should be considered. Although this is one of the largest cohorts of

**Table 3.** Treatment-related risk factors for specific health conditions among survivors of medulloblastoma/PNET

Health Condition <sup>a</sup>	Risk Factor	Category	Hazard Ratio (95% CI)	P
Deafness or hearing loss requiring hearing aid	Age at primary cancer diagnosis	<5 y	1.0 (referent)	--
		5–9 y	1.8 (0.7–4.2)	.20
		10–14 y	1.8 (0.7–4.8)	.23
		≥15 y	1.5 (0.4–5.6)	.52
	Temporal and/or frontal lobe radiation dose	<50 Gy	1.0 (referent)	--
		≥50 Gy	1.9 (1.1–3.3)	.02
	Platinum	No	1.0 (referent)	--
		Yes	1.8 (0.9–3.6)	.12
Recurrence of primary cancer	No	1.0 (referent)	--	
	Yes	2.2 (0.9–5.2)	.08	
Tinnitus	Age at primary cancer diagnosis	<5 y	1.0 (referent)	--
		5–9 y	0.9 (0.4–2.4)	.90
		10–14 y	1.6 (0.6–4.2)	.37
		≥15 y	1.5 (0.4–6.2)	.56
	Temporal and/or frontal lobe radiation dose	<50 Gy	1.0 (referent)	--
		≥50 Gy	2.0 (1.0–3.9)	.04
	Platinum	No	1.0 (referent)	--
		Yes	2.6 (1.2–5.5)	.02
	Subsequent malignant neoplasms	No	1.0 (referent)	--
		Yes	3.4 (0.9–12.8)	.06
Problems with balance, coordination, and/or tremors	Sex	Female	1.0 (referent)	--
		Male	1.5 (0.6–3.8)	.39
	Any chemotherapy	No	1.0 (referent)	--
		Yes	3.1 (1.0–9.6)	.05
	Recurrence of primary cancer	No	1.0 (referent)	--
		Yes	2.5 (0.8–7.3)	.10
	SMN	No	1.0 (referent)	--
		Yes	11.7 (1.0–136.0)	.05
Seizures	Temporal and/or frontal lobe radiation dose	<50 Gy	1.0 (referent)	--
		≥50 Gy	2.1 (1.1–3.9)	.02
	Any chemotherapy	No	1.0 (referent)	--
		Yes	2.4 (1.2–4.9)	.01
	Recurrence of primary cancer	No	1.0 (referent)	--
		Yes	2.9 (1.4–6.3)	.005
Stroke	Temporal and/or frontal lobe radiation dose	<50 Gy	1.0 (referent)	--
		≥50 Gy	3.5 (1.3–9.1)	.01
	Any chemotherapy	No	1.0 (referent)	--
		Yes	2.7 (1.1–6.6)	.04
	Recurrence of primary cancer	No	1.0 (referent)	--
		Yes	3.9 (1.1–14.3)	.04

<sup>a</sup>Treatment-related risk factors were evaluated for all health conditions listed in Table 3. For vertigo, stuttering/stammering and cataracts, no statistically significant associations with treatment factors were found.

**Abbreviations:** SMN, Subsequent malignant neoplasm.

medulloblastoma/PNET cases reported, the total number of participants represent 25%–30% of the children diagnosed with these tumors in the United States from the period 1970–1986.<sup>45</sup> Therefore, there may be limitations

in the generalizability of the results. While all of the treatment-related variables were collected via medical record abstraction and SMNs were validated, chronic neurologic conditions and psychosocial functioning were

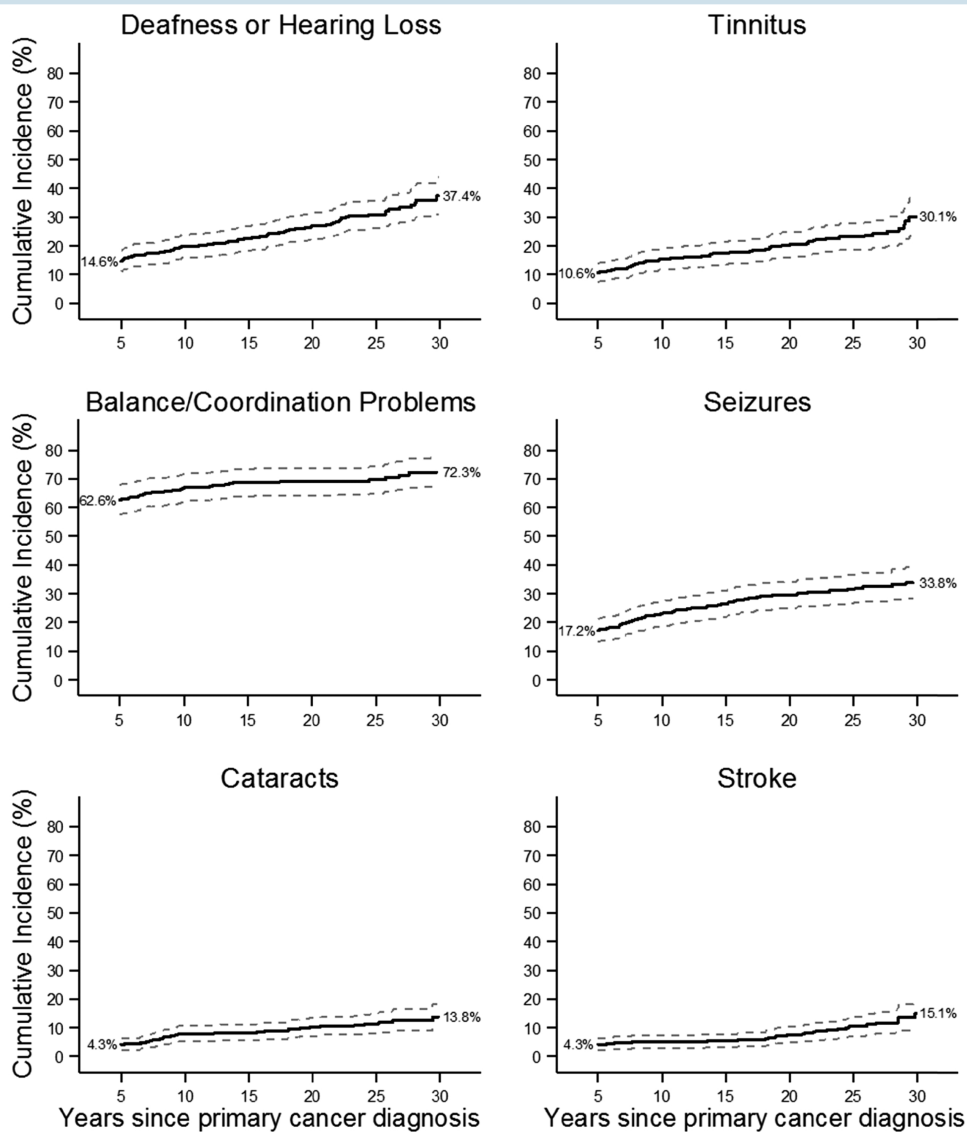
**Table 4.** Sociodemographic outcomes and psychosocial function of survivors of medulloblastoma/PNET

	N	%	Survivor vs Sibling	
			RR <sup>b</sup>	95% CI
<b>Sociodemographic Outcomes</b>				
College degree <sup>a</sup>				
Survivors	66	25.4%	0.49	(0.39–0.60)
Siblings	1797	55.3%	1.0	
Marital status—ever married or lived as married				
Survivors	78	22.2%	0.35	(0.29–0.42)
Siblings	2897	73.4%	1.0	
Independent living*				
Survivors	123	53.0%	0.58	(0.52–0.66)
Siblings	2627	93.6%	1.0	
Employed ≥30 h/wk				
Survivors	84	43.8%	0.59	(0.50–0.69)
Siblings	1635	73.5%	1.0	
Personal income ≥\$40 000/y				
Survivors	18	10.1%	0.19	(0.12–0.29)
Siblings	1159	54.1%	1.0	
<b>Psychological Status</b>				
Current learning or memory problems				
Survivors	120	60.6%	19.8	(15.1–25.9)
Siblings	71	3.0%	1.0	
Impaired on global BSI scale <sup>c</sup>				
Survivors	9	6.8%	2.00	(1.03–3.89)
Siblings	78	3.4%	1.0	
Impaired on BSI depression subscale <sup>c</sup>				
Survivors	14	10.5%	2.62	(1.55–4.45)
Siblings	93	4.1%	1.0	
Impaired on BSI anxiety subscale <sup>c</sup>				
Survivors	5	3.8%	1.18	(0.48–2.88)
Siblings	71	3.1%	1.0	
Impaired on BSI somatization subscale <sup>c</sup>				
Survivors	8	6.0%	1.71	(0.84–3.51)
Siblings	90	4.0%	1.0	
Good/very good/excellent general health status				
Survivors	158	77.8%	0.82	(0.76–0.88)
Siblings	2212	94.2%		
Concerned about future health <sup>c</sup>				
Survivors	84	62.2%	1.05	(0.91–1.21)
Siblings	1364	60.2%		
Survivor level of anxiety/fear as a result of cancer/cancer treatment <sup>c</sup>				
None	92	71.3%		
Small amount	32	24.8%		
Medium amount	4	3.1%		
A lot	1	0.8%		
Extreme	0	0%		

<sup>a</sup>Educational attainment and independent living restricted to observations obtained at age ≥25 years of age.

<sup>b</sup>Cross-sectional analyses adjusted for age at last follow-up, sex, and race.

<sup>c</sup>Analyses of the measures of distress, anxiety, and concerns about the future are restricted to observations self-reported by the subject. Questionnaires that were completed by a parent or other surrogate reporter on behalf of a study subject were not used in these analyses.



**Fig. 1** Cumulative incidence of chronic health conditions among long-term survivors of medulloblastoma and PNET.

self-reported. However, with regard to the impact on daily living, the perspective of the survivor may be the most valuable. Another limitation is inability to separate patients diagnosed with medulloblastoma from those with PNET. During the 1970s through the mid-1980s, medulloblastomas and PNETs were treated in the same manner, although the “boost” site of radiation varied depending on tumor location. It is possible that patients with PNET experience different long-term toxicity, given the supratentorial location of the tumor and increased radiation dose to the cerebrum due to the boost location. However, we were not able to accurately segregate the survivors to complete reliable subgroup analyses because primary tumor location was not collected on the cohort at initial data capture. Lastly, we chose to focus primarily on neurologic side effects, including cognitive and functional

outcomes. Future studies are needed to comprehensively assess and intervene on psychosocial outcomes of these survivors.

Among adult survivors of childhood medulloblastoma/PNET, significant neurologic morbidity and lower levels of educational attainment and social independence exist relative to siblings. Given the high survival rates for these children, interventions to reduce these sequelae and support the survivors should be a high priority.

## Supplementary Material

Supplementary material is available at *Neuro-Oncology* online.



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