Longitudinal assessment of late-onset neurologic conditions in survivors of childhood central nervous system tumors: a Childhood Cancer Survivor Study report

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Abstract

Background. Survivors of childhood central nervous system (CNS) tumors experience high rates of treatment-related neurologic sequelae. Whether survivors continue to be at increased risk for new events as they age is unknown.

Methods. Adverse neurologic health conditions in 5-year survivors of CNS tumors from the Childhood Cancer Survivor Study ($n = 1876$) were evaluated longitudinally at a median 23.0 years from diagnosis (range, 5.1–38.9), median age at last evaluation 30.3 years (range, 6.1–56.4). Multivariable regression estimated hazard ratios (HRs) and 95% CIs.

Results. From 5 to 30 years post diagnosis, cumulative incidence increased for seizures from 27% to 41%, motor impairment 21% to 35%, and hearing loss 9% to 23%. Risks were elevated compared with siblings (eg, seizures HR: 12.7; 95% CI: 9.6–16.7; motor impairment HR: 7.6; 95% CI: 5.8–9.9; hearing loss HR: 18.4; 95% CI: 13.1–25.9). Regional brain doses of radiation therapy were associated with development of new deficits (eg, frontal ≥ 50 Gy and motor impairment HR: 2.0; 95% CI: 1.2–3.4). Increased risk for motor impairment was also associated with tumor recurrence (HR: 2.6; 95% CI: 1.8–3.8), development of a meningioma (HR: 2.3; 95% CI: 0.9–5.4), and stroke (HR: 14.9; 95% CI: 10.4–21.4). Seizure risk was doubled by recurrence (HR: 2.3; 95% CI: 1.6–3.2), meningioma (HR: 2.6; 95% CI: 1.1–6.5), and stroke (HR: 2.0; 95% CI: 1.1–3.4).

Conclusions. CNS tumor survivors remain at risk for new-onset adverse neurologic events across their lifespans at a rate greater than siblings. Cranial radiation, stroke, tumor recurrence, and development of meningioma were independently associated with late-onset adverse neurologic sequelae.

Key words

childhood central nervous system tumor survivors | late effects | neurologic outcomes

Importance of the study

This study estimated risk and investigated risk factors for new-onset adverse neurologic conditions in one of the largest existing cohorts of survivors of childhood CNS malignancies with implications for survivors, patients facing treatment decisions for newly diagnosed disease, and investigators of late effects. Survivors remained at risk for new-onset adverse neurologic events across their lifespan at a rate greater than siblings. Cranial radiation, stroke, tumor recurrence, and development of meningioma were independently associated with

late-onset adverse neurologic sequelae. Finding no plateau for new adverse sequelae even 30 years after diagnosis means that clinical surveillance for neurologic late effects in this population must continue well into adulthood. Changes in relative risk over time indicate that an age-matched comparison group for future risk analyses of this population will be even more important as patients and siblings reach later adulthood, when cerebrovascular events and other neurologic conditions are more common in the general population.

Survivors of CNS tumors are at risk for long-term adverse neurologic sequelae from the tumor and its treatment.¹⁻⁶ As survivors of CNS tumors age, there is a need to better understand the incidence of and risk factors for late-onset adverse neurologic sequelae and how risks for these adverse events may change over time.

The Childhood Cancer Survivor Study (CCSS) includes 14358 five-year survivors of childhood cancer diagnosed from the period 1970–1986.⁷ A previous cross-sectional analysis assessing 5-year survivors of CNS tumors who completed the baseline CCSS questionnaire demonstrated that survivors have an increased risk compared with siblings of both early- and late-onset neurologic and neurosensory impairment.⁸ Whether the incidence of adverse neurologic sequelae continues to increase over time as this population ages is not known.

The current study utilizes longitudinal assessment at 3 time-points to extend the observation window on these aging survivors of childhood CNS tumors an additional decade beyond previous reports. Aims were to (i) determine the cumulative incidence of neurologic late effects into middle adulthood, (ii) compare risk for developing new neurologic impairment in survivors of CNS tumors to a cohort of siblings of childhood cancer survivors, and (iii) determine risk factors.

headaches”), seizures, focal neurologic dysfunction, and auditory and ocular outcomes. Motor impairment was defined as weakness or inability to move arms or legs. Hearing loss was defined as requiring a hearing aid or deafness in one or both ears.

Treatment exposures were abstracted from the medical records. To determine cranial radiation therapy regional dosimetry, the CCSS radiation physics center individually codes the treatment fields for each patient, which includes field isocenter, orientation, energy, size, and blocking. Fields are then placed on an age-specific phantom and dose computed to a 3-dimensional grid of points throughout the brain. The average dose was then calculated for the entire brain and 4 regional brain segments, including frontal cortex, temporal lobe, posterior fossa, and parietal or occipital cortex (Supplementary Figure S2).⁸ Radiation exposure for each segment was categorized as 0 plus scatter, 1–49 Gy, and ≥50 Gy. In analyses, the term “any radiation” did include patients who received scatter only. Chemotherapy exposure was extracted. Subsequent malignant neoplasms (SMN, excluding nonmelanoma skin cancers) and benign meningiomas were identified via self- or next-of-kin proxy report or death certificate and confirmed by pathology report or, when unavailable, death certificate, medical records, or both.

Methods

Population and Outcome Measures

Self-reported neurologic health conditions in 1876 long-term survivors of childhood CNS tumors were examined using the CCSS baseline and 2 subsequent follow-up questionnaires, with questions focusing on new symptoms (Supplementary Figure S1).⁹⁻¹¹ CCSS questionnaires are available for reference online at <http://ccss.stjude.org>. An institutional review board at each participating institution approved this human subject research. Participants provided informed consent prior to completion of study procedures. Participants were asked to report new-onset neurologic and neurosensory symptoms identified or confirmed by a health professional and to report patients’ ages at first occurrence. Conditions included headaches (“migraines or other frequent

Statistical Methods

Neurologic health conditions were analyzed as time-to-event outcomes. When a survivor or sibling reported a condition but was missing age at first occurrence, multiple imputations for age at first occurrence were performed with 10 ages imputed using models that included sex, age, and, for cancer survivors, primary cancer diagnosis and type of therapy received.¹² Parameter estimates and confidence intervals were obtained using standard formulas for combining analyses across the imputed datasets.¹³

Neurologic health conditions, recurrence of primary malignancy, and diagnosis of an SMN were summarized by cumulative incidence, using death as a competing risk, assessed from time of study entry at 5 years post cancer diagnosis forward. Health conditions with onset prior to 5 years post cancer diagnosis were treated as prevalent cases at the start of follow-up. Late mortality >5 years from

diagnosis was summarized with a Kaplan–Meier curve for survivors in the United States, using death dates obtained from the National Death Index.

Cox regression analysis identified demographic and cancer treatment factors associated with development of late-onset (>5 y post cancer diagnosis) neurologic health conditions. Covariates included age at diagnosis, sex, surgery, chemotherapy, and radiation exposure. Histologic diagnosis was not included in the risk factor analysis as a covariate because it was highly correlated with treatment. The risk factor analysis for headaches also evaluated the impact of a history of smoking (ever smoked—yes/no) and, for females, hormone therapy use (ever take birth control or hormone replacement—yes/no) as time-varying covariates. Risk factors found to have an association with a P -value ≤ 0.10 in univariable analysis were candidates for multivariable modeling. In the multivariable modeling, factors that did not show significant independent association with the outcome were removed, unless their omission would cause more than a 10% change in the hazard ratio (HR) estimate for a factor remaining in the model. Recurrence and SMN were modeled as time-varying covariates and included in the modeling as surrogates of additional treatment. In order to evaluate the extent to which intervening stroke or meningioma diagnoses might account for associations between the primary cancer treatment exposures and late adverse neurologic events, each neurologic outcome model was estimated 2 ways, once with and once without inclusion of time-varying covariates for stroke and meningioma. Additionally, to address the concern that progressive or recurrent disease and subsequent treatment could significantly impact results, Cox modeling and cumulative incidence analyses of time to “recurrence-free” neurologic events were conducted as supplementary. Participants who recurred in the first 5 years were excluded and events for other participants were censored at the time of recurrence so that the HR and cumulative incidences could be assessed among participants who have not yet recurred.

Cox regression estimated HRs for late-onset neurologic events in survivors versus events in siblings,⁹ with adjustment for sex and race, and with age at occurrence as the time scale. Because the HRs were often nonproportional across time, further analyses compared events by time period to determine whether and when the HRs change as the survivor and sibling populations age. HRs for specific intervals along the time (age) axis were estimated for those outcomes where there was significant evidence of nonproportional hazards. The breakpoint for this data analysis was the age at which there was a significant change in HR, which varied by outcome.

Results

Participant characteristics are summarized in Table 1. A cohort of 1876 pediatric CNS tumor survivors was evaluated longitudinally at a median of 23.0 years from diagnosis (range, 5.1–38.9 y); median age at last evaluation was 30.3 years (range, 6.1–56.4 y).

Cumulative Incidence of Late-Onset Neurologic Health Conditions

The cumulative incidence of headaches increased from 38% at 5 years from diagnosis to 53% at 30 years from diagnosis (Fig. 1). Seizures increased from 27% to 41%, coordination problems increased from 50% to 61%, and motor impairment increased from 21% to 35% during this time period. Adverse neurosensory outcomes also increased, with cumulative incidences at 5 and 30 years post diagnosis being 9% and 23% for hearing loss, 8% and 21% for tinnitus, and 9% and 17% for vertigo, respectively. For adverse ocular effects, cumulative incidence of glaucoma and retinal conditions remained less than 2%, legal blindness in one or both eyes increased from 14% at 5 years to 17% at 30 years, and cataracts increased from 1.5% to 6%.

Thirty years after the primary cancer diagnosis, the cumulative incidence for recurrence or progression of the primary cancer was 22%, for SMN 6%, and for benign meningioma 6% (Supplementary Figure S3). The median time to recurrence was 5.3 years and to an SMN 17.8 years. The mortality estimate at 30 years from diagnosis was 25%. By tumor type, the cumulative incidence of recurrence at 30 years post primary cancer diagnosis was 23.9% for astroglial tumors, 18.2% for medulloblastoma/primitive neuroectodermal tumor, 21.9% for ependymoma, and 11.3% for other CNS tumors (Supplementary Figure S4).

Risk for Late-Onset Neurologic Health Conditions Relative to Siblings

Survivors of childhood CNS tumors had elevated relative risks for all neurologic adverse outcomes compared with siblings (Supplementary Table S1). Late-onset headaches were significantly more common in survivors than siblings (HR: 1.3; 95% CI: 1.1–1.5). Late-onset seizures were 12 times more common in childhood CNS tumor survivors than siblings (HR: 12.7; 95% CI: 9.6–16.7), late-onset coordination problems were nearly 10 times that of siblings (HR: 9.6; 95% CI: 7.5–12.3), and late-onset motor impairment more than 7 times (HR: 7.6; 95% CI: 5.8–9.9). The risk for late-onset hearing loss in survivors was 18 times that of siblings (HR: 18.4; 95% CI: 13.1–25.9).

For some outcomes, the HRs for survivors versus siblings remained elevated but were attenuated as both survivors and siblings aged (further) into adulthood. This age-related change in risk was particularly striking for motor problems, where the HR for participants age 5–19 was 31.6 (95% CI: 18.0–55.5) versus an HR for age 20 and older of 3.9 (95% CI: 2.8–5.3). Large age-related changes in effect sizes were also seen for seizures, coordination problems, cataracts, and glaucoma (Table 2).

Risk Factors Associated with Late-Onset Neurologic Health Conditions

Significant risk factors were found for each condition (Table 3). Headaches were twice as frequent in female survivors compared with males (HR for males: 0.5; 95% CI: 0.4–0.7), and recurrence of the primary cancer increased the risk for headache (HR: 1.7; 95% CI: 1.2–2.7). A history of

Table 1 Participant demographic and treatment characteristics

Characteristic	CNSTumor Patients (<i>n</i> = 1876)	CCSS Sibling Cohort (<i>n</i> = 4031)
	No. (%)	No. (%)
Age at last completed follow-up questionnaire, y		
<20	294 (16)	369 (9)
20–29	610 (33)	1130 (28)
30–39	668 (36)	1364 (34)
40–49	280 (15)	927 (23)
≥50	24 (1)	241 (6)
Sex		
Males	1033 (55)	1943 (48)
Females	843 (45)	2088 (52)
Race		
White	1702 (91)	3569 (89)
Black	76 (4)	113 (3)
Other/mixed	80 (4)	199 (5)
Unknown	18 (1)	150 (4)
Age at diagnosis, y		
<5	644 (34)	
5–9	555 (30)	
≥10	677 (36)	
Diagnosis		
Astroglial	1233 (66)	
Medulloblastoma/primitive neuroectodermal tumor	380 (20)	
Ependymoma	168 (9)	
Other CNS	95 (5)	
Treatment		
Surgery alone	425 (23)	
Surgery + radiation	698 (37)	
Surgery + chemotherapy	29 (2)	
Surgery + radiation + chemotherapy	463 (25)	
Radiation alone	19 (1)	
Chemotherapy alone	0	
Radiation + chemotherapy	7 (<1)	
No treatment	7 (<1)	
Unknown	228 (12)	
Chemotherapy agents		
Any platinum agents	142 (9)	
Vincristine	298 (18)	
Nonplatinum alkylating agent	364 (22)	

smoking was associated with increased risk for headaches (HR: 1.9; 95% CI: 1.2–3.1). In a subset analysis of women only, a history of using birth control pills or female hormone medication was not significantly associated with increased headache risk.

The risk for late-onset seizures was associated with frontal lobe radiation of 50 Gy (HR: 1.8; 95% CI: 1.0–3.0) and temporal lobe radiation in a dose-dependent fashion (HR:

1.9; 95% CI: 1.1–3.4 for 1–49 Gy; HR: 2.2; 95% CI: 1.4–3.5 for ≥50 Gy). Other factors associated with increased risk for late-onset seizures were recurrence (HR: 2.3; 95% CI: 1.6–3.2), development of a meningioma (HR: 2.6; 95% CI: 1.1–6.5), and history of stroke (HR: 2.0; 95% CI: 1.1–3.4). The risk of motor impairment was increased by radiation ≥50 Gy to the frontal region (HR: 2.0; 95% CI: 1.2–3.4) and by cancer recurrence (HR: 2.6; 95% CI: 1.8–3.8). For meningioma, the

Fig. 1 Cumulative incidence with 95% CIs for late-onset neurosensory and neurologic sequelae.

HR was 2.3 (95% CI: 0.9–5.4). Late-onset stroke was associated with risk of subsequent motor impairment by a factor of 14 (HR: 14.9; 95% CI: 10.4–21.4).

In an alternative model formulation (not shown) which omitted adjustment for stroke and meningioma, the magnitude of the association between motor problems and frontal lobe irradiation ≥ 50 Gy remained the same; however, the HR for temporal lobe irradiation ≥ 50 Gy was elevated slightly and reached statistical significance (HR: 1.6; 95% CI: 1.0–2.5). “Motor problems” was the only outcome for which including adjustment for stroke and meningioma had an impact on the cancer treatment factors reaching statistical significance.

Of the survivors in this study who reported seizures, 73% listed anti-epileptic/antiseizure medications on at least one of the questionnaires. On the baseline questionnaire, 58% of seizure patients using medication listed just one type of anti-epileptic/antiseizure medication for the 2-year period preceding the questionnaire, 25% listed 2 types, and 17% listed 3 or more types. The proportion of patients listing multiple medications at follow-up in 2000 was similar to the distribution at baseline.

For neurosensory outcomes, radiation to the temporal lobe or posterior fossa was associated with an increased risk for late-onset hearing loss (see Table 4 for breakdown by dose and age), as well as use of vincristine (HR: 1.5; 95% CI: 1.0–2.1) and cancer recurrence (HR: 2.4; 95% CI: 1.6–3.6). The risk of developing late-onset tinnitus was doubled by posterior fossa radiation (HR: 2.0; 95% CI: 1.1–3.7 for 1–49 Gy; HR: 2.3; 95% CI: 1.4–3.8 for ≥ 50 Gy) or receipt of a platinum agent (HR: 2.1; 95% CI: 1.2–3.9) and tripled by SMN (HR: 2.8; 95% CI: 1.2–6.5). Risk for cataracts was increased by frontal lobe radiation (HR: 4.8; 95% CI: 2.4–9.5 for 1–49 Gy), the use of vincristine without nonplatinum alkylators (HR: 3.9; 95% CI: 1.5–10.2), and cancer recurrence (HR: 1.9; 95% CI: 0.9–4.0).

Supplementary analyses of neurologic and neurosensory outcomes were performed in progression-free patients to evaluate risk factors without the additional confounders of progressive or recurrent disease and additional treatment exposures. Results are available in Supplementary Figures S5 and S6. Hazard ratio estimates for treatment factors in the progression-free setting were similar to those obtained

Table 2 Age-specific survivor versus sibling comparison of late-onset adverse neurologic and neurosensory events in 1876 childhood CNS tumor survivors

Outcome	Age-Specific HR (95% CI) at 5+ Years Post Diagnosis ^a	
	Age 5–14	Age 15+
Headaches	2.5 (1.9–3.2)	0.9 (0.8–1.2)
Seizures	27.2 (15.9–46.5)	8.8 (6.4–11.9)
Coordination problems	24.3 (16.4–35.9)	4.4 (3.2–6.2)
Motor problems	31.6 (18.0–55.5)	3.9 (2.8–5.3)
Dizziness or vertigo	4.4 (2.7–7.2)	2.1 (1.5–2.9)
Cataracts	28.0 (10.9–71.8)	6.6 (3.6–12.0)
Glaucoma	9.4 (3.0–29.4)	1.1 (0.3–3.8)

^aHazard ratios for specific intervals along the time (age) axis were estimated for those outcomes where there was significant evidence of nonproportional hazards. Breakpoint was age at which there was a significant change in HR.

in the main risk factor analyses shown in [Tables 3](#) and [4](#). Cumulative incidence estimates were also evaluated in the progression-free setting. Estimates obtained this way were slightly lower than those obtained in the main analyses. For the more common outcomes, the cumulative incidence estimates at 30 years decreased by between 1% and 3.5%. For the rarer outcomes (cataracts, glaucoma, retinal conditions), the changes in the 30-year cumulative incidence estimates were between 0.1% and 0.3%.

Discussion

While long-term neurologic outcomes in survivors of childhood CNS tumors have been previously reported, the cumulative incidence and risk factors for development of new neurologic sequelae as survivors age through middle adulthood have not been previously described in this high-risk population. We have identified that the cumulative incidences of new-onset neurologic conditions continue to increase across the lifespan and that, in addition to therapeutic exposures, late-onset stroke, meningioma, and tumor recurrence are independently associated with a substantially increased risk of later-onset seizures, focal neurologic dysfunction, and neurosensory abnormalities.

This study confirmed previous reports that region-specific, dose-dependent brain radiation exposure is an important risk factor for adverse neurologic and neurosensory effects.⁸ Findings about chemotherapy exposure were limited, although the association between vincristine and late-onset cataracts is a new finding. One of the

main contributions from this longitudinal assessment was the ability to better understand how risks change over time. Finding no plateau for new adverse sequelae even 30 years after diagnosis means that clinical surveillance for neurologic late effects in this population must continue well into adulthood. Risk factor analysis of patients who did not experience progressive or recurrent disease looked very similar to the larger group, despite the strong impact of disease recurrence on most outcomes. For several outcomes, the survivor versus sibling HRs were high during childhood and adolescence and more attenuated as the study population aged into adulthood. These results are likely due to the increasing incidence of these adverse outcomes in healthy siblings as they age (ie, general aging effects). Findings indicate that using an age-matched comparison group for future risk analyses of this population will be even more important as patients and siblings reach later adulthood, when cerebrovascular events and other neurologic conditions are more common in the general population.¹⁴

In this population, stroke was a significant and independent risk factor for later-onset neurologic impairment. Childhood CNS tumor survivors have a 43-fold elevated risk of stroke compared with siblings, and stroke contributes to late mortality.^{15,16} Previously identified risk factors for vasculopathy and stroke in childhood CNS survivors include cranial radiation therapy (dose-dependent), baseline atherosclerosis, hypertension, and African American ethnicity.^{14,17,18} In a recent CCSS study, treatment with ≥ 50 Gy cranial radiation elevated stroke risk by 1% at 12 years and 12% at 30 years.¹⁹ Stroke recurrence risks in childhood cancer survivors remain elevated even decades after initial stroke.²⁰ There have been no prospective studies assessing utility of preventative strategies such as expanded neuroimaging screening for vasculopathy or silent infarcts, antiplatelet therapy, or more aggressive treatment of modifiable risk factors. This study did not evaluate neuroimaging, and therefore we are unable to make any specific recommendations about the role of expanded neuroimaging, including magnetic resonance angiography (MRA). A high index of suspicion for cerebrovascular events and better preventative strategies are needed to prevent initial and recurrent strokes and to reduce mortality and neurologic morbidity in this population.

A subset analysis restricted to the female survivors evaluated a history of using birth control pills or female hormone medications and found no association with increased headache risk. However, the data available on use of female hormone medications have limitations. No information was collected regarding age at first use of such medications until the follow-up 2003 questionnaire. Information on whether use has been continuous or intermittent since first starting is also not available.

Three-fourths of patients reporting seizures reported use of an anti-epileptic medication at some point. The questionnaires did not ascertain whether reported seizures were considered provoked or unprovoked. Because of the way medication questions were structured, it was not possible to determine how many drugs were being taken simultaneously. It also was not possible to assess antiseizure medication use over time because the questions about medication use changed across the longitudinal follow-up questionnaires.

Table 3 Multivariable risk factor analysis of neurologic outcomes in childhood CNS tumor survivors

Outcome	Factor	Level	Hazard Ratio (95% CI)
Headaches [‡]	Sex	Female	1.0
		Male	0.5 (0.4–0.7)**
	Ever smoked	No	1.0
		Yes	1.9 (1.2–3.1)*
	Recurrence	No	1.0
		Yes	1.7 (1.2–2.7)*
Seizures	Frontal lobe irradiation	None/scatter only	1.0
		1–49 Gy	1.0 (0.6–1.8)
		≥50 Gy	1.8 (1.0–3.0)*
	Temporal lobe irradiation	None/scatter only	1.0
		1–49 Gy	1.9 (1.1–3.4)*
		≥50 Gy	2.2 (1.4–3.5)*
	Parietal lobe irradiation	None/scatter only	1.0
		1–49 Gy	1.2 (0.6–2.3)
		≥50 Gy	1.9 (1.1–3.4)*
	Posterior fossa irradiation	None/scatter only	1.0
		1–49 Gy	0.9 (0.5–1.6)
		≥50 Gy	0.8 (0.5–1.3)
	Recurrence	No	1.0
		Yes	2.3 (1.6–3.2)**
	Meningioma	No	1.0
		Yes	2.6 (1.1–6.5)*
	Stroke	No	1.0
		Yes	2.0 (1.1–3.4)*
Coordination problems	Maximum irradiation to any brain region	None/scatter only	1.0
		1–49 Gy	2.0 (1.2–3.2)*
		≥50 Gy	1.8 (1.2–2.7)*
	Recurrence	No	1.0
		Yes	2.4 (1.5–3.7)*
	Meningioma	No	1.0
		Yes	4.3 (1.7–10.7)*
	Stroke	No	1.0
		Yes	6.5 (4.0–10.5)**
Motor problems	Frontal lobe irradiation	None/scatter only	1.0
		1–49 Gy	1.0 (0.6–1.7)
		≥50 Gy	2.0 (1.2–3.4)*
	Temporal lobe irradiation	None/scatter only	1.0
		1–49 Gy	1.2 (0.7–2.1)
		≥50 Gy	1.4 (0.9–2.3)
	Recurrence	No	1.0
		Yes	2.6 (1.8–3.8)**
	Meningioma	No	1.0
		Yes	2.3 (0.9–5.4)
	Stroke	No	1.0
		Yes	14.9 (10.4–21.4)**

* $P < 0.05$, ** $P < 0.001$.[‡]Stroke and meningioma were not statistically significant risk factors for headaches.

Table 4 Multivariable risk factor analysis of neurosensory outcomes in CNS tumor survivors

Outcome	Factor	Level	Hazard Ratio (95% CI)
Hearing loss ^{†,‡}	Temporal lobe irradiation	None/scatter only	1.0
		1–49 Gy	1.7 (0.9–3.1)
		≥50 Gy	2.7 (1.6–4.5)**
	Posterior fossa irradiation (cancer dx age <5)	None/scatter only	1.0
		1–49 Gy	1.2 (0.5–2.9)
		≥50 Gy	2.2 (1.1–4.4)*
	Posterior fossa irradiation (cancer dx age 5–9)	None/scatter only	1.0
		1–49 Gy	3.2 (1.3–8.1)*
		≥50 Gy	2.8 (1.3–6.1)*
	Posterior fossa irradiation (cancer dx age 10–14)	None/scatter only	1.0
		1–49 Gy	0.8 (0.2–2.8)
		≥50 Gy	3.2 (1.5–6.7)*
	Posterior fossa irradiation (cancer dx age 15–21)	None/scatter only	1.0
		1–49 Gy	11.6 (2.5–53.5)*
		≥50 Gy	7.2 (1.5–33.8)*
Tinnitus [‡]	Recurrence	No	1.0
		Yes	2.4 (1.6–3.6)**
	Vincristine	No	1.0
		Yes	1.5 (1.0–2.1)*
	Age at primary cancer diagnosis	<5 y	0.4 (0.2–0.8)*
		5–9 y	0.4 (0.2–0.7)*
		10–14 y	0.6 (0.3–1.0)*
		≥15 y	1.0
	Frontal lobe irradiation	None/scatter only	1.0
		1–49 Gy	0.8 (0.5–1.3)
		≥50 Gy	0.4 (0.2–0.9)*
	Temporal lobe irradiation	None/scatter only	1.0
		1–49 Gy	1.5 (0.8–2.9)
		≥50 Gy	1.7 (1.0–3.0)
	Posterior fossa irradiation	None/scatter only	1.0
		1–49 Gy	2.0 (1.1–3.7)*
		≥50 Gy	2.3 (1.4–3.8)*
Vertigo [‡]	Second malignant neoplasm	No	1.0
		Yes	2.8 (1.2–6.5)*
	Platinum	No	1.0
		Yes	2.1 (1.2–3.9)*
	Sex	Female	1.0
		Male	0.6 (0.4–0.9)*
	Maximum irradiation to the frontal and/or parietal lobes	None/scatter only	1.0
		1–49 Gy	0.8 (0.5–1.4)
		≥50 Gy	1.9 (1.2–3.2)*
	Second malignant neoplasm	No	1.0
		Yes	3.1 (1.1–8.5)*
Blindness	Surgical treatment for primary cancer	Surgery	1.0
		No surgery	6.9 (2.1–23.2)*

Table 4 *Continued*

Outcome	Factor	Level	Hazard Ratio (95% CI)
	Age at primary cancer diagnosis	<5 y	0.2 (0.1–0.9)*
		5–9 y	0.2 (0.1–0.7)*
		10–14 y	0.2 (0.1–0.8)*
		≥15 y	1.0
	Recurrence	No	1.0
		Yes	4.7 (2.4–9.5)**
	Meningioma	No	1.0
		Yes	6.5 (1.5–28.3)*
	Stroke	No	1.0
		Yes	3.8 (1.5–9.2)*
Cataracts [‡]	Frontal lobe irradiation	None/scatter only	1.0
		1–49 Gy	4.8 (2.4–9.5)**
		≥50 Gy	2.5 (1.0–6.5)
	Nonplatinum alkylators (ALK), vincristine (VIN)	No ALK, no VIN	1.0
		ALK only	0.9 (0.3–3.2)
		VIN only	3.9 (1.5–10.2)*
		Both VIN and ALK	0.9 (0.4–2.0)
	Platinum	No	1.0
		Yes	2.1 (0.9–4.9)
	Recurrence	No	1.0
		Yes	1.9 (0.9–4.0)

* $P < 0.05$, ** $P < 0.001$.

[†]There was a statistically significant interaction between posterior fossa irradiation and age at cancer diagnosis for the hearing loss outcome. Therefore, estimates of the posterior fossa HRs are presented by age-group category. Within each of the age strata, each radiation category had at least 23 observations (maximum 279).

[‡]Stroke and meningioma were not statistically significant risk factors for hearing loss, tinnitus, vertigo, or cataracts.

The main limitation of the study was relying on self-report about late events, without the ability to examine medical records. The CCSS study takes several steps to limit the length of time for participants to recall the onset of symptoms. Specifically, interaction between the researchers and participants occurs every 2 to 3 years. The longest time between queries was 1994 to 1998. Additionally, this particular study focuses on symptoms rather than diagnosed conditions and diseases. Self-reported symptoms from large cohorts have been used in other publications, most notably the National Health Interview Survey (NHIS), which is administered by the Centers for Disease Control and Prevention's National Center for Health Statistics to examine disease burden in the United States. Nevertheless, it was not possible to ascertain additional, confirmatory medical details such as how strokes, meningiomas, and recurrences were treated, to review the neuroimaging, or to discuss neurologic outcomes from a disease perspective.

Another limitation is that results may not necessarily apply to childhood CNS tumor survivors treated under modern treatment regimens. Relatively few patients in the CCSS CNS tumor cohort received chemotherapy and those who did often also received high-dose radiation, possibly obscuring

the independent contributions of chemotherapy. The association between vincristine and hearing loss was surprising. We reviewed our data to see if other factors were associated, but we could not find an explanation. This association will need confirmation in other studies. Additionally, 63% of long-term survivors of astrocytomas in the CCSS received radiation therapy, which is higher than another study reporting radiation in 736 of 4040 (18%) astrocytoma patients treated from 1973 to 2008.²¹ There are 2 likely explanations: (i) radiation treatment for low-grade astrocytoma was more common during the CCSS period of 1970–1985 and (ii) although grading is not available, patients in the original CCSS cohort were less likely to be low-grade/pilocytic because brain tumors were coded differently at the time of CCSS treatment, with pilocytic astrocytomas not necessarily coded as brain tumors.

Management of childhood CNS tumors has changed substantially since the initial CCSS cohort was diagnosed and treated, due to efforts to increase the chance of cure and minimize adverse treatment effects. Surgery has become more precise with better imaging and improved perioperative care, although the posterior fossa syndrome has been a relatively common complication.^{22,23} Photon radiation has become more targeted with less scatter, and proton

radiation is increasing in availability.²⁴ Chemotherapy is used more extensively to delay radiation therapy or to reduce the dose and field of radiation therapy.²⁵ Newer regimens contain cis-platinum agents in most protocols for embryonal tumors, less methotrexate overall, and more alkylator-based regimens across all tumor types. Autologous stem cell rescue has enabled patients to tolerate higher doses of chemotherapy.²⁶ Nevertheless, maximally tolerated doses of radiation therapy and traditional myelosuppressive chemotherapy remain the backbone of treatment plans for most patients with CNS tumors.²⁷ While conclusions about chemotherapy-specific effects are limited, the substantial contribution of radiation to late neurologic impairment in the current study supports previous reports.^{8,28} In this longitudinal assessment, regional brain dosimetry was associated with specific neurologic outcomes, including motor problems (frontal lobe), seizures (frontal lobe, temporal lobe), hearing loss (temporal lobe, posterior fossa), and tinnitus (posterior fossa).

Despite reaching the 5-year survivorship milestone, 25% of CCSS participants with childhood CNS tumors died within 30 years of their diagnosis, as previously published.²⁹ A recent study by the Surveillance, Epidemiology, and End Results program showed that patients treated after 1986 experienced a small improvement in mortality compared with earlier cohorts; however, 5-year survivors of a childhood CNS tumor experienced a nearly 13-fold increased risk of death compared with their peers, due at least in part to recurrent disease, SMNs, and cerebrovascular and cardiovascular events.³⁰ Although the current study does not explain the causes of these early deaths, discovering new-onset neurologic morbidity as survivors age further supports the need to monitor these patients carefully and to explore causes of late medical and neurologic morbidity and mortality. Continued neurologic follow-up of survivors of childhood CNS tumors is indicated, ideally within or in close association with a multidisciplinary cancer survivor clinic. Additional follow-up of original CCSS participants and new cohorts treated with modern therapy will enhance our understanding of risks and risk factors and ideally lead to improved management for aging survivors and inform treatment decisions and clinical trial development for newly diagnosed patients.

Supplementary Material

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

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Conflict of interest statement. The authors report no conflicts of interest.

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