

# Long-Term Neurologic and Neurosensory Sequelae in Adult Survivors of a Childhood Brain Tumor: Childhood Cancer Survivor Study

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**Purpose:** To describe the neurologic and neurosensory deficits in children with brain tumors (BTs), compare incidence of these deficits with that of a sibling control group, and evaluate the factors associated with the development of these deficits.

**Patients and Methods:** Detailed questionnaires were completed on 1,607 patients diagnosed between 1970 and 1986 with a primary CNS tumor. Neurosensory and neurologic dysfunctions were assessed and results compared with those of a sibling control group. Medical records on all patients were abstracted, including radiotherapy dose and volume.

**Results:** Seventeen percent of patients developed neurosensory impairment. Relative to the sibling comparison group, patients surviving BTs were at elevated risk for hearing impairments (relative risk [RR], 17.3;  $P < .0001$ ), legal blindness in one or both eyes (RR, 14.8;  $P < .0001$ ), cataracts (RR, 11.9;  $P < .0001$ ), and double vision (RR,

8.8;  $P < .0001$ ). Radiation exposure greater than 50 Gy to the posterior fossa was associated with a higher likelihood of developing any hearing impairment. Coordination and motor control problems were reported in 49% and 26%, respectively, of survivors. Children receiving at least 50 Gy to the frontal brain regions had a moderately elevated risk for motor problems (RR, 2.0;  $P < .05$ ). Seizure disorders were reported in 25% of patients, including 6.5% who had a late first occurrence. Radiation dose of 30 Gy or more to any cortical segment of the brain was associated with a two-fold elevated risk for a late seizure disorder.

**Conclusion:** Children surviving BTs are at significant risk for both early and late neurologic or neurosensory sequelae. These sequelae need to be prospectively monitored. *J Clin Oncol* 21:3255-3261. © 2003 by American Society of Clinical Oncology.

**B**RAIN TUMORS, which are composed of histologically diverse neoplasms of the CNS, are the second most common form of cancer occurring in children younger than 20 years.<sup>1,2</sup> Improvements in treatment have resulted in an increased rate of survival among those with childhood brain tumors, especially medulloblastoma.<sup>3-9</sup> Concomitant with improved survival rates is the recognition that many long-term survivors have permanent neurologic, neurocognitive, endocrinologic, and neuropsychologic deficits.<sup>10-13</sup> The greatest attention in clinical research has been paid to endocrinologic and neurocognitive sequelae.<sup>14-17</sup> It is well documented that children with tumors arising in the suprasellar region have a high likelihood of permanent long-term hormonal dysfunction.<sup>16,17</sup> High-dose irradiation to the hypothalamic region may result in delayed-onset hormonal deficiency.<sup>12,16,17</sup> In addition, neurocognitive dysfunction has consistently been documented years after treatment in children receiving brain irradiation.<sup>10,18,19</sup> The likelihood of such deficits occurring has been related to early age at diagnosis and treatment; type, extent, and location of tumor; and the dose of radiation and volume received.<sup>10,13,14,18,19</sup>

The incidence of neurologic sequelae suffered by children with brain tumors, and the time of onset of such difficulties, has not been extensively evaluated.<sup>10,20</sup> The Childhood Cancer Survivor Study (CCSS), a retrospective cohort study of persons who survived a childhood cancer for at least 5 years postdiagnosis, includes more than 1,800 young adults with a prior brain tumor.<sup>21</sup> The brain tumor survivors in CCSS provide a unique opportunity to evaluate long-term neurologic effects from cancer treatment. The aims of this analysis were to describe the

incidence of adverse neurologic conditions, stratified by the time period in which the outcome was reported to first occur; to compare late-onset ( $\geq 5$  years postdiagnosis) adverse neurologic conditions among survivors to that of a group of participating siblings; and to evaluate the effect of treatment on the risk of developing a late adverse neurologic condition.

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*Submitted January 27, 2003; accepted June 5, 2003.*

*Supported by National Cancer Institute Grant U24 CA 55727.*

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*0732-183X/03/2117-3255/\$20.00*

## PATIENTS AND METHODS

### Inclusion Criteria

The complete methodology for CCSS has been published previously.<sup>21</sup> An abbreviated description relevant to this analysis follows. CCSS includes individuals who received their primary cancer treatment at one of 25 collaborating institutions (listed in the Appendix) and who survived at least 5 years after diagnosis, independent of disease status. Eligibility was restricted to those with a primary malignant brain tumor, leukemia, Hodgkin's disease, non-Hodgkin's lymphoma, kidney tumor, neuroblastoma, soft tissue sarcoma, or bone tumor, diagnosed between 1970 and 1986, at age 20 years or younger. The human subjects committees at the University of Minnesota (the study coordinating center) and each collaborating hospital approved the CCSS protocols and documents. Each patient in this analysis (or their proxy) provided informed consent to participate in the study, and consent to obtain his or her medical records. To recruit the sibling comparison group, a random sample of participating patients was selected and asked to contact their closest-age sibling if they had one or more living siblings for possible recruitment onto the study.

Among the 20,276 5-year survivors (patients) identified by the collaborating institutions, 14,054 were enrolled and completed an interview at the time of this analysis, 3,132 declined to participate, 2,996 were lost to follow-up and never offered enrollment, and 94 patients are pending inclusion into the study cohort. Of the 1,818 participating patients with a prior brain tumor who completed the baseline questionnaire, treatment information was obtained about 1,607 patients (88%); these patients were included in this report.

### Data Collection

Participants completed a 24-page questionnaire with a wide range of information on demographic characteristics, health habits, and medical conditions. A copy of the survey instrument is available for review and downloading at [www.cancer.umn.edu/ccss](http://www.cancer.umn.edu/ccss). It is planned that the Web site, which is continually upgraded, will maintain the questionnaire indefinitely. The participant, or a parent for those younger than 18 years of age, completed the questionnaire either by mail or by telephone with a trained interviewer. The questions on medical conditions were introduced with "Have you ever been told by a doctor or other health care professional that you have or have had. . . ?" Participants who responded "yes" were asked to provide the age when the condition first occurred. Medical records from the referring institution were abstracted to obtain information on cancer diagnosis and treatment, including details of prior surgeries, chemotherapies, and radiotherapy.

### Radiation Dosimetry

Of the 1,607 children enrolled onto the study, 1,159 (72%) had received radiation therapy. To quantify radiation exposure, the brain was partitioned into four anatomic segments (frontal cortex, temporal lobe, posterior fossa, and parietal or occipital cortex) and maximum radiation doses were estimated for each region (Fig 1). A segment was said to be included in a radiation field if at least 50% of the segment was included in the primary radiation volume; otherwise the segment was considered to have received scatter dose. Treatment diagrams and photographs taken in the treatment position were reviewed to make the determination of which brain segments were irradiated. If diagrams were not available, a written description from the medical record was used to estimate the regions included and the dose administered. Segment-specific dosimetry could not be determined for 142 patients who received radiation. These patients were aggregated together as a separate category for the radiation dose-response analysis. For those who received radiotherapy, radiation exposure in each brain segment was categorized as less than 30, 30 to 49, and  $\geq 50$  Gy. Most patients (84% to 93%, depending on the exposed brain segment) whose treatment corresponded with the lowest exposure category (< 30 Gy) received only scatter doses of radiation.

### Statistical Analysis

Three types of neurologic outcomes were considered: neurosensory deficits, focal neurologic dysfunction, and seizures. Neurosensory deficits

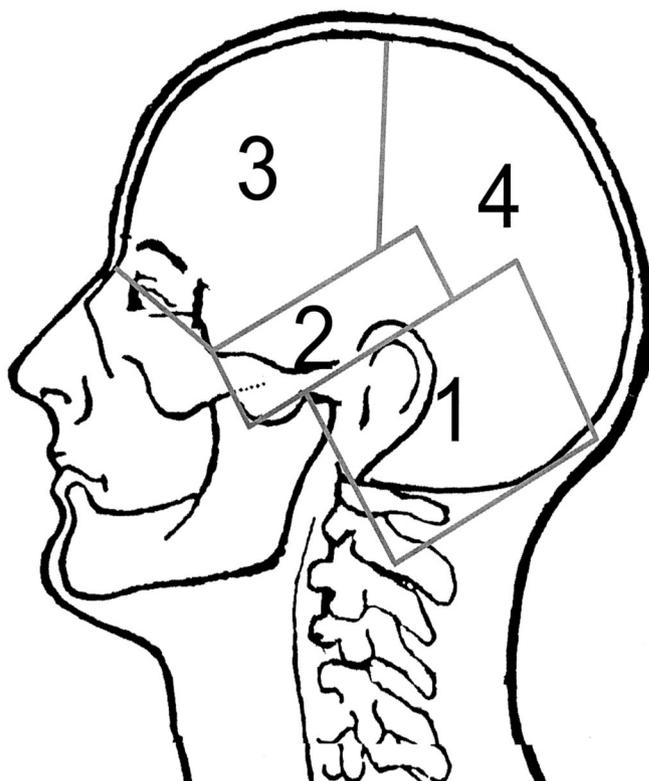


Fig 1. Anatomic segments used for calculation of radiation dosimetry.

included the following medical conditions: hearing loss requiring a hearing aid, deafness in one or both ears not completely corrected by hearing aid, complete deafness in either ear, tinnitus, persistent dizziness, legally blind in one or both eyes, and cataracts. Hearing loss, deafness, or complete deafness was aggregated into the "yes" or "no" variable for "any hearing problem." Focal neurologic dysfunction included deficits related to problems with balance, tremors, or movements, as well as the weakness or inability to move arm(s) or leg(s). An aggregated variable for "any coordination problem" was derived from balance problems or tremors. Similarly, a variable for "any motor problem" was derived from weakness or inability to move arms(s) or leg(s). "Any seizure disorder" was composed of responses for epilepsy, or repeated seizures, convulsions, or blackouts. A "yes" response to any component of an aggregated variable constituted a "yes" for that variable.

If a "yes" response was recorded without an accompanying age at first occurrence, the time period of occurrence was imputed using multiple imputation methodology<sup>22</sup> employed for event-time imputations, with slight modifications.<sup>23</sup> The percentage of imputed values for the aggregated variables was 0.7% for any hearing impairment, 3.1% for any motor problem, 3.4% for any seizure disorder, and 7.0% for any coordination problem. Because of the imputed values, in Table 1 the total numbers shown in the Reported Outcome column for some conditions are not an exact sum of the time period-specific numbers shown. Poisson regression was used to calculate incidence rates, and Cox proportional hazard models were used to estimate hazard ratios, reported as relative risks (RRs). Of the 3,418 siblings who agreed to participate, 399 are siblings of a participant of this study who survived a brain tumor. As such, to control for intrafamily correlations, SE estimates were adjusted using the sandwich method for correlated data.<sup>24</sup>

## RESULTS

### Characteristics of the Study Population

Table 2 shows demographic characteristics for participating patients and siblings, and tumor and treatment-related informa-

**Table 1. Incidence Rates and Relative Risks by Time Period of Onset of Adverse Neurologic Outcomes**

Conditions	Neurosensory Deficits					Focal Neurologic Dysfunction			
	Any Hearing Impairment	Tinnitus	Persistent Dizziness	Legal Blindness in One or Both Eyes	Cataracts	Problems With Double Vision	Any Coordination Problem	Any Motor Problem	Any Seizure Disorder
<b>Reported outcome</b>									
<b>Yes*</b>									
No.	192	171	155	211	48	278	784	425	401
%	12	11	10	13	3	17	49	26	25
<b>No†</b>									
No.	1,402	1,422	1,439	1,384	1,557	1,315	757	1,159	1,114
%	87	88	90	86	97	82	47	72	69
<b>Diagnosis to end of treatment</b>									
Yes, No. of patients	46	45	76	92	6	130	408	196	141
Rate‡	16.6	15.9	25.5	32.8	2.0	43.7	189.4	79.7	54.4
95% CI	12.4 to 22.1	11.8 to 21.4	20.2 to 32.2	26.5 to 40.5	0.9 to 4.5	36.4 to 52.5	170.7 to 210.2	69.3 to 91.6	45.9 to 64.5
RR§,	42.8	17.2	44.9	93.2	9.8	123.5	158.8	121.4	55.3
95% CI	27.1 to 67.5	11.8 to 25.0	32.1 to 62.9	59.8 to 145.4	3.9 to 24.6	83.6 to 182.3	127.2 to 198.4	92.7 to 159.0	41.5 to 73.6
<b>End of treatment to 5 years after diagnosis</b>									
Yes, No. of patients	58	33	26	77	11	73	189	94	101
Rate‡	9.4	7.2	6.2	14.8	2.2	17.1	67.0	21.6	23.1
95% CI	7.3 to 12.1	5.2 to 9.8	4.6 to 8.5	12.0 to 18.3	1.2 to 3.8	13.9 to 20.9	59.4 to 75.6	18.1 to 25.9	19.3 to 27.6
RR§,	26.7	7.0	9.6	55.1	11.2	43.5	60.2	35.8	24.7
95% CI	17.4 to 40.9	4.8 to 10.2	6.4 to 14.3	34.6 to 87.8	5.4 to 23.4	29.2 to 64.9	47.8 to 75.9	26.6 to 48.3	18.5 to 33.1
<b>5 years after diagnosis to end of follow-up</b>									
Yes, No. of patients	76	59	35	19	22	41	74	85	105
Rate‡	5.9	5.4	2.9	1.9	1.7	3.9	11.8	7.6	10.3
95% CI	4.8 to 7.4	4.3 to 6.9	2.1 to 4.0	1.3 to 2.8	1.1 to 2.5	3.0 to 5.3	9.5 to 14.7	6.1 to 9.3	8.5 to 12.4
RR§,	17.3	3.7	3.2	14.8	11.9	8.8	12.6	12.4	12.6
95% CI	11.6 to 25.8	2.7 to 5.1	2.2 to 4.8	7.5 to 29.2	5.7 to 24.8	5.6 to 13.8	9.1 to 17.5	8.7 to 17.5	9.2 to 17.1

Abbreviation: RR, relative risk.

\*Excludes conditions prior to diagnosis.

†Includes "not sure" and missing responses.

‡Rate per 1,000 person-years.

§Adjusted for sex; relative to siblings.

|| $P < .0001$ .

tion for patients. A higher proportion of patients than siblings were male. Patients tended to be younger at interview than were siblings. Approximately 64% of patients were younger than age 10 years at diagnosis. The distribution of tumor subtypes was consistent with population-based statistics, with approximately 66% astroglial tumors and 21% primitive neuroectodermal tumors or medulloblastomas (PNET). Nearly 98% of patients underwent surgical intervention. Adjuvant chemotherapy was included in the treatment of 30% of patients. Brain radiation was administered in 72% of patients. The estimated doses by brain segment are shown in Table 3.

The frequency of reported neurologic conditions, along with incidence rates per 1,000 person-years stratified by time period of first occurrence, are shown in Table 1 for each outcome group. This table also lists the estimated RRs and 95% confidence intervals comparing rates in patients to those of the sibling group. These results are discussed according to type of outcome.

*Neurosensory Deficits: Hearing and Vision Sequelae*

**Vision.** The percentage of patients reporting visual deficits ranged from 3% for cataracts to 17% for double vision (Table 1). Thirteen percent of patients reported being legally blind in one or both eyes, including 19 patients (1.2%) who reported late onset of this outcome ( $\geq 5$  years postdiagnosis). Relative to the sibling comparison group, patients were at substantially elevated risk for

late-onset legal blindness in one or both eyes (RR, 14.8;  $P < .0001$ ), cataracts (RR, 11.9;  $P < .0001$ ), and double vision (RR, 8.8;  $P < .0001$ ).

**Hearing.** A hearing impairment was reported by 12% of patients. As shown in Table 4, children who survived a PNET had a higher frequency of a late-onset hearing impairment (7%) than those who survived an astroglial tumor (4%) or ependymoma (3%). No other large histology-specific differences in late effects related to hearing were observed. Radiation exposure of 50 Gy or more to the hearing apparatus (posterior fossa segment) was associated with a 3.7-fold increased risk ( $P < .001$ ) of developing any hearing impairment, relative to a dose of less than 30 Gy (Table 5). Aside from that one exception, no significant differences were found in any RR of hearing impairments from either treatment with platinum-containing chemotherapy or from differences in radiation dose to any specific segment of the brain (data not shown). Compared with the sibling comparison group, patients had a substantially elevated risk of a late-onset hearing impairment (RR, 17.3;  $P < .0001$ ).

*Focal Neurologic Dysfunction: Motor and Coordination Problems*

A coordination problem or a motor control problem was reported in 49% and 26%, respectively, of this population of brain tumor survivors (Table 1). Although the incidence of such

**Table 2. Characteristics of Childhood Brain Cancer Patients and the Sibling Comparison Group**

Characteristic	Patients (N = 1,607)		Siblings (N = 3,418)	
	No.	%	No.	%
Age at interview, years				
< 20	621	38.6	1,001	29.3
20-29	693	43.1	1,221	35.7
30-39	274	17.1	941	27.5
≥ 40	19	1.2	255	7.5
Sex				
Males	873	54.3	1,645	48.1
Females	734	45.7	1,773	51.9
Vital status at time of interview				
Alive	1,433	89.2	3,418	100
Dead	174	10.8	0	0
Age at diagnosis, years				
≤ 4	547	34.0	NA	NA
5-9	480	29.9	NA	NA
≥ 10	580	36.1	NA	NA
Histology			NA	NA
Astroglial	1,066	66.3	NA	NA
Primitive neuroectodermal tumor	343	21.3	NA	NA
Ependymoma	118	7.3	NA	NA
Other CNS	80	5.0	NA	NA
Treatment			NA	NA
Surgery + radiation	682	42.4	NA	NA
Surgery + radiation + chemotherapy	446	27.8	NA	NA
Surgery	414	25.8	NA	NA
Surgery + chemotherapy	26	1.6	NA	NA
Radiation	19	1.2	NA	NA
Chemotherapy + radiation	8	0.5	NA	NA
No treatment	7	0.4	NA	NA
Unknown	5	0.3	NA	NA

Abbreviation: NA, not applicable.

problems was greatest during treatment and declined notably over time, even as a late effect a coordination problem (RR, 12.6;  $P < .0001$ ) or a motor problem (RR, 12.4;  $P < .0001$ ) was far more common among patients than siblings. One or more motor problems as a late effect were reported by 4.6% of patients ( $n = 74$ ), occurring with approximately the same frequency between those with an astroglial tumor and those with a PNET (Table 4). Patients who received at least 50 Gy to the frontal region of the brain had a modestly elevated risk for a motor problem (RR, 2.0;  $P < .05$ ; Table 6) compared with those who received a radiation dose lower than 30 Gy. There was no increased risk for either a motor problem or coordination problem associated with receiving platinum-containing chemotherapy.

#### Seizure Disorders

A seizure disorder was reported in 25% of patients, including 6.5% of the study population who had first occurrence of seizure 5 or more years after diagnosis (Table 1). The risk of a seizure disorder as a late effect, relative to the sibling comparison group, was high (RR, 12.6;  $P < .0001$ ). There was little difference in frequency of a late-effect seizure disorder between those with an

**Table 3. Radiation Dose to Brain Regions**

Radiation Site and Dose	Patients (N = 1,607)	
	No.	%
Posterior fossa, Gy		
< 30*	307	19.1
30-49	184	11.5
≥ 50	526	32.7
Temporal lobe, Gy		
< 30*	155	9.7
30-49	281	17.5
≥ 50	581	36.2
Frontal cortex, Gy		
< 30*	447	27.8
30-49	381	23.7
≥ 50	189	11.8
Parietal or occipital, Gy		
< 30*	451	28.1
30-49	356	22.2
≥ 50	210	13.1
No radiation to brain	448	27.9
Dose uncertain (insufficient records)	142	8.8

\*Includes indirect or "scatter" doses.

astroglial tumor (7%) and those with a PNET (8%). As shown in Table 6, a radiation dose of 30 Gy or more to any segment of the brain, with the exception of the posterior fossa, was associated with more than a two-fold elevated risk for a late-effect seizure disorder.

#### DISCUSSION

The results of this study demonstrate that children surviving brain tumors are at high risk for neurologic and neurosensory difficulties. Children with all types of brain tumors suffered sequelae, and the development of these deficits were recognized not only during treatment, but also many years after treatment. A caveat in interpreting the results of this study is that all information concerning occurrence and time of onset of sequelae was obtained by self-report. Although patients may report a deficit as a new problem 5 years after diagnosis and treatment, it may have been present earlier than realized by the patient. It is also possible that the late effects reported in some children could have been due to progressive disease because patients who were alive, but had active disease at the 5-year follow-up points, were eligible for study. Although this was likely a small number of patients, the methods of data capture do not allow a separate analysis of disease state at time of completion of the questionnaire.

Another issue is that the rates reported in this study during the two early time periods (ie, diagnosis to end of treatment and end of treatment to 5 years postdiagnosis) may not estimate the true incidence of neurologic sequelae among all children diagnosed with brain tumors. Patients who died within the first 5 years of diagnosis were not eligible for the study, and it is likely that children who died had more frequent neurologic deficits before death. If they were included, it would be difficult to separate the effects of the original tumor from that of tumor progression on neurologic function. Outcome data reported during the two early time periods for the survivors are included in this report to provide a more global picture of difficulties encountered.

**Table 4. Late-Onset (5 years postdiagnosis) Neurologic Outcomes by Brain Tumor Histology**

	Astroglial (n = 1,066)		PNET (n = 343)		Ependymoma (n = 118)		Other (n = 80)		Total (N = 1,607)	
	No.	%	No.	%	No.	%	No.	%	No.	%
Any hearing impairment	45	4	23	7	4	3	4	5	76	5
Tinnitus	35	3	15	4	4	3	5	6	59	4
Persistent dizziness	27	3	5	1	2	2	1	1	35	2
Any seizure disorder	70	7	28	8	5	4	2	3	105	7
Any coordination problem	57	5	13	4	2	2	2	3	74	5
Any motor problem	64	6	14	4	3	3	4	5	85	5

Abbreviation: PNET, primitive neuroectodermal tumor.

The influence of neurosensory deficits on cognitive abilities and the ability to function and succeed later in life among long-term brain tumor survivors has been poorly assessed in other studies. Hearing loss or other hearing deficits such as tinnitus (ringing in the ear) were quite common both early and late in illness. No association between late hearing impairment and cisplatin was found, although this agent was not routinely used in treatment protocols between 1970 and 1986.<sup>3,4</sup> Hearing impairment was statistically related to posterior fossa irradiation of greater than 50 Gy; however, the direct relationship between irradiation and the sequelae is not completely clear because children with an ependymoma or a PNET would have received similar doses of radiation to similar regions of the brain, but late hearing loss varied between children with different tumor types and was noted in 7% of children with PNETs as compared with 3% of children with ependymomas. It is likely that wider use of cisplatin, especially for children with a PNET, will increase the rate of hearing impairment of patients treated later than 1986.<sup>4-9</sup> The high incidence of tinnitus and dizziness, impairments that are not routinely thought of as long-term sequelae of a brain tumor or its treatment, may also significantly influence the quality of life of survivors. Cataracts are a recognized long-term complication of radiotherapy, as is late-onset optic neuropathy, but the reason for the delayed onset of diplopia is unclear.

It is not surprising that children surviving brain tumors have a high incidence of motor and coordination difficulties, but it is

unclear why patients may first note these difficulties years after diagnosis. It is impossible to separate completely the relative contribution of the tumor location from the potential deleterious effects of local radiotherapy to the occurrence of adverse events. Similarly, it is impossible, from the retrospective nature of the study and the data available, to evaluate the influence of surgical complications on the incidence and type of neurologic sequelae seen, although it is probable that these would more likely have been early deficits. Cranial irradiation may cause leukoencephalopathy or cerebrovascular damage (or both) years after treatment and both can result in impaired motor function.<sup>10,20</sup> Late motor control problems were more frequently noted in children who had received more than

**Table 6. Effects of Radiation Site and Dose on the Risk of Late-Onset (5 years postdiagnosis) Motor and Seizure Disorders**

Disorders	30-49 v < 30 Gy	50+ v < 30 Gy
Any motor disorder		
Posterior fossa		
RR	1.1	0.9
95% CI	0.4 to 2.7	0.5 to 1.8
Temporal lobe		
RR	0.5	1.1
95% CI	0.2 to 1.5	0.5 to 2.4
Frontal cortex		
RR	1.8	2.0*
95% CI	0.6 to 4.8	1.0 to 3.9
Parietal or occipital		
RR	0.8	1.3
95% CI	0.3 to 2.0	0.6 to 2.6
Any seizure disorder		
Posterior fossa		
RR	1.3	0.9
95% CI	0.6 to 2.8	0.4 to 1.8
Temporal lobe		
RR	2.7†	2.5†
95% CI	0.9 to 7.7	1.0 to 6.5
Frontal cortex		
RR	0.6	2.5‡
95% CI	0.3 to 1.4	1.3 to 4.6
Parietal or occipital		
RR	2.6*	2.7*
95% CI	1.2 to 5.9	1.3 to 5.7

NOTE. Adjusted for histology, age at diagnosis, and sex. Abbreviation: RR, relative risk.

\*P < .05.

†.05 < P < .1.

‡P < .01.

**Table 5. Effect of Radiation Dose to the Hearing Apparatus of the Posterior Fossa and Platinum-Based Chemotherapy on the Risk of Late-Onset (5 years postdiagnosis) Hearing Impairments, Tinnitus, and Persistent Dizziness**

Condition	Radiation Dose to Posterior Fossa		Platinum-Based Chemotherapy Yes v No
	30-49 v < 30 Gy	50+ v < 30 Gy	
Any hearing impairment			
RR	1.2	3.7*	1.2
95% CI	0.5 to 3.2	1.8 to 7.8	0.5 to 2.8
Tinnitus			
RR	1.3	1.8	1.5
95% CI	0.5 to 3.1	0.8 to 3.8	0.6 to 3.6
Persistent dizziness			
RR	1.3	1.1	1.2
95% CI	0.4 to 4.7	0.4 to 2.9	0.3 to 5.3

NOTE. Adjusted for histology, age at diagnosis, and sex.

Abbreviation: RR, relative risk.

\*P < .001.

50 Gy to the frontal or parietal occipital cortex and those who had received more than 30 Gy to the posterior cortical regions of brain.

Late occurrence of repeated seizures, convulsions, or black-outs were as common in children surviving a PNET as in those surviving an astroglial tumor. This finding may be related to the therapy received and possibly the age of the patients when therapy was given. Compared with children between the ages of 5 and 9 years at diagnosis, seizures were more likely (RR, 1.6;  $P = .041$ ) in children 4 years of age or younger, a period during which PNETs peak in incidence and the brain may be more vulnerable to toxic therapy. Radiation therapy of more than 30 Gy to the temporal lobes, compared with doses greater than 50 Gy to the frontal, parietal, or occipital cortex, was highly statistically related to the likelihood of a late onset of seizures or seizure-like episodes. Cranial irradiation has been linked to the development of cerebral vasculopathy years after treatment, and in other studies, treatment-related mineralizing microangiopathy has been related to the development of seizures.<sup>10</sup>

The applicability of the results of this study to patients now undergoing treatment can be questioned. However, overall survival rates for children with a malignant brain tumor have not improved dramatically since 1986.<sup>1,7</sup> Since the mid 1980s, the posterior-fossa mutism syndrome, a constellation of neurologic deficits after posterior fossa surgery (manifested by delayed-onset mutism, ataxia, and supranuclear cranial nerve palsies) has been reported in as many as 20% of children with medulloblastoma, with permanent neurologic dysfunction including cranial nerve deficits, hypotonia, and ataxia in approximately one half of those involved.<sup>25,26</sup> It is unknown whether this constellation of symptoms was as frequent before initial reports in the 1980s, but, if it is a new surgical complication, it will alter and likely increase the incidence of long-term neurologic compromise for children with a medulloblastoma.<sup>25</sup> It is not known how the routine use of conformal radiation therapy or other advances in radiation technology, such as proton beam irradiation, will influence the rate and type of sequelae seen. In adults with

gliomas, the use of increased doses of focal brain irradiation to the primary tumor sites has been associated with at least transient neurologic worsening.<sup>27-29</sup>

Chemotherapy, which was not routinely used for children with brain tumors between 1970 and 1986, is now an accepted component of the treatment for most children with a medulloblastoma and other PNETs, and it is increasingly being used in infants and young children (predominantly children younger than 3 years of age) with both low-grade and high-grade primary CNS neoplasms.<sup>7</sup> Information about the long-term influence of chemotherapy on neurologic and neurosensory function is relatively scant. Cisplatin, an agent that can cause significant ototoxicity, especially when coupled with radiation therapy, was not widely used before the mid-1980s for primary CNS tumors.<sup>7</sup> It now is a component of many treatment approaches for children of any age with a PNET and of infants with malignant brain tumors.<sup>7,30</sup> High-dose chemotherapy with either autologous bone marrow rescue or peripheral stem-cell support has also been used extensively during the last decade, but was only being explored initially in the 1970s and early 1980s; long-term neurologic sequelae from this approach are just being recognized.<sup>31-33</sup>

Given the high incidence of neurologic long-term sequelae and neurosensory sequelae, treatment approaches may need to be altered to reduce the likelihood of permanent damage. Detailed documentation of neurologic and neurosensory outcome, which has been poorly researched in children with brain tumors, may be highly important in determining the risk of cognitive and quality-of-life impairment in long-term survivors. It is unclear whether the introduction of new surgical, radiotherapy, and chemotherapy approaches will decrease sequelae, and it is plausible to postulate that aggressive surgery, higher doses of more focused radiation therapy, and the use of higher doses or better delivery of potentially neurotoxic therapy to the brain may even increase the rate of neurologic or neurosensory compromise. Such dysfunctions need to be monitored carefully in ongoing and future studies.

## APPENDIX

The appendix is included in the full text version of this article only, available on-line at [www.jco.org](http://www.jco.org).

It is not included in the PDF version.

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