

# Second Neoplasms in Pediatric Patients with Primary Central Nervous System Tumors

## *The St. Jude Children's Research Hospital Experience*

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Supported in part by Cancer Center Support (CORE) Grant P30 CA21765 from the National Institutes of Health and by the American Lebanese Syrian Associated Charities.

The authors thank Julia Cay Jones, Ph.D., for her editorial assistance.

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Received December 29, 2003; revision received February 17, 2004; accepted March 4, 2004.

**BACKGROUND.** Details on second neoplasms (SNs) following pediatric central nervous system (CNS) tumors are scant, because of the rarity of such SNs. The goal of the current study was to investigate and characterize these rare SNs.

**METHODS.** The authors reviewed clinical and treatment data on all institutional patients age < 22 years at diagnosis of a primary CNS tumor who developed any type of SN. Patients with neurofibromatosis type 1 were excluded. Cumulative incidence rates were estimated, and putative risk factors were analyzed.

**RESULTS.** The SNs investigated in the current study included 10 gliomas (42%), 5 meningiomas (21%), 2 desmoid tumors, 2 myelodysplastic syndromes, 2 basal cell carcinomas, 1 leukemia, 1 malignant fibrous histiocytoma, and 1 thyroid carcinoma. Twenty-one patients had previously received radiotherapy, and 12 patients had received chemotherapy. The SN was related to a genetic cause in 7 patients (29%). Eleven patients died of their SNs, including 8 patients with glioma and 2 patients with myelodysplastic syndromes. The estimated 15-year cumulative incidence rate for malignant SNs was 4%. Children with choroid plexus tumors had an estimated 10-year cumulative incidence rate of 20.2%; 2 of those patients had germline *TP53* mutations. Age  $\leq$  2 years was a significant risk factor ( $P = 0.016$ ) for development of an SN only when patients with genetic conditions were included in the analysis. No significant difference in the estimated cumulative incidence of SNs was found among patients who had received different types of therapy.

**CONCLUSIONS.** The risk of lethal SNs after pediatric CNS tumors is small. Young patients and patients with choroid plexus tumors appear to have an increased risk of SNs that is associated with genetic factors. *Cancer* 2004;100:2246-52.

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**KEYWORDS:** second neoplasms, brain, central nervous system, children, risk, genetic predisposition.

**P** rimary central nervous system (CNS) tumors represent the second most common group of neoplasms in childhood.<sup>1</sup> A recent report on the mortality associated with pediatric malignancy in the United States demonstrated that the improvement in outcome of children with CNS tumors continues to lag behind the improvements achieved for children with other common malignancies.<sup>1</sup> In addition, long-term side effects associated with CNS tumors and initial therapy constitute a disproportionate burden for these children and their families. Second neoplasms (SNs) are among the most serious long-term complications that affect these patients.

Children with primary CNS tumors have an increased risk of developing additional neoplasms.<sup>2-18</sup> Because SNs are rare events, the limited numbers of affected children included in reports originating

from single institutions and multicenter studies make it difficult to ascertain specific patient- and therapy-related characteristics that are associated with such increased risk. Data compiled from state or national cancer registries include larger numbers of patients, permitting an analysis of the relative risk of SNs for patients with various histologic subsets of pediatric CNS tumors.<sup>7,16</sup> However, cancer registries lack detailed information on patient, tumor, and treatment characteristics, all of which may be pivotal in the development of SNs.

Herein, we describe one of the largest single-institution experiences with SNs after the diagnosis of a primary CNS tumor in children and adolescents. The current systematic review of clinical, radiologic, and histologic information has allowed us to better define the characteristics of SNs and to identify the risk factors for SNs in subsets of patients.

## MATERIALS AND METHODS

We retrospectively identified 1283 patients age < 22 years with primary CNS tumors who were evaluated and treated at St. Jude Children's Research Hospital (Memphis, TN) between January 1, 1984, and August 1, 2002. The majority of these patients had primary brain tumors; only 31 patients (2.9%) harbored primary spinal cord tumors. Any type of neoplasm that was distinct from the initial tumor with respect to histology and site was considered to be an SN. Three patients with primary low-grade gliomas who developed second high-grade gliomas were included after a review of serial magnetic resonance images (MRIs) appeared to rule out anaplastic transformation of the original lesion. In each of these three patients, it was documented that the SN originated from a site distinct from the initial tumor. All SNs and 22 of 24 primary neoplasm specimens underwent central review. In two instances, including one case of tectal plate glioma at initial diagnosis and one case of brainstem glioma as an SN, histologic verification was lacking. Patients who had a diagnosis of neurofibromatosis type 1 (NF1) were excluded from the study because of their known predisposition toward developing SNs.<sup>2,3,10,12</sup>

### Statistical Analysis

The method of Kalbfleisch and Prentice<sup>19</sup> was used to estimate the cumulative incidence of SNs, second malignant tumors, second brain tumors, and gliomas as SNs for all patients with newly diagnosed primary CNS tumors ( $n = 1046$  of the 1283 patients total who were evaluated during the study period). The cumulative incidences of SNs also were calculated for patients with newly diagnosed medulloblastoma ( $n = 195$ ),

low-grade glioma ( $n = 273$ ), and choroid plexus tumors ( $n = 18$ ). The time at risk was defined as the interval between the diagnosis of the primary neoplasm and either the diagnosis of the SN or the date of last follow-up for survivors without SNs. Death was considered to be a competing event. Included in the above estimates were 16 of 24 patients with SNs who had received all treatment for their primary neoplasms, except for surgery, at our institution.

The Gray test<sup>20</sup> was used to assess the statistical difference in the estimated cumulative incidences of SNs among subgroups that were based on patient characteristics (i.e., age at diagnosis of the primary tumor, gender, and race). In addition, the difference in the estimated cumulative incidence of SNs for all patients, except for 7 patients who had a genetic predisposition, was analyzed according to treatment for the primary tumor (i.e., radiotherapy [RT] and chemotherapy use), with stratification of patients into 4 treatment subgroups: RT only ( $n = 278$ ), chemotherapy only ( $n = 57$ ), RT + chemotherapy ( $n = 486$ ), and neither RT nor chemotherapy ( $n = 218$ ). The use of the Gray test enabled us to adjust for competing risks. Due to the exploratory nature of the current study, our results were not adjusted for multiple comparisons.

## RESULTS

### Patient Characteristics

Twenty-four patients with an initial diagnosis of a primary CNS tumor who subsequently developed  $\geq 1$  SNs were identified. Fourteen females were included in the study group (Table 1). The median age at diagnosis of the primary tumor was 4.6 years (range, 0.4–20.1 years), and the median age at diagnosis of the SN was 15.9 years (range, 2.5–31.6 years). The median interval between diagnosis of the primary tumor and diagnosis of the SN was 7.9 years (range, 0.3–21 years). Two patients developed a third malignancy at ages 13.6 and 17.0 years, 12.6 and 15.9 years, respectively, after diagnosis of the primary tumor.

### Histologic Characteristics

The primary tumors of patients with SNs included medulloblastoma ( $n = 11$ ; 46%); World Health Organization (WHO) Grade I/II glioma ( $n = 4$ ; 17%), as well as 1 unbiopsied tectal plate glioma; choroid plexus tumors ( $n = 4$ ; 17%); ependymoma ( $n = 2$ ); pituitary adenoma ( $n = 1$ ); and germinoma ( $n = 1$ ) (Table 1).

Ten SNs (42%) were gliomas, 5 (21%) were meningiomas, 2 (8%) were desmoid tumors, 2 were basal cell carcinomas, 2 were myelodysplastic syndromes, 1 was a T-cell acute lymphoblastic leukemia (ALL), 1 was a papillary thyroid carcinoma, and 1 was a malignant fibrous histiocytoma (Table 1). All gliomas were dif-

TABLE 1  
Detailed Information on All Primary and Secondary Neoplasms

Patient no.	Age at initial Dx (yrs)	Gender	Primary tumor histology	CT <sup>a</sup>	RT <sup>a</sup>	Interval between first and second tumors (mos)	Second tumor histology	Associated genetic condition
1	0.4	F	Atypical choroid plexus carcinoma	Yes	Yes	2.1	MDS (RAEB)	TP53 mutation
2	0.5	M	Choroid plexus carcinoma	Yes	No	8.5	MDS with myelofibrosis	TP53 mutation
3 <sup>b</sup>	0.9	M	Desmoplastic medulloblastoma	Yes	Yes	5.7	Multiple meningiomas (WHO GI)	Gorlin syndrome
4 <sup>c</sup>	1.1	F	Ependymoma (posterior fossa)	Yes	Yes	12.4	Meningioma (WHO GI)	
5	1.6	M	Juvenile pilocytic astrocytoma (WHO GI)	Yes	Yes	11.5	Gliosarcoma (WHO GIV)	
6	1.9	F	Choroid plexus carcinoma	No	Yes	13.5	Malignant fibrous histiocytoma	
7	2.0	M	Desmoplastic medulloblastoma	Yes	Yes	5.6	Multiple meningiomas (WHO GI)	Neurofibromatosis type 2
8	2.1	F	Ependymoma (posterior fossa)	Yes	Yes	3.3	Astrocytoma (WHO GII)	
9	3.0	F	Atypical choroid plexus papilloma	No	Yes	5.1	GBM (WHO GIV)	
10	3.4	M	Astrocytoma GI/GII (NR)	No	Yes	17.9	High-grade glioma	
11	3.5	M	Desmoplastic medulloblastoma	No	Yes	17.4	GBM, small cell variant (WHO GIV)	
12	4.5	M	Medulloblastoma with large cell anaplastic features	Yes	Yes	0.8	T-cell acute lymphoblastic leukemia	
13	4.8	F	Desmoplastic medulloblastoma	No	Yes	0.3	Basal cell carcinoma	Gorlin syndrome
14	6.1	F	Medulloblastoma (NR)	No	Yes	12.9	Basal cell carcinoma	
15	7.0	M	Juvenile pilocytic astrocytoma (WHO GI)	No	Yes	10.3	Diffuse brainstem glioma (not biopsied)	
16	7.3	F	Medulloblastoma	No	Yes	5.9	GBM (WHO GIV)	
17	10.1	F	Classic medulloblastoma	Yes	Yes	12.2	Meningioma (WHO GI)	
18	10.6	F	Fibrillary astrocytoma (WHO GII)	Yes	Yes	21.0	Meningioma (WHO GI)	
19	11.3	M	Pituitary adenoma	No	No	8.5	Desmoid tumor	Gardner syndrome
20	11.7	F	Medulloblastoma	No	Yes	4.7	Anaplastic astrocytoma (WHO GIV)	
21	12.4	F	Germinoma	No	Yes	7.4	High-grade glioneuronal tumor	
22	14.8	F	Classic medulloblastoma	Yes	Yes	10.1	Desmoid tumor	Gardner syndrome
23	16.7	M	Desmoplastic medulloblastoma	Yes	Yes	4.9	GBM (WHO GIV)	
24	20.1	F	Tectal plate glioma (no biopsy)	No	No	1.4	Papillary thyroid carcinoma	

Dx: diagnosis; RT: radiotherapy; CT: chemotherapy; F: female; M: male; MDS: myelodysplastic syndrome; RAEB: refractory anemia with excess blasts; MM: multiple meningioma; WHO: World Health Organization; GBM: glioblastoma multiforme; G: Grade; NR: not reported.

<sup>a</sup> Treatment for primary neoplasm.

<sup>b</sup> Patient 3 developed a third neoplasm (basal cell carcinoma).

<sup>c</sup> Patient 4 developed a third neoplasm (papillary thyroid carcinoma).

fuse (i.e., nonfocal with infiltrating characteristics), and the majority of them were identified histologically as high-grade neoplasms, including WHO Grade IV glioblastoma multiforme ( $n = 4$ ) and gliosarcoma ( $n = 1$ ), WHO Grade III anaplastic astrocytoma ( $n = 1$ ) and high-grade glioma not otherwise specified ( $n = 1$ ), and a high-grade glioneuronal tumor ( $n = 1$ ). One patient had a diffuse WHO Grade II cerebral astrocytoma, and another patient had an unbiopsied, diffusely infiltrating brainstem glioma. One patient each was diagnosed with a basal cell carcinoma and a papillary thyroid carcinoma as a third neoplasm.

#### Clinical and Initial Therapy Characteristics Associated with Different Types of SNs

##### Glioma

For the 10 patients who were diagnosed with gliomas as their SN, the median age at diagnosis of the primary

tumor was 5.2 years (range, 1.6–16.7 years) (Table 1). The median interval between diagnosis of the primary tumor and diagnosis of the SN was 6.6 years (range, 3.3–17.9 years).

Treatment for the primary neoplasm included RT for all 10 patients, with 3 patients also receiving combination chemotherapy. The median radiation dose delivered to the site at which the SN originated was 50.4 grays (Gy) (range, < 10.0–59.4 Gy; dosimetry results were indeterminate for 1 patient).

##### Meningioma

For the 5 patients who developed a meningioma as an SN, the median age at diagnosis of the primary tumor was 2 years (range, 0.9–10.6 years) (Table 1). The median interval between diagnosis of the primary tumor and diagnosis of the SN was 12.2 years (range, 5.6–21.0 years). All patients received RT and combination che-

**TABLE 2**  
**Estimated Cumulative Incidence of Second Neoplasms**

Variable	Estimated cumulative incidence rate (95% CI)		
	5 yrs <sup>a</sup>	10 yrs <sup>a</sup>	15 yrs <sup>a</sup>
All primary CNS tumors ( <i>n</i> = 1046)			
Second neoplasm	0.6% (0.0–1.0%)	1.9% (0.7–3.0%)	5.3% (2.0–8.5%)
Second malignant neoplasm	0.5% (0.0–0.9%)	1.4% (0.4–2.5%)	4.0% (1.1–7.0%)
Second glioma	0.2% (0.0–0.5%)	0.6% (0.0–1.2%)	1.3% (0.0–2.3%)
Second brain tumor	0.2% (0.0–0.5%)	0.9% (0.1–1.7%)	2.9% (0.5–5.2%)
Second neoplasms			
Medulloblastoma ( <i>n</i> = 195)	1.8% (0.0–3.8%)	4.4% (0.9–8.0%)	ND
Low-grade glioma ( <i>n</i> = 273)	0.4% (0.0–0.8%)	0.4% (0.0–0.8%)	ND
Choroid plexus tumor ( <i>n</i> = 18)	6.3% (0.0–18.8%)	20.2% (0.0–49.6%)	ND

95% CI: 95% confidence interval; CNS: central nervous system; ND: not determined.

<sup>a</sup> Time since diagnosis of the primary tumor.

motherapy for their primary tumor. The median RT dose delivered to the site at which the SN originated was 42.3 Gy (range, 23.9–60.0 Gy). Combination chemotherapy involved the use of an alkylating agent, vincristine with or without a topoisomerase II inhibitor, and methotrexate. Two male patients who developed multiple meningiomas after shorter intervals had associated genetic predisposing syndromes: one patient had Gorlin syndrome, and the other had NF2 (Table 1).

#### **Other neoplasms**

Two patients developed desmoid tumors as SNs, one after initial RT for medulloblastoma and the other after surgery only for pituitary adenoma: the observed latency periods were 10.1 years and 8.5 years, respectively (Table 1). Both patients were diagnosed with Gardner syndrome based on typical clinical findings, including multiple colonic adenomatous polyps and striking family histories of polyposis and colon carcinoma.

Two patients with primary choroid plexus tumors developed myelodysplastic syndrome at 2.1 years and 8.5 years, respectively, after the initial tumor diagnosis (Table 1). One child had an atypical choroid plexus papilloma with leptomeningeal spread, and the other had a choroid plexus carcinoma. Both children received prolonged chemotherapy for their initial neoplasms, including high cumulative doses of alkylating agents, and one child also received craniospinal RT. Germline *TP53* point mutations were detected subsequently in both patients.

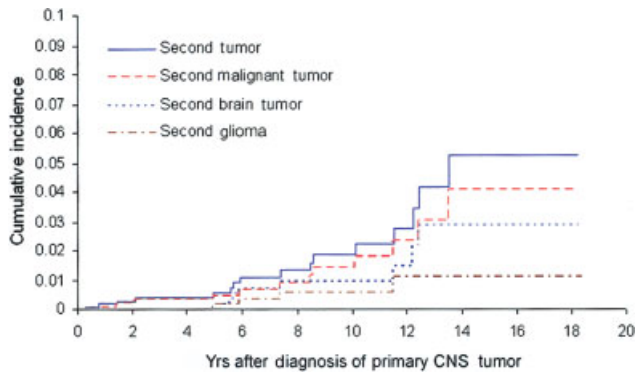
One patient with Gorlin syndrome developed multiple basal cell carcinomas in irradiated areas within 1 month after the completion of craniospinal RT for a desmoplastic medulloblastoma.<sup>21</sup> Another

patient developed a papillary thyroid carcinoma 1.4 years after the diagnosis of a tectal plate glioma; the primary neoplasm was diagnosed on the basis of typical radiologic appearance and was followed with serial MRIs and without antineoplastic intervention. A third child who initially was diagnosed with medulloblastoma was found to have T-cell ALL 9 months after the initial diagnosis (2 months after the end of craniospinal RT and chemotherapy). Cytogenetic analysis of leukemic cells demonstrated both a normal karyotype and a deletion of 15q.

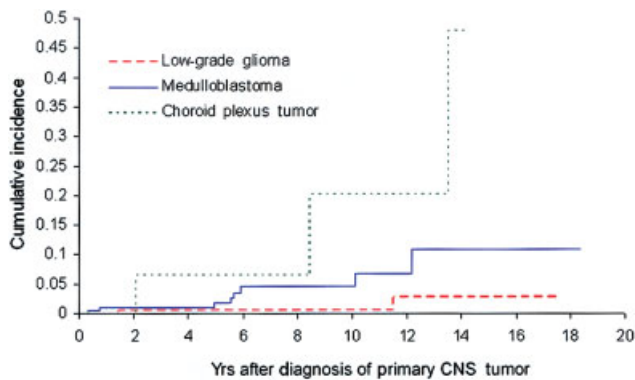
One patient was diagnosed with a basal cell carcinoma 12.9 years after the diagnosis of a medulloblastoma, and another child developed a skull-based malignant fibrous histiocytoma 13.5 years after the diagnosis of a choroid plexus tumor. Both patients received craniospinal RT for the primary tumor. The radiation doses delivered to the areas in which the SNs originated were 41.4 Gy and 35.2 Gy, respectively.

#### **Estimated Cumulative Incidence and Risk Factors for SNs**

The estimated cumulative incidence of all types of SNs for patients who had a primary CNS tumor and the estimated cumulative incidence of SNs for patients who had medulloblastomas, low-grade gliomas, or choroid plexus tumors are shown in Table 2 and in Figures 1 and 2. The 10-year estimated cumulative incidence of second malignant neoplasms for all patients with primary CNS tumors was 1.4% (95% confidence interval [95%CI], 0.4–2.5%). The 10-year estimated cumulative incidence of SNs for patients with medulloblastomas, low-grade gliomas, and choroid plexus tumors were 4.4% (95%CI, 0.9–8%), 0.4% (95%CI, 0–0.8%), and 20.2% (95%CI, 0–49.6%), respectively.



**FIGURE 1.** Estimated cumulative incidence rates for all types of second neoplasms in 1046 pediatric patients with newly diagnosed primary central nervous system (CNS) tumors.



**FIGURE 2.** Estimated cumulative incidence rates for second neoplasms in patients who initially had medulloblastoma, low-grade glioma, or choroid plexus tumors. CNS: central nervous system.

The analysis of risk factors revealed that patients age  $\leq 2$  years had a significantly greater risk of developing an SN compared with patients age  $> 2$  years ( $P = 0.016$ ). However, this cutoff age lost its significance when patients who had known genetic syndromes were excluded. Gender and race were not significant risk factors for SNs.

Neither RT ( $P = 0.57$ ) nor chemotherapy ( $P = 0.94$ ) was associated with a higher cumulative incidence of SNs. When the treatment strata were analyzed, no statistically significant differences were found among the 4 groups ( $P = 0.92$ ) (Table 3).

**Outcome**

Eight of 10 patients with secondary gliomas died of progressive disease at a median of 0.8 years after diagnosis of the SN (range, 0.2–2.1 years) despite having been treated with surgery ( $n = 4$ ), chemotherapy ( $n = 6$ ), RT ( $n = 4$ ), or a combination of all 3 modalities. All 3 patients who had second hematologic malignan-

**TABLE 3**  
Analysis of Chemotherapy and Radiotherapy as Risk Factors for Second Neoplasms<sup>a</sup>

Treatment	Patients with second neoplasms ( $n = 9$ )	All other patients ( $n = 1030$ )	<i>P</i> value
RT			
Yes	8	756	0.57
No	1	274	
CT			
Yes	5	538	0.94
No	4	492	
RT/CT			
RT only	3	275	0.92
CT only	0	57	
RT and CT	5	481	
No CT and no RT	1	217	

RT: radiotherapy; CT: chemotherapy.

<sup>a</sup> Seven patients who had genetic predisposing syndromes and developed second neoplasms were excluded from the analysis.

cies died at a median of 0.3 years after SN diagnosis (range, 0.1–1.1 years). Two patients with myelodysplastic syndromes died of progressive disease, and one patient with acute leukemia died of infectious complications during remission induction. All three patients received combination chemotherapy, and one patient with a myelodysplastic syndrome underwent matched unrelated bone marrow transplantation.

The patient who had a malignant fibrous histiocytoma died of progressive disease 0.6 years after undergoing a macroscopic total resection of the SN. All other patients were alive at a median follow-up of 3.1 years after diagnosis of the SN (range, 0.5–10.9 years). Two patients with second gliomas, 1 of whom harbored a WHO Grade II astrocytoma, remained alive without disease progression at 1.7 and 0.5 years after SN diagnosis, respectively. All patients who had second meningiomas remained alive at a median follow-up of 6 years (range, 2.5–10.9 years) after diagnosis of the SN.

**DISCUSSION**

The current review of 24 institutional pediatric patients who developed an SN after the diagnosis of a primary CNS tumor provides some insight into the genetic predisposition and risk factors related to this rare event. We found associated genetic abnormalities in 7 of 24 patients (29%); in 1 additional patient, genetic abnormalities were suspected based on the lack of adjuvant treatment and the short latency period between diagnosis of the initial tumor and diagnosis of the SN. Like other studies, the current analysis revealed that young age ( $\leq 2$  years) was a significant

risk factor for the development of SNs, but this increased risk was due in part to the overlapping genetic predisposition.<sup>9,14</sup> Despite the size of our single-institution analysis, and unlike a previous report, the current study was unable to document the impact of treatment, and particularly RT, on the development of SNs.<sup>16</sup>

Several reports have established a causal relation between the occurrence of multiple malignancies and a genetic syndrome in children with primary brain tumors.<sup>2,3,10,12,13</sup> The relation between NF1 and subsequent neoplasms has been well documented, although the impact of intervening therapies is less well established. A small number of case reports and only two series have demonstrated this relation with respect to syndromes other than NF1.<sup>3,13,22–24</sup> Kingston et al. reported that a genetic condition other than NF1 was present in 5 of 45 children (11%) with primary CNS tumors who later experienced an SN; 3 of those patients had Gorlin syndrome, 1 patient had Turcot syndrome, and 1 patient had tuberous sclerosis.<sup>3</sup> In the other series, two patients with Gorlin syndrome were among the four patients overall who developed an SN.<sup>13</sup>

The current study excluded patients with NF1. A relatively common genetic syndrome, NF1 predisposes affected individuals to a variety of neoplasms, including brain tumors, leukemias, and malignant peripheral nerve sheath tumors.<sup>25</sup> Approximately 15% of children with NF1 have an optic pathway glioma. It is well recognized that children with NF1 have an increased risk of developing an SN and, in particular, a second brain tumor.<sup>2,3,10,12</sup> The risk of developing a second brain tumor for children with NF1 and an optic pathway glioma is estimated to be between 11% and 52%.<sup>26–28</sup>

The rigorous histologic and radiologic review performed in the current series allowed the exclusion of patients with tumor recurrence or anaplastic progression of low-grade glioma. Although radiation-related neoplasms typically are identified as those occurring at some time after the initial diagnosis (e.g., > 5 years), the early development of multiple neoplasms associated with genetic predisposition or secondary to chemotherapy prompted us to include all SNs, irrespective of the latency period following the primary diagnosis. We also included five patients who had second meningiomas and two patients who had second basal cell carcinomas; these two localized neoplasms have been excluded from other series.<sup>14,16</sup>

We confirmed previously published risk data on malignant SNs for children with primary CNS tumors as a whole, as well as for children with medulloblastoma and children with low-grade glioma.<sup>16</sup> In addition,

we reported risk data on specific types of SNs, including second brain tumors (the most common SN for children in this setting) and second gliomas.

The high cumulative incidence of SNs among patients with choroid plexus tumors should be interpreted with caution, because only small numbers of patients with this type of primary tumor were evaluated. However, this finding is intriguing in light of the documented germline *TP53* mutations noted in two of the three patients with this type of primary tumor who developed an SN. Choroid plexus tumors are rare neoplasms that have been described in families carrying *TP53* germline mutations.<sup>29</sup> Nonetheless, the analysis of small numbers of sporadic cases of choroid plexus carcinoma failed to demonstrate an association with *TP53* mutations.<sup>30</sup>

The current series lacked the types of SNs that often are associated with follow-up intervals > 10 years (in particular, common adulthood carcinomas).<sup>2,7,11,12,14–16</sup> Several previous reports demonstrated a continuing increase in the occurrence of SNs in this setting > 10 years after the primary diagnosis.<sup>6,16</sup> The brain tumor program at our institution began within the last 20 years, providing limited numbers of patients who were followed beyond the first decade postdiagnosis. Due to the short median length of follow-up in the current series (median follow-up, 3.5 years from primary diagnosis), a significant proportion of these patients remain at risk for some of the histologic types of SNs described in this report.

It is interesting to compare our results with our own institutional experience regarding second brain tumors in children who had received cranial RT, albeit at lower doses, as part of their treatment for ALL.<sup>31,32</sup> Both the observed distribution and the time to development of second gliomas and meningiomas were similar, despite a median follow-up of nearly 16 years in this study of patients with ALL.<sup>31</sup> When only patients with follow-up beyond the first decade after diagnosis of ALL were analyzed, meningiomas were found to account for two-thirds of all second brain tumors.<sup>32</sup>

Due to the retrospective nature of the current study, patients were not investigated uniformly for predisposing genetic conditions. However, even the prospective search for a genetic predisposition can involve several complex and conflicting ethical, legal, social, and medical consequences with respect to patients and their families.<sup>33</sup> Often, the parents of children affected with an SN decline genetic evaluation, because it provides little if any advantage to the affected child, and more importantly, the results of such an evaluation may have significant repercussions for other family members.

The main shortcoming of the current study was that we were unable to elaborate on the possible association between primary tumor treatment characteristics and the occurrence of SNs. Multicenter studies involving larger numbers of affected patients represent the only possible way to clarify the importance of RT doses and of cumulative doses and schedules of individual chemotherapeutic agents in the development of SNs after pediatric patients are diagnosed with primary CNS tumors.

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