Cranial Irradiation Increases Risk of Stroke in Pediatric Brain Tumor Survivors

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Background and Purpose—The purposes of this study were to determine the incidence of neurovascular events as late complications in pediatric patients with brain tumor and to evaluate radiation as a risk factor.

Methods—Patients were ascertained using the tumor database of a pediatric tertiary care center. Included patients had a primary brain tumor, age birth to 21 years, initial treatment January 1, 1993, to December 31, 2002, and at least 2 visits with neuro-oncology. Radiation exposure included: whole brain, whole brain plus a focal boost, or focal brain. The primary outcome was stroke or transient ischemic attack.

Results—Of 431 subjects, 14 had 19 events of stroke or transient ischemic attack over a median follow-up of 6.3 years. The incidence rate was 548/100 000 person-years. Overall, 61.5% of subjects received radiation, including 13 of 14 subjects with events. Median time from first radiation to first event was 4.9 years. The stroke/transient ischemic attack hazard ratio for any brain irradiation was 8.0 (95% CI, 1.05–62; P=0.045); for the circle of Willis, radiation was 9.0 (95% CI, 1.2–70; P=0.035); and for focal noncircle of Willis, radiation was 3.4 (95% CI, 0.21–55; P=0.38).

Conclusions—The incidence of neurovascular events in this population is 100-fold higher than in the general pediatric population and cranial irradiation is an important risk factor. By defining the incidence of this late effect, physicians are better able to counsel parents regarding treatment, monitor patients at risk, and target a population for primary stroke prevention in future studies. (Stroke. 2012;43:3035-3040.)

Key Words: childhood brain tumors ▪ stroke ▪ treatment-related stroke

Radiotherapy, an effective therapeutic modality for the treatment of many pediatric brain tumors, poses significant risks, particularly to the developing brain.1–3 Cranial irradiation causes late toxicities including neuroendocrine perturbations,4 cognitive deficits,1,2 cavernous malformations,5 small-vessel occlusive disease,1,6–4 vasculopathy, and stroke.6–9 The population at risk for these complications continues to grow, because brain tumors are the most common solid tumor of childhood and length of survival is increasing (5-year survival of 72%).12 With improved long-term survival, understanding the late effects of these treatments becomes paramount.

Cranial irradiation-induced late vasculopathy is well documented in the literature with 47 case reports10–39 over the past 30 years and 6 case series/cohort studies.5,20–24 Few studies have determined the incidence, interval to symptoms, or risk factors compared with a control group. The largest cohort study, from Bowers et al,22 estimated the incidence and relative risk of stroke compared with sibling control subjects in brain tumor survivors (rate, 267.6/100 000; relative risk, 29). Although this was a landmark study, it did not differentiate between perioperative and late stroke and relied on self-report of stroke. Brain tumor survivors are at risk for stroke mimics (including migraine, seizure, postictal paralysis, acute demyelinizing encephalomyelitis, radiation necrosis, etc)22; thus, estimates based on self-reports may inaccurately estimate incidence in this group.

In contrast, Ullrich et al22 used MRI to investigate vasculopathy incidence in children with primary brain tumors treated with radiation. Because all subjects received radiation, it was not possible to investigate radiation as a risk factor. Two cohort studies reported the physician-confirmed stroke incidence in both irradiated and nonirradiated brain tumor survivors.23,24 Defining the true incidence of stroke in these cohorts may have been hampered by a short follow-up duration (mean, 4.6 years), the inclusion of subjects with...

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neurofibromatosis type 1 who have a known increased risk of spontaneous and radiation-induced neurovascular disease and stroke, and using both ischemic and hemorrhagic strokes as outcome measures despite their distinctive pathogeneses.

The primary aim of this study was to determine the incidence of physician-diagnosed stroke or transient ischemic attack (TIA) as a late complication in pediatric patients with brain tumor at a tertiary care center. The secondary aim was to evaluate cranial irradiation as a risk factor for stroke or TIA; we hypothesized that children receiving brain radiation have a higher risk of neurovascular events than nonirradiated patients with brain tumor and that radiation to the circle of Willis confers the highest risk.

Methods

For this retrospective cohort study, subjects were identified using the tumor registry of the Division of Oncology at The Children’s Hospital of Philadelphia. Potential subjects were <22 years of age at diagnosis of the brain tumor and started treatment (chemotherapy, radiation, or surgery [including biopsy]) between January 1, 1993 and December 31, 2002, at The Children’s Hospital of Philadelphia. Excluded subjects had: <2 follow-up visits in the neuro-oncology clinic, a disease known to be associated with vascular abnormality (eg, neurofibromatosis type 1),26,27 intraoperative or perioperative (within 30 days of surgery) stroke remote from the surgical bed, or a neurovascular event in the setting of disease progression. Patients with peri-/intraoperative strokes within the surgery bed were included, but these strokes were not counted toward the total event number.

The subjects’ medical records were searched for: demographic information (age, sex, race), date of diagnosis, tumor pathology, tumor location, dates and location of tumor-directed surgery, date of radiation, chemotherapy administration, date of most recent imaging study, radiation dose and fields (focal, whole brain, or craniospinal), occurrence of stroke or stroke-like symptoms and date of occurrence, presence or absence of relapse and subsequent therapy, and date of death or last visit. All brain MRI reports for eligible subjects were re-reviewed by one neuroradiologist to verify the presence or absence of diffusion-weighted imaging abnormalities. MR angiography, when available, was reviewed for evidence of large-vessel vasculopathy.

The Children’s Hospital of Philadelphia Institutional Review Board approval with waiver of informed consent was obtained before study initiation.

Outcome was defined as a neurovascular event, including ischemic stroke or TIA. Stroke was defined as an acute neurological syndrome with deficits conforming to a vascular territory and findings on neuroimaging of an acute ischemic infarct corresponding to the clinical deficit. TIA was similarly defined, but lasted <24 hours and MRI revealed no acute ischemia. Three independent investigators assessed possible events before reaching consensus.

To estimate the dose of radiation to the circle of Willis, the radiation field was categorized one of 3 ways: whole brain radiation (dose to circle of Willis equals whole brain dose); focal radiation to areas of brain not including the circle of Willis (eg, parietal and occipital lobes), in which the dose to the circle of Willis is zero; and focal radiation to areas including the circle of Willis (eg, hypothalamus, thalamus), in which the dose to the circle of Willis equals the focal dose. Sites (eg, temporal and frontal lobes) for which the specific circle of Willis dose depended on the specific tumor location within that region were classified in the focal noncircle of Willis group. The circle of Willis was defined as the internal carotid, middle cerebral, anterior cerebral, anterior communicating, posterior communicating, posterior cerebral, and basilar arteries.

Statistical Analysis

To determine the effect of the radiation group exposure (eg, no radiation, radiation involving the circle of Willis, and radiation not involving the circle of Willis), the following analyses were performed: (1) dichotomous exposure, 3-group analysis with \( \chi^2 \) or Fisher exact test; and (2) continuous exposure, 3-group analysis with analysis of variance and parametric analysis on radiation dose. Incidence rates were calculated based on the first event only.

Cox proportional hazard models were used to estimate the hazard ratios (HRs) for the primary outcome, neurovascular events (TIA or stroke) for those patients receiving radiation compared with those who did not, with adjustment for potential confounders including age at diagnosis, tumor type, and chemotherapy. Censoring criteria were death, first stroke/TIA, or last documented visit. HRs were further calculated for dose of radiation and dose of radiation to the circle of Willis. Statistical tests were performed using SPSS 17.0 and STATA SE 10.0. To identify independent risk factors, a multivariate analysis was performed using a Cox proportional hazards model in a stepwise manner, removing variables based on a threshold probability value of 0.20.
Results

Of 649 subjects who met inclusion criteria, 174 (26.8%) were ineligible: 83 with neurofibromatosis type 1, 58 with one visit, 24 received no treatment, 8 had extensive intraoperative or perioperative stroke remote from the surgical bed, and one had TIA in the setting of disease progression. Charts were unavailable for 44 patients (6.8%). This left 431 (66.4%) eligible patients for analysis.

Two hundred sixty-five subjects (61.5%) received cranial irradiation and 323 underwent surgery with 79 undergoing surgery in the region of the circle of Willis (Table 1). Tumor types were distributed as expected for this population (online-only Data Supplement Table I). Median time to death was 1.1 years (SD, 2.6 years) with 311 (72.2%) subjects remaining alive.

There were a total of 19 neurovascular events (8 strokes, 11 TIAs) in 14 subjects (Table 2), 13 of whom received radiation, 12 to the circle of Willis. Median time to first event was 4.9 years (range, 32 days to 12.9 years).

Using only the first event per patient, the overall incidence rate of neurovascular events in this population was 548/100 000 (95% CI, 324–924/100 000) with 102/100 000 (95% CI, 14–721) in the nonirradiated group, 347/100 000 (95% CI, 49–2461) in those receiving radiation to non-circle of Willis areas, and 939/100 000 (95% CI, 533–16540) in those receiving radiation to the circle of Willis (Figure A). The incidence rate of stroke alone (ie, excluding TIAs) was 626/100 000 (95% CI, 313–1252) in those subjects receiving radiation to the circle of Willis and zero in subjects receiving either non-circle of Willis radiation or no radiation (P≤0.001; Figure B).

The HR of stroke or TIA after any cranial irradiation was 8.0 (P=0.045). Circle of Willis radiation conferred a greater risk (HR, 9.0; P=0.035) than focal, noncircle of Willis radiation (HR, 3.4; P=0.38). Neither surgery (P=0.12) nor...
chemotherapy \( (P=0.15) \) showed a significant association with stroke/TIA in univariate analysis (Tables 3 and 4). However, treatment with chemotherapy was more common in patients who were radiated \( (P<0.001) \). Furthermore, radiation plus chemotherapy enhanced stroke rates \( (P<0.001 \text{ for interaction}; \text{Table } 4) \). Stratifying on location of surgery demonstrated no difference between surgery at the circle of Willis and noncircle of Willis surgery \( (HR, 1.42; P=0.62) \). For every additional year of age at diagnosis, the risk of stroke or TIA increased by 13\% \( (95\% \text{ CI, } 1.02–1.25; P=0.018) \). Median total and circle of Willis radiation doses did not differ between subjects who had stroke/TIA \( (54.0 \text{ Gy median; interquartile range, } 54.0–55.8; 52.2 \text{ Gy, interquartile range, } 18–54, \text{ respectively}) \) and those who did not.

A stepwise multivariable model including the following candidate variables was performed: age at diagnosis, radiation, chemotherapy, surgery, and tumor type. The final model identified radiation to the circle of Willis \( (HR, 4.35; 95\% \text{ CI, } 0.97–19.6; P=0.055) \) and chemotherapy \( (HR, 3.38; 95\% \text{ CI, } 9.2–12.5; P=0.067) \) as heightening neurovascular risk. Chemotherapy significantly interacted with radiation \( (P<0.001) \), but an estimate of the interaction between chemotherapy and radiation could not be determined because modeling yielded unstable results.

Of the neurovascular events, 2 were associated with comorbidities. One occurred in the setting of a sinus venous thrombosis and the other 2 weeks after \textit{Staphylococcus aureus} meningitis. To ensure our findings were not altered by these 2 cases, an ad hoc analysis excluding these subjects yielded similar results: HR for circle of Willis radiation, 7.6 \( (95\% \text{ CI, } 0.97–59.6, P=0.05) \) and for noncircle of Willis radiation, 3.4 \( (95\% \text{ CI, } 0.22–54; P=0.39) \).

Of the 14 subjects who experienced events, 10 were initiated on secondary stroke prevention regimens (Table 5). Despite these interventions, 5 subjects with TIA experienced repeat events, 3 of which were stroke.

Vascular imaging by MR angiography was available in a subset of 82 patients and demonstrated a higher incidence of large-vessel vasculopathy \( (6 \text{ of } 8 \text{ (75\%)} \) than in the remainder of the cohort \( (7 \text{ of } 72 \text{ (9.7\%)}; P<0.0001; \text{Table } 5) \). These abnormalities consisted of moyamoya\(^4\) and stenosis.\(^6\) All subjects with vasculopathy on MR angiography received cranial irradiation.

\section*{Discussion}

Our study demonstrates a markedly increased risk of stroke and TIA in pediatric brain tumor survivors. The observed stroke/TIA rate of 548/100 000 represents a 100-fold increase over the rate of 2–8/100 000 in the general pediatric population\(^28,29\) and is greater than double that found in a questionnaire-based study of brain tumor survivors.\(^{21} \) We found that cranial irradiation is the major risk factor for later neurovascular events. As similarly reported by others, radiation exposure to the large intracranial vessels (circle of Willis) conferred the highest risk; not only were neurovascular

\begin{table}[h]
\centering
\caption{Incidence Rates by Treatment Modality}
\begin{tabular}{lllll}
\hline
\textbf{Treatment Modality} & \textbf{Stroke or TIA} & \textbf{Total No.} & \textbf{Incidence*} \\
\hline
Any Radiation & Chemotherapy & Surgery & & \\
\hline
− & − & − & 0 & 5 & 0 \\
+ & − & − & 1 & 31 & 580 \\
− & + & − & 0 & 14 & 0 \\
+ & + & − & 4 & 53 & 2400 \\
− & − & + & 0 & 74 & 0 \\
+ & − & + & 2 & 52 & 490 \\
− & + & + & 1 & 65 & 220 \\
+ & + & + & 6 & 127 & 740 \\
\hline
\end{tabular}
\end{table}

\begin{table}[h]
\centering
\caption{Unadjusted Hazard Ratios From Cox Regression}
\begin{tabular}{lll}
\hline
\textbf{Hazard Ratio} & \textbf{P Value} \\
\hline
Any Brain Radiation & 8.0 \( (CI, 1.05–62) \) & 0.045 \\
COW radiation & 9.0 \( (CI, 1.2–70) \) & 0.035 \\
Non-COW radiation & 3.4 \( (CI, 0.21–55) \) & 0.38 \\
Surgery & 0.38 \( (CI, 0.13–1.1) \) & 0.08 \\
Chemotherapy & 2.53 \( (CI, 0.71–9.1) \) & 0.15 \\
Glioma & 0.23 \( (CI, 0.05–1.03) \) & 0.055 \\
PNET & 2.74 \( (CI, 0.95–7.9) \) & 0.063 \\
Age at diagnosis (annually), y & 1.13 \( (CI, 1.02–1.25) \) & 0.018 \\
\hline
\end{tabular}
\end{table}

\( \text{COW indicates circle of Willis; PNET, primitive neuroectodermal tumor.} \)
event rates highest in this group, but stroke only occurred in those patients receiving radiation to the circle of Willis.24 Radiation induces a large spectrum of changes leading to vascular injury, including accelerated atherosclerosis and vascular insufficiency. The vascular injury identified on MR angiography in patients with stroke support a mechanism involving both large and small intracranial vessel injury. Future studies are needed to investigate neuroimaging techniques that may identify patients with early vasculopathy or perfusional abnormalities who are at highest risk of stroke, because these patients may benefit from primary prevention measures.

In univariate analysis, glioma demonstrated a trend toward protection against neurovascular events, primitive neuroectodermal tumor showed a trend toward an increased risk, and older age at diagnosis was significantly related to increased risk. These effects disappeared in multivariate analysis, likely reflecting the important role radiation plays as a risk factor. Radiation is infrequently used in glioma treatment, but craniospinal radiotherapy is standard practice for primitive neuroectodermal tumor. It is also common practice to delay radiation exposure in children <3 years of age. Radiation therapy heightened the risk of other factors; chemotherapy, an independent risk factor in multivariate analysis, interacted with radiation to increase risk. Although certain alkylating chemotherapy agents such as cisplatin have been reported to increase the risk of ischemic stroke,32,33 more work is needed to understand if an interaction between chemotherapy and radiation exists or if the finding is a surrogate for more aggressive treatment.

In our cohort, we found that 35.7% (5 of 14) of patients with stroke/TIA had repeat events even after initiation of secondary stroke prevention. This finding demonstrates the inadequacy of secondary stroke prevention modalities and highlights the need for more effective primary stroke prevention in this population.

The study data were subject to the limitations and biases of a retrospective analysis, including the limitations of the registry. Collecting the data by chart review enabled cross-referencing of events with neuroimaging and eliminated

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**Table 5. Neuroimaging Changes and Treatment Prescribed**

<table>
<thead>
<tr>
<th>ID</th>
<th>Event</th>
<th>MRI</th>
<th>Vascular Territory</th>
<th>MRA</th>
<th>Treatment</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>Stroke</td>
<td>RD right pons</td>
<td>Basilar artery</td>
<td>Absent bilateral PCAs</td>
<td>Hyperbaric oxygen, steroids, aspirin</td>
</tr>
<tr>
<td>2</td>
<td>1. TIA 1. Stroke</td>
<td>1. NA 2. RD right internal capsule</td>
<td>MCA:M1 lenticulostriate</td>
<td>2. Fetal PCA with hypoplastic P1</td>
<td>1. Aspirin 2. Decreased estrogen replacement, added statin</td>
</tr>
<tr>
<td>3</td>
<td>Stroke</td>
<td>RD right frontoparietal lobe</td>
<td>MCA: M3</td>
<td>NP</td>
<td>None</td>
</tr>
<tr>
<td>4</td>
<td>1. Stroke 2. TIAs</td>
<td>1. RD left frontoparietal lobe 2. NA</td>
<td>MCA: M3</td>
<td>Left MCA and ACA high-grade stenosis</td>
<td>1. Warfarin</td>
</tr>
<tr>
<td>5</td>
<td>Stroke</td>
<td>RD pons</td>
<td>Basilar artery perforators</td>
<td>NP</td>
<td>Hyperbaric oxygen, aspirin, pentoxifylline, vitamin E</td>
</tr>
<tr>
<td>7</td>
<td>1. TIA 2. Stroke</td>
<td>1. NA 2. RD right pons</td>
<td>Left cavernous ICA mild stenosis</td>
<td>NP</td>
<td>Aspirin</td>
</tr>
<tr>
<td>8</td>
<td>TIA</td>
<td>NA</td>
<td>Basilar artery perforators</td>
<td>NA</td>
<td>None</td>
</tr>
<tr>
<td>9</td>
<td>TIA</td>
<td>NA</td>
<td></td>
<td>NA</td>
<td>Aspirin</td>
</tr>
<tr>
<td>10</td>
<td>Multiple TIAs</td>
<td>NA</td>
<td></td>
<td>NP</td>
<td>2. Discontinued sumatriptan and estrogen replacement therapy</td>
</tr>
<tr>
<td>11</td>
<td>TIA</td>
<td>NA</td>
<td></td>
<td>NP</td>
<td>Aspirin</td>
</tr>
<tr>
<td>12</td>
<td>TIA</td>
<td>NA</td>
<td></td>
<td>NP</td>
<td>Aspirin</td>
</tr>
<tr>
<td>13</td>
<td>TIA</td>
<td>NA</td>
<td>Left AICA narrowed, left SCA narrowed</td>
<td>NP</td>
<td>Aspirin</td>
</tr>
<tr>
<td>14</td>
<td>TIA</td>
<td>NA</td>
<td></td>
<td>NP</td>
<td>Aspirin</td>
</tr>
</tbody>
</table>

MRA indicates MR angiography; RD, restricted diffusion on diffusion-weighted imaging; PCA, posterior communicating artery; TIA, transient ischemic attack; NA, no abnormality; P1, first branch of the posterior communicating artery; NP, not performed; MCA, middle cerebral artery; ACA, anterior communicating artery; NNA, no new abnormality; AICA, anterior inferior cerebellar artery; SCA, superior cerebellar artery.
recall bias. The possibility of selection bias remains given the subjects were enrolled at a tertiary care center; however, most children with brain tumors are referred to tertiary care centers; thus, the study population is likely representative of the general pediatric brain tumor population.

This single-institution study was underpowered to evaluate certain risk factors, including tumor type, tumor location, surgery, or chemotherapy type. Furthermore, for simplicity, we grouped patients according to radiation location, although we may have been misclassified as seizures or migraines and therefore understated, or, alternatively, seizures and migraines may have been misclassified as TIsAs. This is an unavoidable problem when using TIA as an outcome, and the separate analysis evaluating only stroke was performed to obviate this possible bias.

Survivors of pediatric brain tumors are at much higher risk for neurovascular events than the general pediatric population, and radiation, particularly to the circle of Willis, is a major risk factor. Multicenter prospective studies are necessary to investigate other risk factors (hypertension, hyperglycemia, hypertriglyceridemia, etc), primary stroke prevention, and tools to identify high-risk patients early such as perfusion MRI and MR angiography. Furthermore, it is important to pursue treatment options that enable reduced radiation doses or replace radiation entirely. Preventing stroke and vasculopathy will help reduce the lifelong toll of childhood brain tumor treatment in this vulnerable population.

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**Disclosures**
None.

**References**

Other
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http://stroke.ahajournals.org/content/43/11/3035

Data Supplement (unedited) at:
http://stroke.ahajournals.org/content/suppl/2012/09/12/STROKEAHA.112.661561.DC1

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<table>
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<th>Tumor Type</th>
<th>N (%)</th>
<th>Sub-Type</th>
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<tr>
<td>Glioma:</td>
<td>246 (57.1)</td>
<td>Low-Grade</td>
<td>189</td>
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<tr>
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<td></td>
<td>High-Grade</td>
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</tr>
<tr>
<td>Ependymoma:</td>
<td>18 (4.2)</td>
<td>Medulloblastoma</td>
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<tr>
<td>Embryonal:</td>
<td>105 (24.6)</td>
<td>Supratentorial Primitive</td>
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<td>Neuroectodermal Tumor</td>
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<td></td>
<td>Pineoblastoma</td>
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<td>Atypical Teratoid Rhabdoid Tumor</td>
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<td>17 (3.9)</td>
<td>Germinoma</td>
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<td>Germ Cell:</td>
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<td>Teratoma</td>
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<td></td>
<td>Non-Germinomatous Germ-Cell Tumor</td>
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</tr>
<tr>
<td>Other:</td>
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<td>Choroid Plexus</td>
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<td>Giant Cell Tumor</td>
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<td>Medulloepithelioma</td>
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<td>Desmoplastic Neuroepithelial Tumor</td>
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