Late-Ocurring Stroke Among Long-Term Survivors of Childhood Leukemia and Brain Tumors: A Report From the Childhood Cancer Survivor Study


ABSTRACT

Purpose
This report examines the incidence of and risk factors for strokes that occur in ≥ 5-year survivors of childhood leukemia and brain tumors.

Patients and Methods
The rate of first occurrence of self-reported late-occurring strokes was determined for leukemia survivors (n = 4,828), brain tumor survivors (n = 1,871), and a comparison group of a random sample of cancer survivor siblings (n = 3,846). Relative risks (RRs) and 95% confidence intervals (CIs) of stroke by treatment exposures were examined by multivariate analyses.

Results
Thirty-seven leukemia survivors and 63 brain tumor survivors reported a late-occurring stroke. The rate of late-occurring stroke for leukemia survivors was 57.9 per 100,000 person-years (95% CI, 41.2 to 78.7). The RR of stroke for leukemia survivors compared with the sibling comparison group was 6.4 (95% CI, 3.0 to 13.8; P < .0001). The rate of late-occurring stroke for brain tumor survivors was 267.6 per 100,000 person-years (95% CI, 206.8 to 339.2). The RR of stroke for brain tumor survivors compared with the sibling comparison group was 29.0 (95% CI, 13.8 to 60.6; P < .0001). Mean cranial radiation therapy (CRT) dose of ≥ 30 Gy was associated with an increased risk in both leukemia and brain tumor survivors in a dose-dependent fashion, with the highest risk after doses of ≥ 50 Gy CRT.

Conclusion
Survivors of childhood leukemia and brain tumors, particularly those with brain tumors treated with CRT at doses of greater than 30 Gy, are at an increased risk of stroke.

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INTRODUCTION

Leukemia and brain tumors account for 53% of all cancers diagnosed among children younger than age 15 years.1,2 In the United States, an estimated 4,450 children and adolescents are diagnosed with either leukemia or a brain tumor annually.2 With current 5-year survival rates of 79.3% for leukemia and 73.3% for brain tumor, the vast majority of these children will become long-term survivors.1

Although there are obvious differences between leukemia and brain tumors, these two childhood cancers share some important features that influence the long-term health and quality of life of survivors. Both cancers require CNS-targeted therapy. Because the peak incidence for both cancers is during a vulnerable neurocognitive developmental period, CNS-directed therapy, in particular moderate- or high-dose cranial radiotherapy (CRT), often has significant long-term consequences, especially in brain tumor survivors. This knowledge has led to efforts to reduce radiation exposure in the treatment of brain tumors and to use other measures of CNS prophylaxis in the treatment of acute lymphoblastic leukemia.

Few studies have suggested that brain tumor survivors are at risk for late-occurring cerebrovascular accidents or strokes.3-8 From these studies, it appears that this risk may be related to CRT. However, interpretation of these studies is limited by small sample sizes, study design limitations, and the lack of a comparison group for perspective. No studies to date estimate the incidence of late-occurring strokes in leukemia survivors.

Stroke is a life-threatening disease, often resulting in death or severe and permanent disability. For this reason, additional study in survivors of childhood leukemia and brain tumors is warranted. The
Childhood Cancer Survivor Study (CCSS) provides a unique opportunity to assess stroke as a late effect among a large and diverse cohort of survivors and a comparison group of siblings of cancer survivors. This analysis had three objectives: to estimate the incidence rate of stroke among leukemia and brain tumor survivors in the period 5 years or longer after diagnosis of cancer (hereafter called a late-occurring stroke); to compare the rate of late-occurring stroke between leukemia and brain tumor survivors and siblings of childhood cancer survivors; and to assess the association of specific treatments and the risk of late-occurring stroke.

**PATIENTS AND METHODS**

**Patient Selection and Contact**

This study from the CCSS examined ≥ 5-year survivors of childhood leukemia or brain tumor (< 21 years of age at diagnosis) who were diagnosed between January 1, 1970, and December 31, 1986, and received initial treatment at one of 26 collaborating CCSS institutions. A comparison group consisting of a random sample of siblings of participating CCSS cancer survivors was used for the study. This analysis included 4,828 leukemia survivors, 1,871 brain tumor survivors, and 3,846 siblings of cancer survivors.

The CCSS protocols and documents were reviewed for assurances of participant protection and confidentiality, and were approved by the investigational review board at each collaborating institution. Each participant (or his or her parent if the patient was younger than age 18 years) provided informed consent to participate in the study and provided consent for release of medical records. Medical record abstraction, according to a structured protocol, was conducted at each CCSS center and included detailed clinical information about cancer type and treatments received. Self-reported baseline data were collected from patients or their parents using a 24-page questionnaire on enrollment onto the cohort. The baseline and follow-up surveys used in data collection are available for review at http://www.cancer.umn.edu/ccss. A detailed description of the CCSS study design, methods, and cohort characteristics, including comparison of respondents and nonrespondents, is provided elsewhere.9

**Treatment Exposures and Other Potential Risk Factors for Stroke**

Potential risk factors examined for an association with stroke included age at time of study, sex, race and ethnicity, vital status, age at cancer diagnosis, and treatment with CRT and/or chemotherapy. The CRT dose for leukemia survivors was grouped into four categories: none, 1 to 19, 20 to 29, or ≥ 30 Gy. For brain tumor survivors, the CRT categories were none, 1 to 29, 30 to 39, 40 to 49, or ≥ 50 Gy. The radiation fields of the brain were categorized into four segments (segment 1 included the cerebellum, fourth ventricle, and brainstem; segment 2 included the temporal lobe and hypothalamus, including the circle of Willis and the origin of the large cerebral arteries; segment 3 included the frontal lobe; segment 4 included the parietal lobe).

Chemotherapy agents examined include methotrexate, anthracycline, corticosteroid (dexamethasone, hydrocortisone, methylprednisolone, or prednisone), alkylating agent (carmustine, lomustine, chlorambucil, procarbazine, or cyclophosphamide), and cyclophosphamide alone.

Selected established risk factors for stroke were assessed, including hypertension, diabetes mellitus, oral contraceptive use by females, tobacco use, and coexisting neurofibromatosis type 1.

**Statistical Analysis**

The occurrence of stroke and age at the first occurrence of stroke were self-reported. Participants were asked if they had ever had a stroke (yes or no) and if so, at what age. Participants were not asked about the specific type (eg, thrombotic or embolic) or location of the stroke. We defined the interval of stroke occurrence as the interval that was exactly one half year past the participant’s birth date to the age when the participant had a stroke.

Stroke incidence rates were calculated as the number of patients with an event divided by the number of person-years at risk for stroke. For survivors, person-years at risk were computed beginning on the date 5 years from the primary cancer diagnosis to the date of the first stroke, time of study, or death. For siblings, person-years at risk were calculated from birth date to the age when the sibling reported having a first stroke or the time of study.

Cox proportional hazards models were used to estimate the age-, sex-, race-adjusted hazard ratio of stroke between leukemia or brain tumor survivors and CCSS siblings using age as the time axis in the Cox models. Hazard ratios are reported here as relative risks (RRs). Variance were adjusted for interfamily correlations using sandwich SE estimates.10 Standard asymptotic inference methods for Cox regression based on the partial likelihood were used to construct 95% CIs and calculate two-sided significance tests.

To assess the treatment exposures and potential modifying factors, the analysis was stratified for brain tumor survivors and leukemia survivors. The relationship of late-occurring stroke with each treatment exposure or potential modifying factor was assessed by bivariate χ² testing. Treatment exposures and other factors with a P < .1 were assessed further in multivariate models.

For brain tumor survivors, the relationship between stroke and radiation therapy to a particular region of the brain was assessed by comparing the incidence rates by the maximum dose of radiation to the four segments. Finally, leukemia survivors and brain tumor survivors were grouped together to assess the relationship of the dose of CRT and risk of stroke.

**RESULTS**

**Sibling Comparison Group**

Of the 3,846 siblings of childhood cancer survivors, 52% were female (Table 1). The mean age of the sibling comparison group was 28.8 years (standard deviation [SD], 9.3 years), which was significantly older than both the leukemia (mean, 24.3 years) and brain tumor (mean, 25.8 years) survivors. Nine siblings of childhood cancer survivors reported a stroke at a mean age of 25 years (SD, 12.9 years), not including one sibling with a stroke who did not report the age at the time of the stroke. The rate of stroke among the sibling comparison group was 8.0 per 100,000 person-years (95% CI, 3.9 to 14.4 per 100,000 person-years).

**Leukemia Survivors**

Of the 4,828 survivors of childhood leukemia included in this analysis, there were 4,368 patients with acute lymphoblastic leukemia, 359 patients with acute myeloid leukemia, 52 patients with chronic myeloid leukemia, and 49 patients classified as having another leukemia. Of these patients, 2,277 (47.2%) were female (Table 1). The mean age at diagnosis of leukemia was 5.9 years (SD, 4.5 years) and the mean interval from diagnosis until time of study interview was 17.9 years (SD, 5.7 years). The mean age of leukemia survivors was 24.3 years (SD, 7.2 years).

Stroke was reported by 97 (1.5%) leukemia survivors. Thirty-seven leukemia survivors reported late-occurring strokes (5 years or more after diagnosis of the cancer). In these 37 patients, the mean interval from diagnosis to late-occurring stroke was 9.8 years (SD, 5.4 years). The rate of late-occurring stroke was 58.0 per 100,000 person-years (95% CI, 41.2 to 78.7 per 100,000 person-years; Table 2). After adjusting for age, sex, and race, the RR of late-occurring stroke for leukemia survivors compared with the sibling group was 6.4 (95% CI, 3.0 to 13.8; P < .0001). Compared with siblings, the risk of late-occurring stroke was increased for both leukemia survivors treated with CRT (RR, 5.9; 95% CI, 2.6 to 13.4; P < .0001) and without CRT (RR, 4.0; 95% CI, 1.4 to 11.5; P = .0107). The actuarial cumulative incidence of stroke among leukemia survivors was 0.73% (95% CI, 0.43% to 1.04%) at 25 years after treatment (Table 3).
Of the 37 leukemia survivors with a late-occurring stroke, 18 (49%) had experienced a relapse or recurrence of their leukemia before the stroke. Seventy-eight percent (14 of 18 patients) of this group experienced their stroke at least 1 year after the relapse. Compared with siblings, the RR of late-occurring stroke in leukemia survivors who had experienced a relapse of their leukemia was 21.6 (95% CI, 8.6 to 54.2; \( P < .0001 \)).

Leukemia survivors treated with chemotherapy only or low-dose CRT (0.1 to 29 Gy) did not differ in risk of late-occurring stroke (\( P = .78 \)). However, leukemia survivors treated with CRT greater than 30 Gy were 7.74 times more likely to report a stroke (95% CI, 2.6 to 23.3; \( P = .0003 \)) than leukemia survivors treated with only chemotherapy. Prior treatment with any of the examined chemotherapy agents was not associated with an increased risk of stroke. Hypertension, diabetes mellitus, oral contraceptive use by women, and tobacco use did not modify the risk of stroke.

**CNS Tumor Survivors**

Of the 1,871 survivors of childhood brain tumors, there were 1,229 patients with an astrocytoma/glioma, 147 patients with an ependymoma, 395 patients with a medulloblastoma/primitive neural ectodermal tumor, and 100 patients with an unspecified brain tumor. Of these patients, 838 (44.8%) were female. The mean age at diagnosis was 7.7 years (SD, 5.2 years), and the mean interval from diagnosis until time of study was 17.6 years.
relapse was 64.5 (95% CI, 27.3 to 152.7; occurring stroke among brain tumor survivors who experienced a least 1 year after the relapse. Compared with siblings, the RR of late-

Eighty-nine percent (16 of 18) of this group experienced their stroke at (29%) had experienced a relapse of their cancer before the stroke. 

7.37%) at 25 years (Table 3).

206.8 to 339.2 per 100,000 person-years; Table 2). After adjusting for age, sex, and race, the RR of late-occurring stroke for brain tumor survivors treated with CRT was 339.5 per 100,000 person-years (95% CI, 249.7 to 448.5 per 100,000 person-years). Compared with siblings, the RR of late-occurring stroke in brain tumor survivors treated with CRT was significantly higher than those not treated with CRT (interaction P < .0001). The actuarial cumulative incidence of stroke among brain tumor survivors was 5.58% (95% CI, 3.80% to 7.37%) at 25 years (Table 3).

Of the 63 brain tumor survivors with a late-occurring stroke, 18 (29%) had experienced a relapse of their cancer before the stroke. Eighty-nine percent (16 of 18) of this group experienced their stroke at least 1 year after the relapse. Compared with siblings, the RR of late-occurring stroke among brain tumor survivors who experienced a relapse was 64.5 (95% CI, 27.3 to 152.7; P < .0001).

The occurrence of late-occurring stroke among brain tumor survivors treated with CRT was significantly higher than those not treated with CRT (P = .02, Fig 1). The rate of late-occurring stroke in brain tumor survivors who were treated with CRT was 339.5 per 100,000 person-years (95% CI, 249.7 to 448.5 per 100,000 person-years). Compared with siblings, the RR of late-occurring stroke in brain tumor survivors treated with CRT was 37.2 (95% CI, 17.5 to 79.1; P < .0001). In comparison with brain tumor survivors treated without CRT, those who were treated with CRT ≥ 50 Gy were 3.3 times more likely to report a late-occurring stroke (95% CI, 1.5 to 7.1).

Cox model analysis was used to compare the RR of stroke by the maximum doses of cranial RT (both ≥ 30 and ≥ 50 Gy) to a specific segment of the brain. With doses of ≥ 30 or ≥ 50 Gy, radiation to a specific segment of the brain was not associated with a significant increased risk.

Treatment with an alkylating agent modified the risk of stroke in brain tumor survivors who had CRT (interaction P < .0001). Compared with siblings, the RR of late-occurring stroke in brain tumor survivors treated with CRT plus an alkylating agent was 78.3 (95% CI, 35.1 to 174.5; P < .0001). Other chemotherapeutic agents were not associated with stroke. Hypertension, diabetes mellitus, oral contraceptive use by women, tobacco use, and coexisting neurofibromatosis type 1 did not modify the risk of late-occurring stroke.

**Combined Leukemia and Brain Tumor Group**

To examine the influence of dose of CRT to the large cerebral arteries on risk of stroke, leukemia survivors and brain tumor survivors were combined and the incidence rate of stroke according to mean dose of CRT to segment 2 of the brain, which contains the circle of Willis and the origin of the large cerebral arteries, was determined. There was a dose-dependent relationship between the dose of CRT to segment 2 and the incidence of late-occurring strokes (Fig 2). There was no difference in the incidence of stroke between survivors treated

<table>
<thead>
<tr>
<th>Group</th>
<th>No. of Patients</th>
<th>No. of Strokes</th>
<th>Percent With Stroke</th>
<th>Rate of Stroke*</th>
<th>95% CI</th>
<th>Relative Risk of Stroke</th>
<th>95% CI</th>
<th>P</th>
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<tbody>
<tr>
<td>Comparison group</td>
<td>3,846</td>
<td>9</td>
<td>0.2</td>
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<td>3.9 to 14.4</td>
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<td>4,768</td>
<td>37</td>
<td>0.8</td>
<td>58.0</td>
<td>41.2 to 78.7</td>
<td>6.4</td>
<td>3.0 to 13.8</td>
<td>&lt; .0001</td>
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<td>Leukemia without CRT</td>
<td>1,363</td>
<td>6</td>
<td>0.4</td>
<td>35.6</td>
<td>14.1 to 72.1</td>
<td>4.0</td>
<td>1.4 to 11.5</td>
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<td>20</td>
<td>0.7</td>
<td>52.1</td>
<td>32.5 to 78.4</td>
<td>5.9</td>
<td>2.6 to 13.4</td>
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<tr>
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<td>802</td>
<td>18</td>
<td>2.2</td>
<td>235.7</td>
<td>142.9 to 362.0</td>
<td>21.6</td>
<td>8.6 to 54.2</td>
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<tr>
<td>Brain tumor survivors</td>
<td>1,817</td>
<td>63</td>
<td>3.4</td>
<td>267.6</td>
<td>206.8 to 339.2</td>
<td>29.0</td>
<td>13.8 to 60.7</td>
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<tr>
<td>Brain tumor survivors without CRT</td>
<td>488</td>
<td>8</td>
<td>1.6</td>
<td>117.9</td>
<td>53.9 to 219.5</td>
<td>12.9</td>
<td>4.8 to 34.5</td>
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<tr>
<td>Brain tumor + CRT</td>
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<td>45</td>
<td>4.3</td>
<td>339.6</td>
<td>249.8 to 448.8</td>
<td>37.5</td>
<td>17.6 to 79.9</td>
<td>&lt; .0001</td>
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<tr>
<td>Brain tumor + relapse</td>
<td>328</td>
<td>18</td>
<td>5.5</td>
<td>707.3</td>
<td>428.8 to 1086.2</td>
<td>64.5</td>
<td>27.3 to 152.7</td>
<td>&lt; .0001</td>
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<td>Brain tumor + CRT + alkylating agents</td>
<td>367</td>
<td>24</td>
<td>6.5</td>
<td>661.1</td>
<td>430.7 to 962.0</td>
<td>78.3</td>
<td>35.1 to 174.5</td>
<td>&lt; .0001</td>
</tr>
</tbody>
</table>

Abbreviation: CRT, cranial radiation therapy.

*Per 100,000 person-years.

<table>
<thead>
<tr>
<th>Diagnosis</th>
<th>Cumulative Incidence (%) at 15 years</th>
<th>95% CI</th>
<th>Cumulative Incidence (%) at 25 years</th>
<th>95% CI</th>
</tr>
</thead>
<tbody>
<tr>
<td>Leukemia</td>
<td>0.57</td>
<td>0.34 to 0.80</td>
<td>0.73</td>
<td>0.43 to 1.04</td>
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<td>Leukemia with CRT</td>
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<td>0.33 to 0.93</td>
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<td>0.45 to 1.22</td>
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<td>0.44</td>
<td>0.09 to 0.80</td>
<td>0.44</td>
<td>0.09 to 0.80</td>
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<tr>
<td>Brain tumor</td>
<td>2.18</td>
<td>1.43 to 2.92</td>
<td>5.58</td>
<td>3.80 to 7.37</td>
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<td>Brain tumor with CRT</td>
<td>2.69</td>
<td>1.69 to 3.70</td>
<td>6.90</td>
<td>4.47 to 9.33</td>
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<tr>
<td>Brain tumor without CRT</td>
<td>1.04</td>
<td>1.33 to 1.95</td>
<td>2.85</td>
<td>0.58 to 5.12</td>
</tr>
</tbody>
</table>

Abbreviation: CRT, cranial radiation therapy.
with 0.1 to 29 Gy to segment 2 and no CRT ($P = .38$). However, there were significant differences between 0.1 to 29 and 30 to 49 Gy ($P < .001$) and between 30 to 49 and $\geq 50$ Gy ($P = .02$). This same dose-dependent relationship was seen when using the mean dose of CRT either to all four segments or to segments 2, 3, and 4 (excluding segment 1, cerebellum, fourth ventricle, and brainstem).

**DISCUSSION**

Survivors of childhood leukemia and brain tumors face a high risk of chronic complications or late effects of their cancer or cancer therapy. Previously recognized and well-described late effects of childhood leukemia and brain tumor survivors include second malignant neoplasms,¹¹ neurocognitive deficits,¹² hormone deficiencies,¹³ cardiac dysfunction,¹⁴ obesity, and short stature.¹⁵,¹⁶

This is the first study examining the risk of late-occurring stroke among childhood leukemia survivors and is by far the largest study examining the risk of stroke among childhood brain tumor survivors.

This study demonstrates an increased risk of late-occurring stroke, particularly in survivors treated with CRT at doses greater than 30 Gy. Importantly, although the risk of stroke among leukemia and brain tumor survivors is significantly increased, it is still a relatively uncommon event during the first two decades after the cancer diagnosis. How this risk will change as these cancer survivors age is not known.

The primary treatment exposure associated with late-occurring stroke risk was CRT at doses of greater than 30 Gy. However, among both leukemia and brain tumor survivors who did not receive CRT, the risk of late-occurring stroke remained significantly increased, albeit modestly, compared with the sibling comparison group. Furthermore, lower dose CRT, ranging from 10 to 29 Gy, was not associated with an increase in risk compared with no CRT. In contrast, treatment with CRT at doses of greater than 30 Gy was associated with an increased risk of late-occurring stroke. In addition, there was a dose-response relationship between radiation therapy dose and risk of stroke; survivors treated with CRT greater than 50 Gy had a significantly greater risk of stroke in comparison with those treated with CRT 30 to 49 Gy.

Two factors modified the risk of late-occurring stroke associated with radiation. First, among both leukemia and brain tumor survivors, a history of relapse further increased risk, likely reflecting additional therapy required for treatment of cancer progression. Second, in brain tumor survivors, treatment with an alkylating agent in addition to CRT increased risk. It is curious that this relationship was not seen in leukemia survivors who were treated with CRT. A potential mechanism may be gonadal failure induced by alkylating agents and testosterone deficiency, which has been reported among men who experienced strokes.¹⁷ However, we suspect that this finding may reflect more aggressive therapy for high-risk brain tumor patients rather than an interaction between alkylating agents and CRT.

The presence of coexisting neurofibromatosis type 1 was not identified as being associated with stroke in this study,⁴ possibly because of limited self-reporting of neurofibromatosis. Other recognized causal factors for stroke in older adults, including hypertension and diabetes mellitus, were not identified as associated with stroke. We recognize that the frequency of these comorbidities is low and that the mean age of participation is relatively young. It is unknown what effect these comorbidities will have, if any, as these patients continue to age.

Several limitations of this study should be considered when interpreting the findings. First, stroke was self-reported by the participants. However, the incidence of stroke in the sibling comparison group is similar to that reported in four studies focusing on strokes in young adults in the general population,¹⁸-²¹ thus suggesting that the self-reported strokes in our study were reasonably accurate. Second, type and location of stroke were not provided in this study. Additional characterization of the stroke is needed in future studies. Finally, the sibling comparison group was somewhat older than both the leukemia and brain tumor survivors; hence, all analyses were adjusted for age.

In conclusion, this report identifies a significantly increased incidence of stroke among long-term survivors of childhood leukemia and brain tumors. This study also identifies the use of CRT, in a dose-dependent fashion, as contributing to the increased risk of stroke, and justifies efforts to continue to reduce radiation doses among both leukemia and brain tumor treatment regimens whenever practical.

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**Fig 1.** The occurrence of stroke over time among ≥ 5-year survivors of childhood leukemia with and without cranial radiation therapy (CRT; log-rank $P = .32$) and brain tumors with and without CRT (log-rank $P = .004$).

**Fig 2.** The occurrence of stroke over time by maximum dose of cranial radiation therapy (CRT) to the temporal lobe, hypothalamus, and circle of Willis comparing no radiation v 0.1 to 29 Gy ($P = .38$); 0.1 to 29 v 30 to 49 Gy ($P < .001$); and 30 to 49 v $\geq 50$ Gy ($P = .02$).
REFERENCES


Acknowledgment

The Childhood Cancer Survivor Study is funded by the National Cancer Institute as a resource to promote and facilitate research among long-term survivors of cancer diagnosed during childhood and adolescence. Investigators interested in potential uses of this resource are encouraged to visit http://www.cancer.umn.edu/ccss.

Appendix

The Appendix is included in the full-text version of this article, available online at www.jco.org. It is not included in the PDF version (via Adobe® Reader®).

Authors’ Disclosures of Potential Conflicts of Interest

The authors indicated no potential conflicts of interest.

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