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Clinical Investigation: Pediatric Cancer

Risk of First and Recurrent Stroke in Childhood Cancer Survivors Treated With Cranial and Cervical Radiation Therapy

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Summary

No data are available on the risk of recurrent stroke in pediatric cancer survivors treated with radiation therapy to the brain and/or neck. We retrospectively evaluated the risk of stroke in 325 children with cancer treated with brain and/or neck radiation therapy. The overall rate of first stroke was 625 per 100,000 person-years. The 5-year cumulative stroke recurrence rate was high at 38% (95% CI 17%-69%). Stroke prevention strategies are needed for this high-risk population.

Purpose: To assess, in a retrospective cohort study, rates and predictors of first and recurrent stroke in patients treated with cranial irradiation (CRT) and/or cervical irradiation at ≤18 years of age.
Methods and Materials: We performed chart abstraction (n = 383) and phone interviews (n = 104) to measure first and recurrent stroke in 383 patients who received CRT and/or cervical radiation at a single institution between 1980 and 2009. Stroke was defined as a physician diagnosis and symptoms consistent with stroke. Incidence of first stroke was number of first strokes per person-years of observation after radiation. We used survival analysis techniques to determine cumulative incidence of first and recurrent stroke.
Results: Among 325 subjects with sufficient follow-up data, we identified 19 first strokes (13 ischemic, 4 hemorrhagic, 2 unknown subtype) occurring at a median age of 24 years (interquartile range 17-33 years) in patients treated with CRT. Imaging was reviewed when available (n = 13), and the stroke was confirmed in 12. Overall rate of first stroke was 625 (95% confidence interval [CI] 378-977) per 100,000 person-years. The cumulative incidence of first stroke was 2% (95% CI 0.01%-5.3%) at 5 years and 4% (95% CI 2.0%-8.4%) at 10 years after irradiation. With each 100-cGy increase in the radiation dose, the stroke hazard increased by 5% (hazard ratio 1.05; 95% CI 1.01-1.09; $P = .02$). We identified 6 recurrent strokes; 5 had available imaging that confirmed the stroke. Median time to recurrence was 15 months (interquartile range 6 months-3.2 years) after first stroke. The cumulative incidence of recurrent stroke was 38% (95% CI 17%-69%) at 5 years and 59% (95% CI 27%-92%) at 10 years after first stroke.
Conclusion: Cranial irradiation puts childhood cancer survivors at high risk of both first and recurrent stroke. Stroke prevention strategies for these survivors are needed. © 2013 Elsevier Inc.

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Introduction

Cranial radiation therapy (CRT) has been associated with significant long-term sequelae, including increased risk of stroke; however, no information is available on the risk of recurrent stroke after first stroke in survivors of childhood cancer (1-3). Analyses from the Childhood Cancer Survivor Study (CCSS), a retrospective cohort study with longitudinal follow-up of 14,358 childhood cancer survivors and 4023 sibling controls, suggest that the risk of stroke is significantly elevated among survivors of pediatric central nervous system (CNS) tumors and acute lymphoblastic leukemia. Cranial radiation therapy was the strongest stroke predictor and increased stroke risk in a dose-dependent manner; not surprisingly, CNS tumor survivors were found to carry a very high stroke risk compared with controls (2).

The underlying mechanism through which radiation therapy increases stroke risk is not well understood. Moyamoya, a specific form of cerebral vasculopathy characterized by nonatherosclerotic progressive stenosis of the terminal internal carotid arteries, is more prevalent in children with acute lymphoblastic leukemia and CNS tumors who undergo CRT than in those children who did not require CRT (4, 5). Head-and-neck cancer studies have shown that radiation therapy causes accelerated atherosclerosis even within 1 year from treatment (6, 7). A recent analysis of the CCSS cohort showed that the risk of late-occurring stroke ($\geq$5 years from initial cancer diagnosis) is CRT dose-dependent and continues to increase as these survivors age. In addition, atherosclerotic risk factors such as hypertension contributed to this elevated stroke risk. Age at time of CRT did not influence stroke risk, although others have reported an increase in silent lacunar infarcts the younger the child at time of radiation therapy (8, 9).

The underlying cellular process of this delayed radiation injury is thought to be related to chronic oxidative stress (10). Cells exposed to radiation have been shown to increase the production of reactive oxygen species causing damage to proteins and lipids. Activation of these pathways can lead to chronic inflammation, increasing the risk of atherosclerotic plaque development and rupture. These data suggest that treatment with radiation therapy may increase the stroke risk by at least 2 mechanisms: (*1*) a non-atherosclerotic radiation-induced cerebral vasculopathy referred to as moyamoya in its most severe form; and (*2*) by accelerated atherosclerosis through chronic inflammation.

A large cohort study of children with stroke showed that those with underlying vasculopathies have an extraordinarily high risk of recurrent stroke: 66% at 5 years (11). Because the mechanism of stroke in pediatric cancer survivors who received CRT is likely a radiation-induced vasculopathy, we hypothesized that risk of recurrent stroke is similarly high in pediatric cancer survivors with first stroke. We identified first and recurrent strokes in a retrospective cohort of children with cancer who were treated with cranial or neck irradiation at $\leq$18 years of age at a single institution. To inform primary and secondary stroke prevention strategies in this high-risk population, we sought to define the incidence and predictors of both first and recurrent stroke after radiation therapy.

Methods and Materials

Setting

This is a retrospective cohort study of patients treated at a single institution from 1980 to 2009 with cranial or cervical irradiation therapy for an underlying malignancy at age $\leq$18 years. Patients were identified through the institutional cancer registry. The institutional review board approved this study.

Patients

Eligibility criteria for enrollment in this study included (*1*) age $\leq$18 years at the time of radiation therapy; (*2*) radiation therapy to the brain and/or cervical area between 1980 and 2009; (*3*) survival $\geq$1 year from radiation therapy; and (*4*) signed consent. The institutional review board granted a waiver of informed consent to perform chart review on patients lost to follow-up.

Data collection

Eligible patients (n = 406) were contacted by mail to invite participation in the study; 23 declined and were excluded from the study. Chart review was performed on the remaining 383 patients; of these, 104 (or surrogates where necessary) consented/assented to a telephone interview. Interviews were carried out with either the patient (if alive and $\geq$18 years of age at the time of the study; n = 71) or the legal guardian of patients currently <18 years of age (n = 20) or deceased (n = 13).

During the interview, participants were asked specific questions about baseline demographics (age, sex, race), the cancer diagnosis and treatment, and complications of treatment or the cancer itself, with a specific focus on stroke, stroke symptoms, potential treatment for stroke, and stroke recurrence. Chart review included abstraction of basic demographic information such as age, race, and sex. Cancer diagnosis was based on pathology report, and date of surgery was confirmed by operative report. We recorded whether patients received chemotherapy as part of their treatment. Clinical records were reviewed for evidence of stroke after radiation therapy and stroke recurrence after first stroke.

Stroke outcomes were identified by either chart review or interview and included ischemic and hemorrhagic stroke. Stroke based on chart review was defined as both physician documentation of a stroke diagnosis and clinical signs or symptoms consistent with an ischemic or hemorrhagic stroke (eg, acute-onset focal neurologic deficits, headache, altered mental status, and/or seizure). Stroke based on interview was similarly defined as a history of a healthcare provider communicating the diagnosis of stroke to the participant and clinical symptoms consistent with stroke. Strokes within 7 days after brain surgery were excluded.

When stroke outcomes were identified, we attempted to obtain all relevant brain imaging, including, with patient/guardian consent, studies performed at outside hospitals. Two pediatric neurologists (H.J.F., S.M.) independently reviewed the imaging to confirm findings consistent with stroke. A radiation oncologist (D.H.-K) reviewed radiation records and location of strokes to assess whether strokes occurred in the territories of arteries within the radiation field.

Statistical analysis

The overall annual incidence of first stroke was calculated as the total number of first strokes divided by the sum of person-years of observation from date of radiation therapy to date of first stroke, death, or last follow up. Last follow-up was defined as the date of the interview or date of last documented medical encounter