Title

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

Journal

International Journal of Radiation Oncology • Biology • Physics, 86(4)

ISSN

0360-3016

Authors

Mueller, Sabine
Sear, Katherine
Hills, Nancy K
et al.

Publication Date

2013-07-01

DOI

10.1016/j.ijrobp.2013.03.004

Peer reviewed

Published in final edited form as:
Int J Radiat Oncol Biol Phys. 2013 July 15; 86(4): 643–648. doi:10.1016/j.ijrobp.2013.03.004.

Risk of First and Recurrent Stroke in Childhood Cancer Survivors treated with Cranial and Cervical Radiation Therapy

Sabine Mueller, MD, PhD[1,2], **Katherine Sear, MPH**[1], **Nancy K Hills, PhD**[1], **Nassim Chettout, MD**[1], **Shervin Afghani, BS**[3], **Erica Gastelum, BS**[4], **Daphne Haas-Kogan, MD**[5], and **Heather J Fullerton, MD, MAS**[1,2]

[1]Department of Neurology, University of California, San Francisco, CA, USA

[2]Department of Pediatrics, University of California, San Francisco, CA, USA

[3]Undergraduate Program, University of California, Berkeley, CA, USA

[4]School of Medicine, University of California, San Francisco, CA, USA

[5]Department of Radiation Oncology and Neurosurgery, University of California, San Francisco, CA, USA

Abstract

Purpose—Radiation therapy increases stroke risk in pediatric cancer patients, but risk of stroke recurrence in this population remains unknown. In a retrospective cohort study, we assessed rates and predictors of first and recurrent stroke in patients treated with cranial irradiation (CRT) and/or cervical irradiation ≤ 18 years of age.

Methods—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 between1980–2009. 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 sub-type) occurring at a median age of 24 years (Interquartile range (IQR) 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% 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% C.I. 2.0–8.4%) at 10 years post irradiation. With each 100cGy increase in the radiation dose, the stroke hazard increased by 5% (Hazard ratio = 1.05; 95% CI 1.01–1.09; p=0.02). We identified 6 recurrent strokes; 5 had available imaging that confirmed the stroke. Median time to recurrence was 15 months (IQR 6 months–3.2 years) after first-stroke. The

Corresponding author: Sabine Mueller, MD, PhD, Department of Neurology, University of California, San Francisco, Sandler Neuroscience Building, 675 Nelson Rising Lane, Room 402, San Francisco, CA 94148, Phone: 415-502-7301, Fax: 415-502-4372, muellers@neuropeds.ucsf.edu.

Part of this work was presented the International Stroke Meeting 2012 and at ASTRO 2012.

Conflicts of Interest Notification:
None of the authors have any conflicts of interest to report.

cumulative incidence of recurrent stroke was 38% (95% CI 17–69%) at 5 years and 59% (95% CI 27–92%) at 10 years post first-stroke.

Conclusion—CRT puts childhood cancer survivors at high risk of both first and recurrent stroke. Stroke prevention strategies for these survivors are needed.

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 4,023 sibling controls, suggest that the risk of stroke is significantly elevated among survivors of pediatric central nervous system (CNS) tumors and acute lymphoblastic leukemia (ALL). CRT 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 to 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 non-atherosclerotic progressive stenosis of the terminal internal carotid arteries, is more prevalent in children with ALL and CNS tumors who undergo CRT than those children who did not require CRT (4, 5). Head and neck cancer studies have shown that radiation therapy causes accelerated atherosclerosis even within one year from treatment (6, 7). A recent analysis of the CCSS cohort showed that the risk of late-occurring stroke (≥ five 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 (HTN) 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 two 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 five 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 ≤ 18 years of age at a single institution. In order 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

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 ≤ age of 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 ≤18 years at the time of radiation therapy, (2) radiation therapy to the brain and/or cervical area between 1980 and2009 (3) survival ≥ one 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 ≥18 years of age at the time of the study; n=71) or the legal guardian of patients currently <18 years (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 or not 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 (e.g., acute onset focal neurological deficits, headache, altered mental status, and/or seizure). Stroke based on interview was similarly defined as a history of a health care provider communicating the diagnosis of stroke to the participant and clinical symptoms consistent with stroke. Strokes within seven 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 (HF, SM) independently reviewed the imaging to confirm findings consistent with stroke. A radiation oncologist (DHK) reviewed radiation records and location of strokes to assess if 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 (admission or clinic visit), whichever came last. We used survival analysis techniques to determine the cumulative incidence of first-stroke; the time period at risk began with the date of the first radiation therapy and subjects who did not have an event were censored at the time of death or date of last follow up. Cox proportional hazards models were used to assess risk factors for first-stroke within this cohort; hazard ratios (HR) and associated confidence intervals (CI) were calculated as a measure of relative risk. We examined as predictors in univariate analyses: age at time of radiation therapy and diagnosis, radiation therapy dose, treatment with chemotherapy, race, and gender. The multivariable model was based on univariate screening, and included those predictors that were significantly associated with risk of first stroke ($p<0.05$). Among the subcohort of patients with first-stroke, we used survival analysis techniques to determine the cumulative incidence of recurrent stroke; the time period at risk began with the date of the first stroke, and subjects who did not have a recurrence were censored at death or last follow-up.

Results

Of the 383 patients subjected to chart review, 325 had sufficient longitudinal clinical data and constituted the final study cohort. There were no differences in baseline characteristics between the 58 subjects excluded due to loss to follow-up and the 325 with follow-up data (data not shown). The final cohort had a median follow-up time of 7.3 years (Interquartile range (IQR) 2.4–15.0 years). The majority of patients were alive (n=227; 70%), and only 5 patients in our cohort had a history of neurofibromatosis type 1 (NF1). Patients who were available for interview (in addition to chart review) had similar characteristics compared to patients who could not be interviewed in terms of gender ($p=0.21$), race ($p=0.43$), age at diagnosis ($p=0.63$) and history of NF1 ($p=0.63$) (supplemental Table 1). However, patients who were not interviewed were significantly younger at the last follow-up than patients who were interviewed ($p=0.01$) and as expected were more likely to have died ($p<0.0001$) (supplemental Table 1).

First Stroke after Radiation Therapy

In this cohort, we identified a total of 19 first strokes after CRT (Table 1): 6 from chart review (5 out of 6 confirmed by imaging), 9 from interviews (3 out of 9 confirmed by imaging), and 4 from both sources (all 4 confirmed by imaging). Out of 13 cases with available imaging, 12 had imaging findings consistent with stroke. The other had extensive brain calcifications that precluded definitive confirmation of a stroke; however, we decided to include this stroke outcome in the analysis based on the clinical diagnosis. The median age at first-stroke was 24 years (IQR 17–33 years). Median time to develop a first stroke after CRT was 12 years (IQR 5–18 years). A total of 11 patients received treatment for their stroke (Table 1). Thirteen strokes were ischemic, 4 were hemorrhagic, and the stroke type was unknown in two.

The overall rate of first-stroke was 625 per 100,000 person-years (95% CI 378–977 per 100,000). It was 429/100,000 person-years for patients identified by chart review only and 198/100,000 for patients identified based by interview only. As shown in Figure 1 and Table 2, the cumulative incidence of first stroke after radiation therapy increased over time elapsed since radiation therapy.

Risk Factors of First Stroke after Cranial Radiation Therapy

Table 3 lists results of the univariate analysis. Each 100cGy increase in CRT dose increased the risk of stroke by 5% (HR 10.5; 95% CI 1.01–1.09; $p=0.02$). Males had an increased

stroke risk compared to females (HR 3.2 95% CI 1.0– 9.6; p= 0.04). For every additional year of age at time of radiation therapy, risk of stroke increased by 12% (95% CI 1.0–1.2 p=0.01) (Table 3). In the multivariable analysis, dose of radiation retained borderline significance, even when adjusted for age at radiation and gender (HR 1.04, 95% CI 1.00, 1.09, p=0.07).

Recurrent Stroke in Children treated with Radiation Therapy

Of the 19 subjects who had a first stroke, 6 had recurrent strokes (5 identified by interview and one by chart review) (Table 1). One out of these 6 had more than one recurrent event. We confirmed 5 out of 6 recurrent strokes on imaging. For one patient we were unable to attain the images. The earliest recurrent stroke occurred 6 months after first stroke, with the last recorded recurrence at 9 years. The median time between first stroke and recurrence was 15 months (IQR 6 months–3.2 years) (see Figure 2); stroke recurrence occurred at a median age of 27 years (IQR 26–34). The cumulative incidence of recurrent stroke was 20% (95% CI 7–50%) at 1 year after first-stroke, 38% (95% CI 17–69%) at 5 years and 59% (95% CI 27–92%) at 10 years. Of the 6 patients with recurrent strokes, 4 had been treated with aspirin after their first stroke. One subject carried a diagnosis of NF1. Imaging reports commenting on vascular findings were available in 2 out 6 patients; one patient had evidence of moyamoya and one patient had evidence of internal carotid calcifications, a finding seen in atherosclerosis.

Discussion

In this retrospective cohort study of cancer patients treated with CRT and/or cervical irradiation under 18 years of age, we identified 19 first strokes after CRT and identified a high 5-year cumulative recurrence rate of 38%. To our knowledge this is the first report that specifically investigated the risk of stroke recurrence in this high-risk population. We found that with each 100 cGy increase in radiation dose the risk of first stroke increases by 5%. This is in concordance with other reports showing a dose dependent effect of radiation on stroke risk (2, 5). As expected, the majority of patients with stroke carried a diagnosis of a brain tumor that most likely reflects the use of higher radiation dosages in this population. None of the patients with just cervical irradiation were found to have a stroke. The overall rate of first stroke in this study was 625 per 100,000 person-years after radiation therapy. Prior studies have estimated stroke rates of 2.3 per 100,000 in children and between 7–15 per 100,000 in young adults defined as < 45 years of age (12, 13). A recent retrospective analysis from Children's Hospital in Philadelphia reports a similar stroke rate of 548 per 100,000 in patients receiving CRT (14). Radiation to the circle of Willis has been shown to be an important predictor of cerebrovascular disease (1, 14). Of the 19 patients with first strokes in our cohort, 12 patients received radiation to the circle of Willis as defined by Campen, et al (14). However, we were unable to assess radiation to the Circle of Willis as a stroke predictor in this current study because incomplete radiation records precluded measurement in a significant number of patients.

As suggested by results of the CCSS, which described self-reported first-strokes, childhood cancer survivors continue to be at significant stroke risk even decades after initial treatment as they enter adulthood. We similarly found that the cumulative incidence of first stroke increases more than 8-fold from 2% at 5 years to 17% at 20 years after radiation therapy; these strokes are occurring in adolescence to young adulthood when the stroke risk in the general population is still very low. Enhanced awareness of these risks by healthcare providers, caregivers, and patients alike would help ensure that there are no delays in stroke diagnosis.

Surprisingly, we found that each additional year of age at time of radiation increased stroke risk by 12%. Similar results were found by Campen, *et al.* (14), who reported a 13% increase in the risk of cerebrovascular events [including transient ischemic attacks (TIA) and stroke] with each additional year at age of cancer diagnosis. These results contrast with reports by others indicating that age less than 5 years at time of radiation therapy is a strong predictor of lacunar infarcts, thought to be secondary to small vessel vasculopathy (9). Results from CCSS, however, suggest that age at time of diagnosis as a surrogate for age at radiation therapy does not influence the risk of stroke (2). If and how age at time of radiation therapy influences the risk of stroke requires additional studies.

This is the first study to specifically assess the risk of recurrent stroke in this high-risk population. We identified 6 recurrent strokes: of these, 2 had evidence of vasculopathies based on imaging review. In a large population-based pediatric cohort study, the overall cumulative rate of recurrent ischemic stroke was 19% at 5 years post stroke, with the highest risk in children who had evidence of vasculopathies: a 5-year cumulative recurrence rate of 66% (11). In our current study we also found a high 5-year cumulative recurrence rate of 38%. Children with evidence of cerebral vasculopathies or history of first ischemic stroke are often started on anti-platelet agents. Out of 6 patients with recurrent stroke 4 were treated with an anti-platelet agent after first stroke. It is conceivable that the underlying mechanism of radiation-induced vasculopathies is a chronic inflammatory process and therefore other treatment strategies such as anti-inflammatory agents may prove more efficacious. Additional investigations are required to better characterize the group of pediatric cancer survivors at highest risk of recurrent strokes in order to develop strategies for secondary stroke prevention.

Our study is limited by the biases and limitations of retrospective analyses as well as recall bias of patients and/or their proxies that participated in interviews. However, we were able to confirm on imaging the majority of stroke outcomes. Furthermore, 4 patients had confirmed stroke outcomes based on both chart reviews and interviews. All patients whose outcomes could only be measured by interview and not chart review had only brief follow-up. As a tertiary care center patients are often referred only for radiation therapy and are then followed locally. Additional factors such as presence of atherosclerotic risk factors (*e.g.* hypertension) may play a critical role in this population as suggested by a recent analysis from the CCSS (8); we were unable to capture these reliably by chart review or by interviews and therefore were unable to include such factors in the current analysis. A further limitation was that the median follow up time for the cohort was 7.3 years (IQR 2.4 – 15 years) but median time to first stroke was 12 years (IQR 5–18 years). With longer duration of follow up we would likely have identified more first strokes, as well as more recurrent strokes; hence, our stroke rates may be under estimates. Further, to estimate the rate of recurrent stroke we used survival technique analysis and censored patients either at time of death or last follow up. It is conceivable that patients who contribute more person-years of observation to follow up are different from the patients who died and are less ill. That could also potentially lead to under estimates of recurrent strokes.

In conclusion, pediatric cancer patients treated with CRT, have an elevated stroke risk and a high risk of recurrent stroke after first stroke. To date, we have limited information on the timing and incidence of radiation induced vasculopathies since vascular imaging is not routinely obtained. Prospective studies are urgently needed to better characterize the vascular effects of radiation therapy and to assess if additional factors such as modifiable atherosclerotic risk factors are contributing to stroke risk. We have initiated a prospective cohort study using MR-angiography of the head and neck in children who are receiving radiation therapy; results will inform the incidence of radiation-induced vasculopathies, strokes, and stroke recurrence in this high-risk group of patients.

Supplementary Material

Refer to Web version on PubMed Central for supplementary material.

Acknowledgments

This research was supported in part by National Institute of Neurological Disorders And Stroke grants K12NS001692 (SM) and K02 NS053883 (HF), the Hellman Fellow Foundation (SM) and a private donation from the LaRoche family.

References

1. Haddy N, Mousannif A, Tukenova M, et al. Relationship between the brain radiation dose for the treatment of childhood cancer and the risk of long-term cerebrovascular mortality. Brain. 2011; 134:1362–1372. [PubMed: 21596770]
2. Bowers DC, Liu Y, Leisenring W, et al. Late-occurring stroke among long-term survivors of childhood leukemia and brain tumors: a report from the Childhood Cancer Survivor Study. J Clin Oncol. 2006; 24:5277–5282. [PubMed: 17088567]
3. Bowers DC, McNeil DE, Liu Y, et al. Stroke as a late treatment effect of Hodgkin's Disease: a report from the Childhood Cancer Survivor Study. J Clin Oncol. 2005; 23:6508–6515. [PubMed: 16170160]
4. Kikuchi A, Maeda M, Hanada R, et al. Moyamoya syndrome following childhood acute lymphoblastic leukemia. Pediatr Blood Cancer. 2007; 48:268–272. [PubMed: 16615044]
5. Ullrich NJ, Robertson R, Kinnamon DD, et al. Moyamoya following cranial irradiation for primary brain tumors in children. Neurology. 2007; 68:932–938. [PubMed: 17372129]
6. Muzaffar K, Collins SL, Labropoulos N, et al. A prospective study of the effects of irradiation on the carotid artery. Laryngoscope. 2000; 110:1811–1814. [PubMed: 11081590]
7. Dorresteijn LD, Kappelle AC, Scholz NM, et al. Increased carotid wall thickening after radiotherapy on the neck. Eur J Cancer. 2005; 41:1026–1030. [PubMed: 15862751]
8. Mueller S, Fullerton HJ, Stratton K, et al. Radiation and modifiable Stroke Risk Factors in adult Survivors of Pediatric Cancer: Results from the Childhood Cancer Survivor Study. Stroke. 2012; 43 A8 [Abstract].
9. Fouladi M, Langston J, Mulhern R, et al. Silent lacunar lesions detected by magnetic resonance imaging of children with brain tumors: a late sequela of therapy. J Clin Oncol. 2000; 18:824–831. [PubMed: 10673524]
10. Robbins ME, Zhao W. Chronic oxidative stress and radiation-induced late normal tissue injury: a review. Int J Radiat Biol. 2004; 80:251–259. [PubMed: 15204702]
11. Fullerton HJ, Wu YW, Sidney S, et al. Risk of recurrent childhood arterial ischemic stroke in a population-based cohort: the importance of cerebrovascular imaging. Pediatrics. 2007; 119:495–501. [PubMed: 17332202]
12. Griffiths D, Sturm J. Epidemiology and etiology of young stroke. Stroke Res Treat. 2011;209370
13. Fullerton HJ, Wu YW, Zhao S, et al. Risk of stroke in children: ethnic and gender disparities. Neurology. 2003; 61:189–194. [PubMed: 12874397]
14. Campen CJ, Kranick SM, Kasner SE, et al. Cranial Irradiation Increases Risk of Stroke in Pediatric Brain Tumor Survivors. Stroke. 2012; 43(11):3035–3040. [PubMed: 22968468]

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.

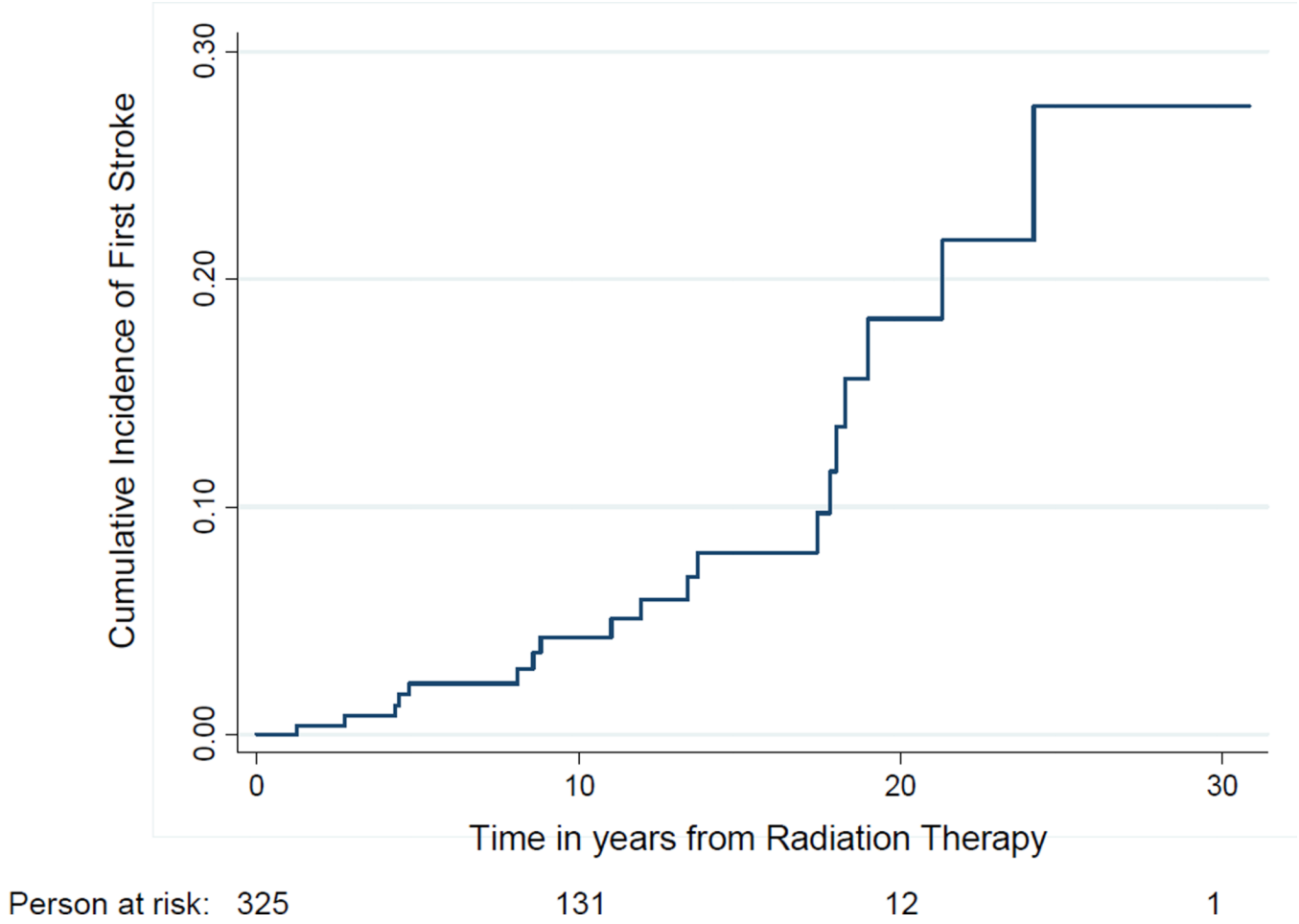

Figure 1.
Cumulative Incidence of First Stroke after Cranial Radiation Therapy in Pediatric Cancer Patients

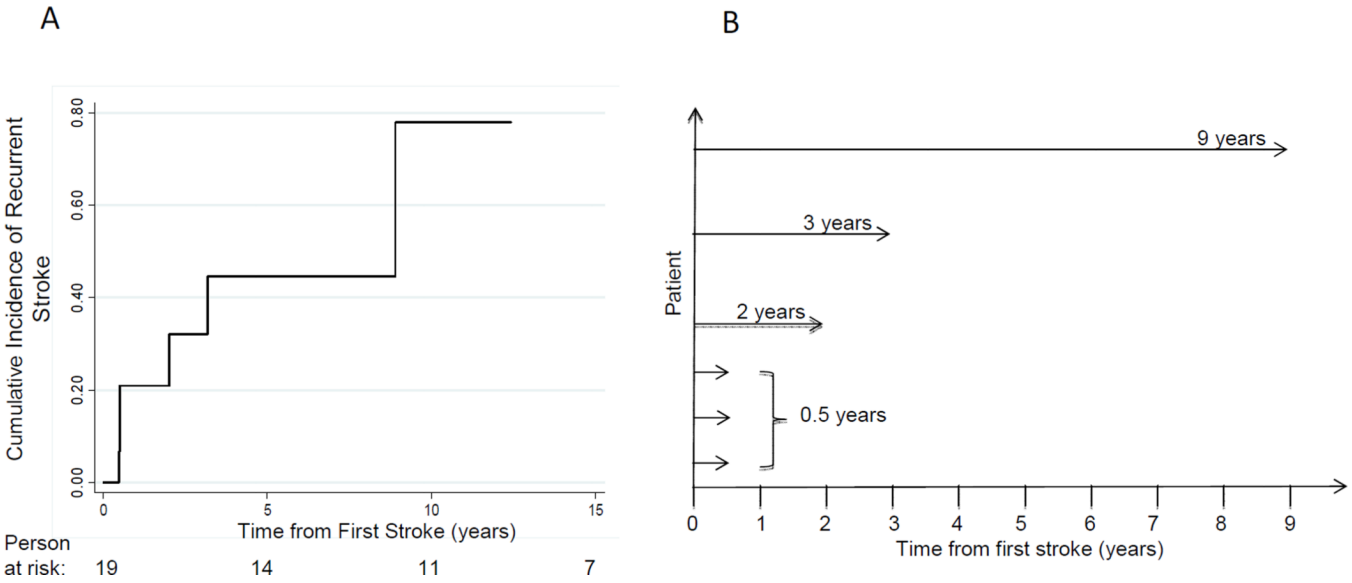

Figure 2.

(A) Cumulative Incidence of First Stroke after First Stroke in Pediatric Cancer Patients. (B) Depicted is the time from first to recurrent stroke for each patient with a histor of stroke recurrence (n=6)

Table 1

Clinical Characteristics of Patients with First and Recurrent Stroke after Cranial Radiation Therapy

ID	Sex/Race	Tumor Type	Tumor Location	Radiation Dose (cGy)*	Age at XRT (years)	Time from XRT to First Stroke (years)	Stroke Event	Treatment	Recurrent Stroke Event
1	M/C	HGG	Right parietal lobe Posterior	5040	3	19	Hemorrhagic	None	Hemorrhagic
2	M/C	MED	fossa	7300†	4	5	Hemorrhagic	None	–
3	F/C	LGG	Hypothalamus	5640	6	11	Ischemic	ASA	Hemorrhagic
4##	M/C	LGG	Brainstem	5600	6	1	Ischemic	ASA	–
5	M/C	HGG	Left BG Suprasellar	7600	7	18	Ischemic	ASA	–
6	M/C	EPD	region	5400 3600 CSI + 7300	11	4	Ischemic	ASA	–
7	F/MR	MED	PF	to PF 3600 CSI + 5950	12	13	Ischemic	Unknown	–
8	M/C	MED	PF Left temporal	to PF	13	4	Hemorrhagic	None	–
9	M/MR	HGG	lobe Suprasellar	5580	14	14	Ischemic	ASA	–
10	M/C	HGG	region	5400	14	21	Ischemic	Unknown	–
11	M/AA	GRM	Pineal region	5500	14	7	Hemorrhagic	None	–
12##	M/C	HGG	Brainstem Suprasellar	7200	14	8	Unknown	None	–
13	M/L	LGG	region	5580	15	24	Ischemic	Aggrenox	–
14	M/C	LGG	Brainstem	6800	15	18	Ischemic	ASA	Unknown
15	M/C	HGG	PF	6000	15	9	Ischemic	ASA	Ischemic
16	F/MR	RB	Left eye	2950	16	3	Unknown	Unknown	–
17##	F/C	HGG	Pineal region Temporal	5400	16	12	Ischemic	Heparin	Ischemic
18	M/L	HGG	Lobes Left temporal	6600	17	18	Ischemic	ASA	–
19	M/C	HGG	lobe	6000	17	17	Ischemic	ASA	Hemorrhagic

Abbreviations: AA: African-American; ASA: aspirin; C: Caucasian; cGy: centi-gray; CSI: cranio-spinal irradiation; EPD: ependymoma; MED: medulloblastoma; MR: Mixed race; HGG: high-grade glioma; LGG: low-grade glioma; PF: posterior fossa; XRT: radiation therapy; y: years.

* Dose involved the primary tumor bed unless otherwise indicated that patient received CSI.

† Patient did not receive CSI based on parental preference.

positive history of Neurofibromatosis 1

Table 2

Cumulative Incidence of First Stroke after Cranial Radiation Therapy in Pediatric Cancer Patients

Identification of Stroke	5 years		10 years		20 years	
	%	(95% CI)	%	(95% CI)	%	(95% CI)
Total cohort	2.0	(0.01−5.2)	4.0	(2.1−8.3)	16.8	(10−28)
Chart only	1.0	(0.002−3.3)	2.0	(0.01−5.9)	4.0	(1.4−10.9)
Interview and chart	1.4	(0.4−4)	2.0	(0.8−5.4)	13.4	(7.2−24)

Table 3

Univariate Cox Proportional Hazards Regression of First Stroke in Pediatric Cancer Patients treated with Cranial and/or Neck Irradiation

	Patients with stroke (n=19)	Patients without stroke (n=306)	Univariate Cox proportional hazards regression analysis		
Characteristic	**n (%)**	**n (%)**	**Hazard Ratio**	**95% CI**	**p-value**
Alive	11 (57.9)	216 (70.6)	0.24	(0.09, 0.61)	0.003
Male gender	15 (78.9)	165 (53.9)	3.41	(1.13, 10.3)	0.03
White race vs. other			0.99	(0.73, 1.33)	0.93
African-American	1 (5.3)	18 (5.9)			
Caucasian	13 (68.4)	163 (53.3)			
Asian American	0	34 (11.1)			
Latino	2 (10.5)	35 (11.4)			
Other/unknown	3 (15.8)	56 (18.3)			
Age at diagnosis, median (IQR)	13.6 (6.9, 15.2)	7.5 (3.9, 12.2)	1.13	(1.03, 1.23)	0.006
Age at radiation therapy, median (IQR)	14.0 (7.0, 15.0)	8 (4, 12)	1.13	(1.03, 1.23)	0.007
History of NF1	3 (15.8)	2 (0.7)	14.8	(4.2, 52.1)	<0.0001
Tumor type					
Medulloblastoma	3 (15.8)	44 (14.4)			
High-grade glioma	9 (47.4)	58 (19.0)			
Low-grade glioma	3 (15.8)	50 (16.3)			
Brainstem glioma	1 (5.3)	4 (1.3)			
Retinoblastoma	1 (5.3)	34 (11.1)			
ALL	0	8 (2.6)			
Others *	2 (10.5)	95 (31.0)			
Tumor location					
Frontal	1 (5.3)	56 (18.3)			
Parietal-occipital	1 (5.3)	20 (6.5)			

Characteristic	Patients with stroke (n=19) n (%)	Patients without stroke (n=306) n (%)	Univariate Cox proportional hazards regression analysis Hazard Ratio	95% CI	p-value
Temporal	7 (36.8)	37 (12.1)			
Posterior fossa	10 (52.6)	139 (45.4)			
Face	0	20 (6.5)			
Neck/spine	0	6 (2.0)			
Other †	0	28 (9.2)			
Dose of radiation therapy (Gy), mean (SD)	5938.9 (1067.4)	5394.5 (1275.2)			
Per 100 Gy			1.05	(1.01, 1.09)	0.02
Per 1000 Gy			1.64	(1.08, 2.47)	0.02
Cervical radiation	0	18 (5.9)	N/A		
Treatment with chemotherapy			0.83	(0.32, 2.18)	0.71
Treated	9 (47.4)	191 (62.4)			
Missing	2 (10.5)	11 (3.6)			

Abbreviations: Gy: gray; IQR: interquartile range; NF1: Neurofibromatosis 1; SD: standard deviation.

*Other tumor types include carcinoma, ependymoma, germinoma, meningioma, lymphoma, rhabdomyosarcoma, and sarcoma.

†Others include patients with leukemia (n=8) or brain tumors (n=20) for which location was not clearly specified.