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Authors

Nordstrom, Matthew
Felton, Erin
Sear, Katherine
et al.

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Large vessel arteriopathy after cranial radiation therapy in pediatric brain tumor survivors

Matthew Nordstrom, MD[a], **Erin Felton**[b], **Katherine Sear, MPH**[b], **Benita Tamrazi, MD**[c], **Joseph Torkildson, MD**[d], **Karen Gauvain, MD**[e], **Daphne A. Haas-Kogan, MD**[f], **Josephine Chen, PhD**[g], **Benedict Del Buono**[b], **Anuradha Banerjee, MD**[a,h], **David Samuel, MD**[i], **David Saloner, PhD**[j], **Bing Tian, MD**[j], **Erika Roddy, BA**[k], **Christopher Hess, MD, PhD**[j,b], **Heather Fullerton, MD, MAS**[a,b], and **Sabine Mueller, MD, PhD, MAS**[a,b,h]

[a]Department of Pediatrics, University of California, San Francisco [b]Department of Neurology, University of California, San Francisco [c]Department of Radiology, Children's Hospital of Los Angeles [d]Department of Pediatrics, UCSF Benioff Children's Hospital Oakland [e]Department of Pediatrics, Washington University, St. Louis, Missouri [f]Department of Radiation Oncology, Brigham and Woman's Hospital, Dana-Farber Cancer Institute, Boston Children's Hospital, Harvard Medical School [g]Department of Radiation Oncology, University of California, San Francisco [h]Department of Neurological Surgery, University of California, San Francisco [i]Department of Pediatrics, Valley Children's Hospital, Madera [j]Department of Radiology and Biomedical Imaging, University of California, San Francisco [k]School of Medicine, University of California, San Francisco

Abstract

Among childhood cancer survivors, increased stroke risk after cranial radiation therapy (CRT) may be caused by radiation-induced arteriopathy, but limited data exists to support this hypothesis.

Corresponding Author: Sabine Mueller MD PHD MAS, Department of Neurology, Neurosurgery and Pediatrics, University of California, San Francisco, Sandler Neuroscience Building, 675 Nelson Rising Lane, Room 402C, San Francisco, CA 94185, Phone: 415-502-7301 | Fax: 415-502-7299, sabine.mueller@ucsf.edu.

Matthew Nordstrom: Matthew.Nordstrom@ucsf.edu. Performed statistical analysis, interpretation of data, primary author of manuscript. Matthew Nordstrom reports no disclosures.

Erin Felton: Erin.Felton@ucsf.edu. Data collection and manuscript editing. Erin Felton reports no disclosures.

Katherine Sear: Katherine.Sear@ucsf.edu. Study design and data analysis. Katherine Sear reports no disclosures.

Benita Tamrazi: btamrazi@chla.usc.edu. Study design and data analysis. Benita Tamrazi reports no disclosures.

Joseph Torkildson: jtorkildson@mail.cho.org. Study design; data collection. Joseph Torkildson reports no disclosures.

Karen Gauvain: Gauvain_K@kids.wustl.edu. Study design; data collection. Karen Gauvain reports no disclosures.

Daphne A. Haas-Kogan: Dhaas-kogan@lroc.harvard.edu Study design and analysis. Daphne A. Haas-Kogan reports no disclosures.

Josephine Chen: JoChen@RadOnc.ucsf.edu. Data analysis. Josephine Chen reports no disclosures.

Benedict Del Buono: Benedict.Delbuono@ucsf.edu. Data collection and analysis. Benedict Del Buono reports no disclosures.

Anuradha Banerjee: Anu.Banerjee@ucsf.edu. Data collection. Anuradha Banerjee reports no disclosures.

David Samuel: DSamuel@valleychildrens.org. Data collection. David Samuel reports no disclosures.

David Saloner: David.Saloner@ucsf.edu. Data collection and analysis and editing of manuscript. David Saloner reports no disclosures.

Bing Tian: Bing.Tian@ucsf.edu. Data collection and analysis. Bing Tian reports no disclosures.

Erika Roddy: Erika.Roddy@ucsf.edu. Editing manuscript. Erika Roddy reports no disclosures.

Christopher Hess: Chris.Hess@ucsf.edu. Data collection, editing of manuscript. Christopher Hess reports no disclosures.

Heather Fullerton: Heather.Fullerton@ucsf.edu. Study design, data analysis, and writing manuscript. Heather Fullerton reports no disclosures.

Sabine Mueller: sabine.mueller@ucsf.edu. Study design, data analysis, and writing of manuscript. Sabine Mueller reports no disclosures.

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Herein we assess the timing and presence of cerebral arteriopathy identified by magnetic resonance angiography (MRA) after CRT in childhood brain tumor survivors. In a cohort of 115 pediatric brain tumor survivors, we performed chart abstraction and prospective annual follow up to assess the presence of large vessel cerebral arteriopathy by MRA. We identified 10 patients with cerebral arteriopathy. The cumulative incidence of arteriopathy five years post-CRT was 5.4% (CI 0.6–10%) and 10 years was 16% (CI 4.6–26%). One patient had an arterial ischemic stroke 2.4 years post-CRT in the distribution of a radiation-induced stenotic artery. We conclude that large vessel arteriopathies can occur within a few years of CRT and can become apparent on MRA in under a year.

Keywords

Stroke; Brain Tumor; MRI; Pediatric; Neurooncology

Introduction

Cranial radiation therapy (CRT) is an integral treatment for children with brain tumors despite conferring a dose-dependent increased risk of stroke[1–5]. Additionally, CRT has been associated with the development of large vessel cerebral arteriopathies, including moyamoya – progressive steno-occlusion of the large intracranial arteries[3,6–10]. However, the fact that dedicated vascular imaging is not routinely performed on a clinical basis has limited progress in better understanding these sequelae of CRT. Thus the incidence and timing of arteriopathy and the association with stroke in pediatric brain tumor survivors remains largely unknown, despite being critical to the development of stroke prevention strategies.

The underlying pathophysiology of radiation-induced arteriopathies is poorly understood, though there is evidence of carotid atherosclerosis in adults and children following radiation therapy of the neck[11,12]. New imaging protocols, such as vessel wall imaging (VWI) with magnetic resonance imaging (MRI) allows for characterization of pathologic changes of vessel walls. Post-contrast enhancement features on VWI are likely surrogates of inflammatory changes[13,14]. Detection of arterial inflammation or atherosclerotic disease prior to the onset of overt arteriopathy may act as an early imaging marker of disease and could indicate the use of therapeutic interventions such as anti-inflammatory agents.

To address this important gap in understanding the effects of CRT on pediatric brain tumor survivors, we evaluated a series of patients with magnetic resonance angiography (MRA) and VWI. We report the timing and cumulative incidence of radiation-induced cerebral arteriopathy.

Methods

Patient Characteristics

Patients are part of the ongoing Radiation Arteriopathy (RadArt) study, a multi-site cohort study of childhood cancer survivors that began enrollment in 2011[15]. Patients of any age are recruited with the following inclusion criteria for case enrollment: radiation therapy to the brain or neck at age ≤ 21 years, survival >1 year after diagnosis, and ability to undergo MRI.

Patients in the study are prospectively followed with the collection and central review of clinically obtained brain and cerebrovascular imaging that varies in frequency by institution. Participating institutions include University of California San Francisco (UCSF) Benioff Children's Hospitals Oakland and San Francisco, Valley Children's Hospital in Madera, California, and Washington University/St. Louis Children's Hospital in St. Louis, Missouri.

This analysis is based on 154 eligible patients enrolled into RadArt between October, 2011 and October, 2015. Patients without MR imaging post-CRT were excluded (n = 39) (Figure 1). The final analysis included 115 out of 154 eligible patients.

Data Collection

Trained research assistants used standardized data collection tools to perform chart abstraction. Data audits were performed to ensure internal consistency and correct data collection. We collected detailed demographic, clinical, tumor and radiation related information for each subject. Variables extracted included age at initiation of CRT, radiation dose and field, sex, gender, race, presence of known genetic disorders, tumor type and location, surgical intervention, type of MR imaging as well as presence of stroke symptoms. Chemotherapies were determined to be associated with vascular injury in cases where agents had previously reported risk for stroke or vasculitis. These chemotherapies included: adriamycin, avastin, carboplatin, cisplatin, cyclophosphamide, etoposide, ifosfamide, irinotecan, isotretinoin, methotrexate and vorinostat. Patients were evaluated prospectively starting in October 2011 with scheduled interviews every six months to assess for presence of stroke symptoms. MR imaging prior to study enrollment was obtained if deemed clinically necessary per the providing physician, with the primary indication being routine screening for disease progression and vasculopathy following radiation therapy. Following study enrollment, participants received regular MR imaging, with most patients receiving an MRA annually. Total radiation dose was calculated as the highest dose delivered either as whole brain or focal boost radiation. The arteriopathy was determined to be in the field of radiation for focal radiation through comparison of tumor and arteriopathy location. MR angiography data were procured from outside institutions when available. VWI data were available only for subjects evaluated at UCSF Benioff Children's Hospital San Francisco.

Vessel Wall Imaging

Vessel Wall Imaging was performed using a 3D CUBE T1, a volumetric, variable flip angle fast spin echo sequence, on a 3T GE Discovery 750 MRI scanner. Image acquisition was performed with whole brain coverage prescribed with a sagittal volume using isotropic spatial resolution that permitted reformations in arbitrary planes. The imaging parameters were: TR/TE = 600ms/8ms; ETL = 20; acceleration factor = 3; and number of averages, 1. The FOV was 200 × 180 × 120 mm^3 at a matrix of 256 × 230 × 140 for an acquired voxel volume of 0.8 × 0.8 × 0.8 mm^3 (scan time, 5 min 40sec). Images were acquired pre- and post-contrast with a single dose of gadolinium chelate (Gadavist).

Standard Protocol Approvals, Registrations and Patient Consents

This study has local IRB approval for prospective and retrospective study of human subjects. Written informed consent, and assent when appropriate, was obtained for all patients or guardians of patients in the study.

Magnetic Resonance Imaging Evaluation

All MRA data were reviewed by a board certified radiologist with certificate of additional qualification in neuroradiology (BT), blinded to patient identity and clinical characteristics. MRA data were evaluated for presence, number and location of arterial stenosis or occlusion. Vascular abnormalities thought to represent congenital variants or compression by the tumor were not classified as arteriopathies. All arteriopathies identified were confirmed by secondary review (SM, HF). Previous scans were reviewed to determine the first radiographic appearance. When available, vessel-wall images were interpreted by study neuroradiologist (BT) for the presence or absence of arterial wall enhancement, thinning or thickening. MR imaging was not performed according to a standardized protocol and differed according to the institution and year of origin.

Statistical analysis

Chi-squared tests were used to determine differences between the sample of patients with and without arteriopathy. Kaplan-Meier survival analysis techniques were used to determine the cumulative incidence of radiographically-defined arteriopathies. The primary outcome was time to first radiographic appearance of intracerebral arteriopathy, calculated from the start of CRT to the date of first MRA with evidence of arteriopathy. Censoring criteria were date of first MRA with evidence of arteriopathy (the failure event) or last follow-up MRA without evidence of arteriopathy. Given that actual time to arteriopathy development cannot be known, we used detection date to calculate incidence rates.

Results

Patient Characteristics

For the 115 patients included in this analysis, the median age at time of CRT was 8.4 years (interquartile range (IQR), 5.0–11.7). Patients had a median follow-up time (defined as time from CRT to last MRA) of 4.6 years (IQR, 2.9–8.6). The median time from CRT to first MRA was 3.9 years (range, 0.04–26.1) and the median interval between MRA scans was 1.4 years (range, 0.16–15) (Table 1 and Figure 2). Patients in our cohort received a median radiation dose of 54 Gy (IQR, 54–55.8). The percentage of patients with an arteriopathy and without an arteriopathy who were exposed to chemotherapy that is associated with vascular injury was 50% and 45%, respectively (p-value, 0.92). None of the patients in the cohort had hypertension, diabetes mellitus or hyperlipidemia prior to diagnosis and treatment.

Large Vessel Arteriopathy

In the cohort of 115 study participants, we identified 10 patients (8.7%) with a large vessel cerebral arteriopathy by MRA (Figure 2 and Table 2). Baseline demographics of the patients with cerebral arteriopathy show that most were female (n = 8, 80%) and carried a diagnosis

of a low-grade glioma (n = 4, 40%). Median age at time of CRT was 6.3 years (IQR, 4.5–8.5) compared to 9.0 years (IQR, 5.0–11.9) for those without an arteriopathy. All 10 patients received a total radiation dose greater than 50 Gy to the whole brain and/or tumor bed. The radiation field for these patients included the Circle of Willis and the involved arteries, though the exact dose to the region of arteriopathy could not be determined. Three of the 10 patients with arteriopathy received proton beam therapy, compared to only one of the 105 patients without arteriopathy. One patient within the arteriopathy group had neurofibromatosis type 1 (NF1) while there were three patients with NF1 in the non-affected group. Five of the 10 patients with arteriopathy had moyamoya, with four displaying Suzuki stage 1 moyamoya with only narrowing of the distal ICA, while one patient had clear collateral formation (Table 1 and 2)[16].

Of the patients with arteriopathies, three had a prior normal MRA for comparison. The remaining seven patients' arteriopathies were found on first MRA. These arteriopathies were determined to be most consistent with a radiation-induced arteriopathy on the basis of focality of disease, localization to the radiation field and absence of other findings to suggest dissection, occlusive disease or widespread vasculopathy. The median latency of arteriopathy diagnosis (defined as the time from CRT to first abnormal MRA) was 4.8 years post-CRT (IQR, 2.4–7.8) (Table 2). The cumulative incidence of arteriopathy at five years following CRT was 5.4% (95% CI 0.6–10%) and at 10 years was 16% (95% CI 4.6–26%) (Figure 3). Of the three patients with prior normal MRA data, one did not have regular imaging after CRT resulting in a 12-year gap between the last normal MRA and the subsequent MRA with evidence of arteriopathy. The other two patients were found to have evidence of arteriopathy on imaging performed 9 and 10 months following their last prior normal MRA (Figure 2 and 4). For the patients with no prior normal MRA, the time to detection of arteriopathy ranged from 1.4 to 8.5 years post-CRT.

Vessel Wall Imaging

Four of the subjects with an identified arteriopathy had VWI performed, of which three had 3D images available for review. Patient 2 demonstrated a well-defined focal narrowing of the lumen of the right middle cerebral artery with eccentric thickening of the wall with more pronounced thickening on the inferior aspect of the artery. The lesion is best delineated on the post-contrast study where there is noticeable enhancement of the vessel wall (Figure 4). This lesion was identified on this patient's first VWI, 1.4 years after identification of an arteriopathy in the same vessel. The three other subjects showed no other evidence of arterial wall abnormalities on VWI.

Stroke

Two patients (2%) in the study population had a confirmed stroke that occurred following CRT. One patient had a hemorrhagic stroke, possibly secondary to a bleeding cavernous malformation, 6.6 years following CRT and had no evidence of arteriopathy on MRA. The other patient (patient 4) had an acute ischemic stroke 2.4 years following CRT. The stroke was in the distribution of the stenotic artery found on MRA (Table 2). This patient had subjective symptoms suggestive of transient ischemic attack (TIA) and eventually had a completed stroke event 11 days after first TIA in the absence of prophylactic therapy.

Following the stroke, this patient was started on aspirin and has been maintained on antiplatelet therapy since. One of the other nine patients with arteriopathies experienced symptoms concerning for a TIA although a complex migraine disorder could not be excluded - prompting the MRA that identified the arteriopathy. The other 8 were identified with a routine screening MRA and have not reported symptoms concerning for cerebral ischemia. Of the 10 patients with arteriopathies, half of them have been started on prophylactic aspirin.

Discussion

In this multi-center prospective cohort study, we found that children treated with CRT for intracranial tumors are at risk of developing a large vessel arteriopathy and that this radiation-induced arteriopathy can develop within the first years after completion of radiation therapy. Three of the 10 patients with arteriopathy were treated with proton beam therapy, although an association cannot be concluded.

Despite the known risk of arteriopathy following CRT, our understanding of the cumulative incidence and association with stroke remains limited[7–11,17]. We know that children with arteriopathy have increased risk for stroke and recurrent stroke, with a 5-year cumulative recurrence rate of 66%[8,9,18].

Several factors have limited our progress, including that dedicated vascular imaging is not routinely performed on a clinical basis. In our study population of patients evaluated with MRA, one in twenty patients developed an arteriopathy by five years following CRT. Two previous studies have reported on the cumulative incidence of arteriopathy following CRT, though they have looked only at moyamoya rather than other focal arteriopathies in the anterior, middle and/or posterior cerebral arteries. They reported dramatically different values, with one study reporting the seven year cumulative incidence to be 7% in a pediatric brain tumor population while the other reporting an eight year cumulative incidence of 0.46% in a pediatric acute lymphoblastic leukemia (ALL) population – a difference that might be attributed to the lower dose of CRT children with ALL receive[8,9]. The reported cumulative incidence in our study is similar to what has been identified in the previous study using a brain tumor population[9]. The slightly higher cumulative incidence in this study is likely due to the use of MRA as dedicated vascular imaging and inclusion of all large vessel arteriopathies, not just moyamoya syndrome which only account for five of the 10 subjects with arteriopathies in our data set.

Higher radiation doses have also been associated with an earlier time to intracranial arteriopathy in the pediatric brain tumor population[9,17]. The majority of large vessel arteriopathies, including moyamoya, occur in the first five to six years following CRT[7,9,17]. Our study cohort had a latency time to detection of arteriopathy that was slightly longer, with the majority of patients being diagnosed by 7.8 years post-CRT. However, we suspect the true latency time to be shorter than 7.8 years since half of the patients with arteriopathies did not receive an MRA until six to 12 years following CRT. Additionally, we had a relatively low proportion of patients with NF1 compared to prior studies, a known risk factor for arteriopathies[9]. Despite this longer latency, our data show that arteriopathies can develop

over the span of months following a normal MRA and in the absence of symptoms. This suggests that follow-up imaging every six to 12 months may be indicated to ensure prompt detection of arteriopathy.

Three of the 10 patients with arteriopathy received proton beam therapy, compared to only one of the 105 patients without arteriopathy. Additionally these 3 patients developed arteriopathies sooner than anticipated with all of them diagnosed before the median latency time to detection of 4.8 years. While there are limited data on the long-term vascular effects of proton beam therapy for brain tumors, there is a case report of moyamoya following proton beam radiation and evidence of radiation vasculopathy in eyes following proton beam therapy for ocular metastases[19,20]. Unfortunately, this study was not powered to determine a risk difference between the two radiation therapy modalities. In addition to proton beam therapy, there is data to suggest that children with brain tumors treated with brachytherapy may also be at an increased risk of developing vasculopathy[21]. These data in conjunction with concerns associated with proton beam therapy suggest that more research is needed to evaluate the risk of vasculopathy following other forms of radiation therapy.

We found one patient with a well-documented middle cerebral artery stenosis following CRT that had transient ischemic attacks followed by an acute ischemic stroke in the distribution of the affected vessel. This represents an example of a potential causal pathway that explains the known elevated risk of stroke and recurrent stroke in patients with arteriopathy[1,3–5,22]. The one patient's hemorrhagic stroke without evidence of arteriopathy may have been secondary to cavernous malformations which can hemorrhage at a rate of 2% per year, though there was no evidence of cavernous malformations on prior imaging[23,24]. The absence of symptoms in the remaining nine patients with arteriopathy indicates they have sufficient collateral blood flow or insufficient narrowing of the vessel. The subset of these nine patients followed at Benioff Children's Hospital San Francisco are being monitored closely for symptoms suggestive of stroke, evaluated and advised regarding atherosclerotic risk factors including hyperlipidemia, smoking and hypertension. Five patients were started on prophylactic aspirin following identification of arteriopathy based on the recommendation of the treating team. We know that patients with arteriopathies could be at risk of developing a late-occurring stroke and may benefit from initiating atherosclerotic risk reducing therapies[3].

To further our understanding of the underlying pathophysiology involved in the formation of large vessel arteriopathies, VWI was attempted when possible to allow for direct characterization of pathologic changes of the vessel wall. VWI allows for direct visualization of post-contrast enhancement features that are putative surrogates of inflammatory changes, with some data to suggest these changes can be seen in adults with radiation induced arteriopathy[13,25]. We know that several animal studies have shown that radiation therapy leads to inflammatory changes in a dose-and time-dependent manner[26,27]. Using PET/CT imaging, evidence of radiation-induced inflammation has also been reported in neck vessels in adult head and neck cancer patients[28]. While MRA studies (and indeed catheter-injected angiography studies) are valuable in delineating changes in the caliber of the vascular lumen, they provide little or no information on the status of the vessel wall. State-of-the-art VWI studies can demonstrate the presence of vessel wall thickening and

indicate whether the lesion is eccentric and whether it enhances post-administration of gadolinium-based agents. The presence of vessel wall thickening in the region of a CRT-induced arteriopathy, as shown for one of the subjects in this study, suggests imaging modalities such as VWI may offer the promise of better understanding the clinical significance of a given lesion. To expand our understanding of the temporal relationship between vessel wall changes and arteriopathies, regular VWI imaging following CRT would be required.

The key limitations in our study include the inability to determine the exact time of arteriopathy formation, inconsistent availability of VWI and the relatively short prospective follow-up period thus far. The presence of arteriopathy can only be determined at the time of imaging and the limited availability of prior normal MRA inhibits the ability to definitively state that the arteriopathies occurred following CRT and prevents accurate time-to-event analysis. Despite that limitation, we believe these arteriopathies to have developed following CRT since these patients had no other reason to have developed an arteriopathy. Due to the relative short follow up, we were not able to better assess an association between arteriopathy and stroke. Further, as proton beam therapy becomes more easily accessible, future studies will be significantly powered to determine if the risk of radiation-induced arteriopathy is influenced by the type of radiation therapy.

Conclusion

We conclude that large vessel arteriopathies can occur within a few years of CRT and can become apparent on MRA in under a year and thus regular MRA screening may be warranted. A better understanding of the timing and mechanisms of arteriopathy formation is critical as it may present an opportunity for primary stroke prevention in the pediatric brain tumor survivor population.

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References

1. 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]
2. Bowers D, 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(33):5277–5282. [PubMed: 17088567]
3. Mueller S, Fullerton HJ, Stratton K, et al. Radiation, Atherosclerotic Risk Factors, and Stroke Risk in Survivors of Pediatric Cancer: A Report From the Childhood Cancer Survivor Study. Int J Radiat Oncol Biol Phys. 2013; 86(4):649–655. [PubMed: 23680033]
4. Mueller S, Sear K, Hills NK, et al. Risk of First and Recurrent Stroke in Childhood Cancer Survivors Treated With Cranial and Cervical Radiation Therapy. Int J Radiat Oncol Biol Phys. 2013; 86(4):643–648. [PubMed: 23623405]
5. Fullerton HJ, Stratton K, Mueller S, et al. Recurrent stroke in childhood cancer survivors. Neurology. 2015; 85(12):1056–1064. [PubMed: 26311747]

6. Bitzer M, Topka H. Progressive cerebral occlusive disease after radiation therapy. Stroke. 1995; 26(1):131–136. [PubMed: 7839383]
7. Desai SS, Paulino AC, Mai WY, Teh BS. Radiation-induced moyamoya syndrome. Int J Radiat Oncol Biol Phys. 2006; 65(4):1222–1227. [PubMed: 16626890]
8. Kikuchi A, Maeda M, Hanada R, et al. Moyamoya syndrome following childhood acute lymphoblastic leukemia. Pediatr Blood Cancer. 2007; 48(3):268–272. [PubMed: 16615044]
9. Ullrich NJ, Robertson R, Kinnamon DD, et al. Moyamoya following cranial irradiation for primary brain tumors in children. Neurology. 2007; 68(12):932–938. [PubMed: 17372129]
10. Omura M, Aida N, Sekido K, Kakehi M, Matsubara S. Large intracranial vessel occlusive vasculopathy after radiation therapy in children: clinical features and usefulness of magnetic resonance imaging. Int J Radiat Oncol Biol Phys. 1997; 38(2):241–249. [PubMed: 9226309]
11. Meeske KAP, Siegel SEM, Gilsanz VM, et al. Premature Carotid Artery Disease in Pediatric Cancer Survivors Treated With Neck Irradiation. Pediatr Blood Cancer. 2009 Nov 4.53:615–621. [PubMed: 19533651]
12. Cheng SWK, Wu LLH, Ting ACW, Lau H, Lam LK, Wei WI. Irradiation-induced extracranial carotid stenosis in patients with head and neck malignancies. Am J Surg. 1999; 178(4):323–328. [PubMed: 10587192]
13. Aoki S, Hayashi N, Abe O, et al. Radiation-induced arteritis: thickened wall with prominent enhancement on cranial MR images report of five cases and comparison with 18 cases of Moyamoya disease. Radiology. 2002; 223(3):683–688. [PubMed: 12034935]
14. Küker W, Gaertner S, Nägele T, et al. Vessel Wall Contrast Enhancement : A Diagnostic Sign of Cerebral Vasculitis. Cerebrovasc Dis. 2008; (26):23–29. [PubMed: 18511868]
15. Roddy E, Sear K, Felton E, et al. Presence of cerebral microbleeds is associated with worse executive function in pediatric brain tumor survivors. Neuro Oncol. 2016 Feb.18 now163.
16. Suzuki J, Kodama N. Moyamoya disease–a review. Stroke. 1983; 14(1):104–109. [PubMed: 6823678]
17. Wang C, Roberts KB, Bindra RS, Chiang VL, Yu JB. Delayed Cerebral Vasculopathy Following Cranial Radiation Therapy for Pediatric Tumors. Pediatr Neurol. 2014; 50(6):549–556. [PubMed: 24739378]
18. Fullerton H, Wu Y, Sidney S, Johnston S. Risk of Recurrent Childhood Arterial Ischemic Stroke in a Population-Based Cohort: The Importance of Cerebrovascular Imaging. Pediatrics. 2007; 119(3): 495–501. [PubMed: 17332202]
19. Zwagerman N, Foster K, Jakacki R, Khan F, Yock T, Greene S. The development of Moyamoya syndrome after proton beam therapy. Pediatr Blood Cancer. 2014; 61(8):1490–1492. [PubMed: 24501091]
20. Kamran, Sophia C., Collier, John M., Lane, Anne Marie, et al. Outcomes of Proton Therapy for the Treatment of Uveal Metastases. Int J Radiat Oncol Biol Phys. 2014; 90(5):1044–1050. [PubMed: 25442038]
21. Tacke U, Karger D, Spreer J, Berlis A, Nikkhah G, Korinthenberg R. Incidence of vasculopathy in children with hypothalamic/chiasmatic gliomas treated with brachytherapy. Child's Nerv Syst. 2011; 27(6):961–966. [PubMed: 21416133]
22. MacKay MT, Wiznitzer M, Benedict SL, Lee KJ, DeVeber GA, Ganesan V. Arterial ischemic stroke risk factors: The international pediatric stroke study. Ann Neurol. 2011; 69:130–140. [PubMed: 21280083]
23. Gross B, Lin N, Du R, Day A. The natural history of intracranial cavernous malformations. Neurosurg Focus. 2011; 30(6):E24. [PubMed: 21631226]
24. Al-Holou WN, O'Lynnger TM, Pandey AS, et al. Natural history and imaging prevalence of cavernous malformations in children and young adults. J Neurosurg Pediatr. 2012; 9(2):198–205. [PubMed: 22295927]
25. Mandell DM, Mossa-Basha M, Qiao Y, et al. Intracranial Vessel Wall MRI: Principles and Expert Consensus Recommendations of the American Society of Neuroradiology. AJNR Am J Neuroradiol. 2016 [Epub ahead of print].

26. Patties I, Haagen J, Dörr W, Hildebrandt G, Glasow A. Late inflammatory and thrombotic changes in irradiated hearts of C57BL/6 wild-type and atherosclerosis-prone ApoE-deficient mice. Strahlenther Onkol. 2015; 191(2):172–179. [PubMed: 25200359]

27. Hoving S, Heeneman S, Gijbels MJJ, et al. Irradiation induces different inflammatory and thrombotic responses in carotid arteries of wildtype C57BL/6J and atherosclerosis-prone ApoE −/− mice. Radiother Oncol. 2012; 105(3):365–370. [PubMed: 23245647]

28. Wang Y-C, Hsieh T-C, Chen S-W, Yen K-Y, Kao C-H, Chang K-C. Concurrent Chemo-Radiotherapy Potentiates Vascular Inflammation: Increased FDG Uptake in Head and Neck Cancer Patients. JACC Cardiovasc Imaging. 2013; 6(4):512–514. [PubMed: 23579012]

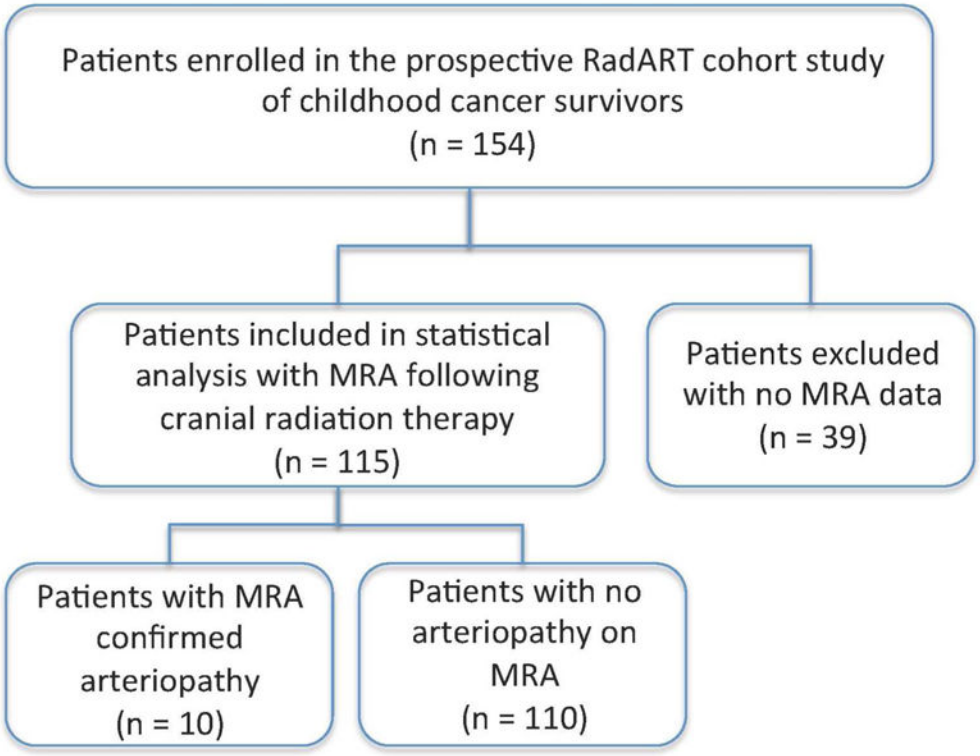

Figure 1. Study Inclusion Flow Diagram

Flow diagram of the recruitment and selection of the 115 subjects for analysis

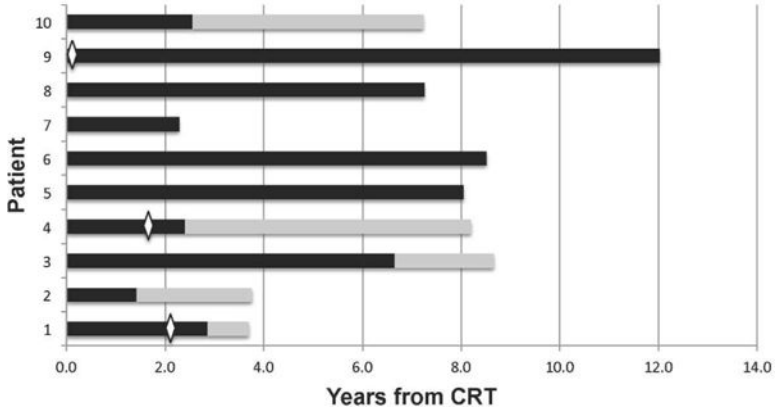

Figure 2. Latency Time to Arteriopathy

Black bars indicate the latency time to arteriopathy diagnosis from start of CRT. Grey bar indicates the added follow-up time from start of CRT. ◊ indicates the time of last normal MRA data.

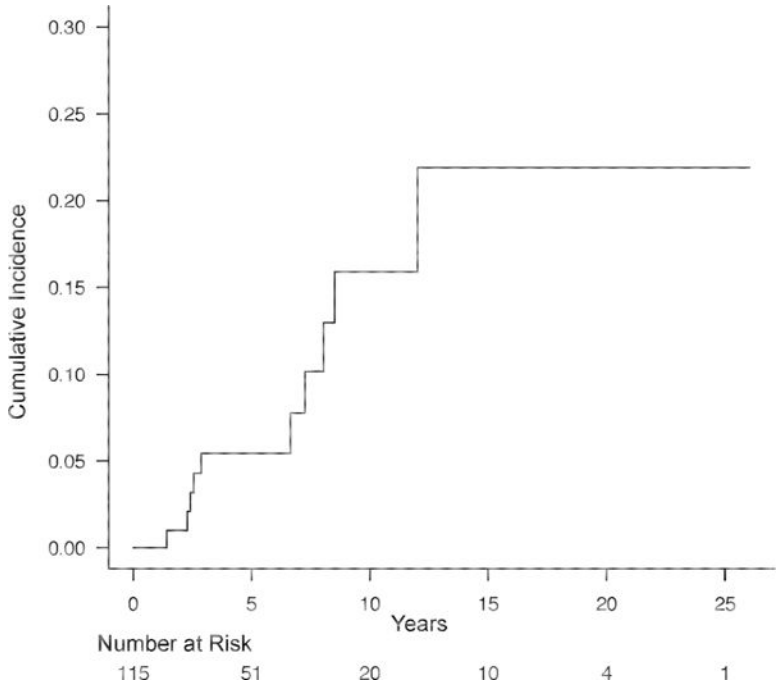

Figure 3. Cumulative incidence of arteriopathy after cranial radiation therapy in pediatric brain tumor patients

Kaplan-Meier survival analysis. Years measured from start of CRT to either date of MRA with evidence of arteriopathy or last follow-up MRA without evidence of arteriopathy.

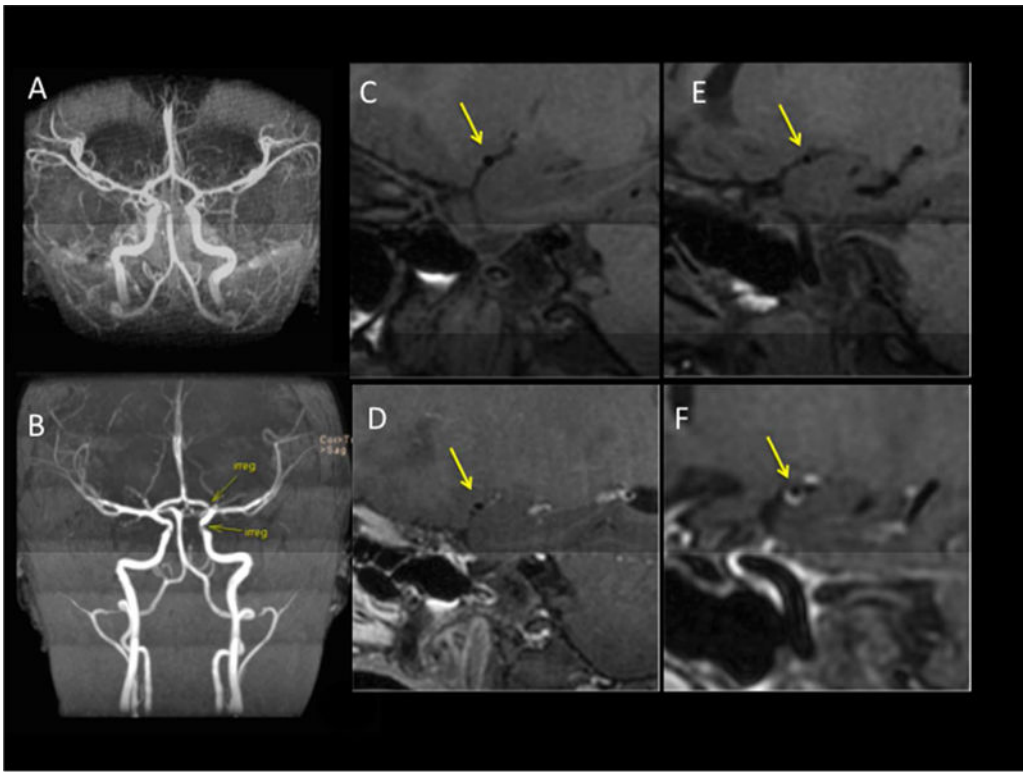

Figure 4. Imaging Evidence of CRT induced Arteriopathy

A and B. Magnetic resonance angiography (MRA) of patient 9 showing formation of arteriopathy after CRT. (A) No evidence of vessel stenosis. (B) Narrowing of distal left internal carotid artery and A1 segment of left anterior cerebral artery. C and D. Transverse cross-section of left MCA of patient 2 (Table 2) showing normal vasculature in pre-contrast (C) and post-contrast (D) VWX. E and F. Transverse cross-section of right MCA of patient 2 showing asymmetric wall thickening in pre-contrast (D) and post-contrast (E) VWX. Data obtained on a 3 Tesla magnet as 3 dimensional data and projected in 2 dimensions.

Table 1

Patient Characteristics of Study Cohort

Characteristic	Patients with Arteriopathy (n = 10) n (%)	Patients without Arteriopathy (n = 105) n (%)	P-Value
Female gender	8 (80%)	48 (46%)	0.0382
Race			
African American	2 (20%)	12 (10%)	
White	6 (60%)	62 (54%)	
Latino	0	29 (25%)	
Asian	1 (10%)	8 (7%)	
Other/Unknown	1 (10%)	4 (4%)	
Type of tumor			
High grade glioma	0	9 (8%)	
Low grade glioma	4 (40%)	18 (16%)	
Medulloblastoma	1 (10%)	30 (26%)	
sPNET	1 (10%)	7 (6%)	
Ependyoma	1 (10%)	20 (18%)	
Germinoma		12 (10%)	
Craniopharyngioma	1 (10%)	4 (3%)	
Other	2 (20%)	15 (13%)	
Age at cancer diagnosis, median (IQR)	3.1 (2.5–6.0)	7.2 (3.8–10.6)	
Age at CRT, median (IQR)	6.3 (4.5–8.5)	8.4 (4.9–11.7)	
Total radiation dose (Gy), median (IQR)	54 (54–55)	54 (54–55.8)	
Follow-up time, median (IQR)	8.1 (4.6–8.6)	4.6 (2.9–8.6)	
Proton Beam	3 (30%)	1 (1%)	<0.0001
Neurofibromatosis 1	1 (10%)	3 (3%)	0.2388
Chemotherapy associated with vascular injury	5 (50%)	47 (45%)	0.9203
Surgery	8 (80%)	98 (94%)	0.09244

Abbreviations: IQR, interquartile range; sPNET, supratentorial primitive neuro-ectodermal tumor

Table 2

Patient Characteristics of those with arteriopathy

Patient	Gender	Cancer type	Age at CRT (Y)	CRT dose (Gy)	Radiation field	Arteriopathy	Time to arteriopathy detection (Y)
1[ac]	Female	sPNET	3.5	50.4	Frontal	L ACA: A1	2.9
2[c]	Male	Ependyoma	6.3	59.4	Midbrain, Frontal	Distal R ICA R MCA: M1 R ACA: A1	1.4
3	Female	Low grade glioma	10.0	54	Optic Pathway	Distal L ICA	6.6
4[abc]	Female	Meningioma	9.0	54	HPA, Temporal, Posterior fossa	R MCA: M1	2.4
5	Female	Medulloblastoma	6.3	55.8	Midbrain, Posterior fossa	Bilateral MCA: M1 and M2	8.0
6	Female	Low grade glioma	6.3	54	Optic pathway, HPA	L ACA: A1	8.5
7	Male	Mixed malignant glioma	8.9	59.4	Frontal	L ACA: A1 L MCA: M1	2.3
8	Female	Craniopharyngioma	3.1	54	HPA, Suprasellar	Bilateral distal ICA L MCA: Moyamoya R MCA: M1 L ACA: A1	7.3
9[a]	Female	Low grade glioma	5.4	54	Optic pathway	Distal L ICA L ACA: A1	12.0
10	Female	Low grade glioma	4.2	50.4	Whole brain	Distal ICA Bilateral ACA and MCA	2.6

Abbreviations: ACA, anterior cerebral artery; CRT, Cranial Radiation Therapy; HPA, hypothalamic-pituitary axis; ICA, internal carotid artery; MCA, middle cerebral artery; sPNET, supratentorial primitive neuro-ectodermal tumor

Definitions: A1, anterior cerebral artery from origin to anterior communicating artery; M1, middle cerebral artery from origin to bi/trifurcation; M2, middle cerebral artery from bi/trifurcation to circular sulcus of insula

[a]Patients with prior normal MRA data

[b]Patients with stroke

[c]Patients received proton beam therapy