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Characteristics of Radiation-Related Intracranial Aneurysms: A Multicenter Retrospective Study

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ABSTRACT

BACKGROUND AND PURPOSE: Intracranial aneurysms, a rare complication of radiation therapy, have been reported mainly in case reports or case series. We performed a multicenter, retrospective cohort study to investigate the characteristics of radiation-induced intracranial aneurysms.

MATERIALS AND METHODS: Data on 2641 patients with intracranial aneurysms were retrospectively collected from 3 hospitals between January 2005 and June 2014. An additional 1519 patients were recruited from a single center between July 2014 and March 2020. Aneurysms in patients with a history of radiation therapy for at least 6 months were defined as radiation-related aneurysms. Patients' demographic profiles, clinical characteristics, and aneurysm parameters detected on CTA were compared between radiation-related and control groups.

RESULTS: Of the 4160 patients, the average age was 57.9 (SD, 13.5) years, 2406 (57.8%) were women, 477 (11.5%) had multiple aneurysms, 3009 (72.3%) had SAH, and 34 (0.8%) had radiation-related aneurysms. The male-to-female ratio in the radiation-related group was significantly higher than that in the control group (2.4:1 versus 0.72:1, $P = .001$). The mean age of the radiation-related group was significantly younger than in the control group (51.4 [SD, 15.0] years versus 58.2 [SD, 13.5] years, $P = .003$). More patients in the radiation-related group presented with SAH than in the control group (without age and sex matching, 88.2% versus 72.2%, $P = .037$; with age and sex matching, 88.2% versus 58.8%, $P = .006$). Of the 4813 intracranial aneurysms, only 43 (0.9%) aneurysms were categorized as in the radiation-related group, whereas 4770 (99.1%) aneurysms constituted the control group. Compared with the control group, there was a significantly higher proportion of sidewall aneurysms (46.5% versus 32.3%, $P = .048$) and a predilection for aneurysms involving the ICA and posterior circulation arteries (72.1% versus 52.2%, $P = .046$) in the radiation-related group.

CONCLUSIONS: Compared with the control group, radiation-related aneurysms are more prone to occur in men and young patients, with a higher percentage of sidewall aneurysms located in the ICA and posterior circulation arteries. Furthermore, SAH is highly prevalent in patients with radiation-induced aneurysms, indicating that dedicated screening for aneurysms after radiation therapy is necessary, but further studies are needed to determine when and how to screen.

Radiation therapy is one of the mainstay treatment modalities for head and neck tumors, including nasopharyngeal carcinoma and medulloblastoma.[1,2] Nasopharyngeal carcinoma is characterized by a distinct geographic distribution and is particularly prevalent in East and Southeast Asia.[1,3] Medulloblastoma is an ordinary childhood CNS tumor.[4] Clinicians can precisely deliver effective therapeutic doses to the target zone for patients with head and neck tumors while preserving adjacent functionally important tissues using modern devices. Nevertheless, radiation therapy fields often encompass the skull base neurovascular structures,[1,4,5] and attendant radiation-related vasculopathies may be unavoidable due to the destructive effects on arteries of irradiation.[6-8]

The short-term sequelae of radiation have been extensively described during the past century, but long-term complications of radiation therapy were not well-understood.[6,7,9,10] With the improvement of radiation therapy technology and comprehensive treatment, there has been a remarkable increase in the survival rates of patients with head and neck cancer. With this increase in life span, clinicians have had the opportunity to study potential delayed effects of radiation therapy, such as cognitive decline, hearing impairment, secondary cancers, stroke, and vascular diseases,[2,4,6,7] which may require specific monitoring and screening.

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From the Department of Diagnostic Radiology and Nuclear Medicine (Z.-Q.H., W.-J.Y.), University of Maryland, Baltimore, Maryland; Departments of Neurosurgery (G.X.), and Neurology (Z.Y.), and Medical Image Center (J.-W.Z., X.-W.Z.), Yuebei People's Hospital, Shantou University Medical College, Shantou, Guangdong Province, China; Department of Radiology (H.Y.), The Affiliated Hospital of Jining Medical University, Jining, Shandong Province, China; Department of Radiology (J.-W.W.), Fujian Provincial Hospital, Provincial Clinic Medical College of Fujian Medical University, Fuzhou, Fujian Province, China; and Department of Radiology (S.-S.L.), The First Affiliated Hospital of Guangxi Traditional Chinese Medical University, Nanning, Guangxi Province, China.

Please address correspondence to Xin-Wei Zhou, MD, Yuebei People's Hospital, 133 Huiming Rd, Shaoguan, 512025, China; e-mail: xinwe.2019@gmail.com

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The delayed vascular diseases include atherosclerosis, cavernous malformation, and intracranial aneurysm, but previous studies mainly focused on the risk of intracranial atherosclerosis.[4,10] Intracranial aneurysm is one of the most common vascular diseases,[7] but an aneurysm following radiation therapy is a rare complication and less commonly recognized, sometimes leading to a catastrophic event of spontaneous SAH.[5,6] Despite the scarcity of reported cases, previous reports concluded that various radiation therapy methods can cause aneurysms, including external beam radiation therapy, gamma knife surgery, and brachytherapy,[5,7] as well as the histopathologic features of radiation-related aneurysms, including irregular fibrous thickening of the media and intima with smooth-muscle loss, necrosis of the media with lipid-laden macrophages, and mononuclear cell infiltration within the intima and media wall of the aneurysm.[9,11] However, there is limited information available in the literature about the clinical characteristics of patients with radiation-related aneurysms, and previous studies on such aneurysms mostly consisted of case reports that lack statistical analysis with a comparison group. We, therefore, conducted this retrospective cohort study to explore the unique characteristics of the radiation-related aneurysm by comparing it with a cohort.

MATERIALS AND METHODS

Patient Selection and Data Collection

This retrospective study was approved by the institutional review board (Yuebei People's Hospital), and patient informed consent was waived due to the study design that entailed no diagnostic tests or treatment. Patients who were diagnosed with intracranial aneurysms by CTA with at least 64 sections were recruited. Patient exclusion criteria for the study were the following: 1) an insufficient clinical data set and image data set on record; 2) fusiform, traumatic, or mycotic aneurysms; and 3) an intracranial aneurysm related to arteriovenous malformation or comorbidity with Moyamoya disease. Patients were dichotomized into the radiation-related aneurysm group and control group. The inclusion criteria for the radiation-related aneurysm group were the following: 1) a previous diagnosis of head and neck tumor with a history of radiation therapy, and 2) at least a 6-month time interval between radiation therapy and a diagnosis of an intracranial aneurysm. Patients with aneurysms without a history of radiation therapy constituted the control group.

Among all patients with intracranial aneurysms, 2641 consecutive patients were retrospectively included from 3 hospitals (Yuebei People's Hospital, The Second Affiliated Hospital of Guangzhou Medical University, and Zhujiang Hospital) from January 2005 to June 2014, as previously described,[12] and the following 1519 patients were recruited consecutively from a single center (Yuebei People's Hospital) between July 2014 and March 2020. The demographic profiles and cerebrovascular risk factors (including diabetes, hypertension, and hyperlipidemia) were collected for this study through chart reviews on each site. Diabetes was defined as a random serum glucose level of ≥11.1 mmol/L, glycosylated hemoglobin level of ≥5.8%, or the use of antidiabetic medication. Hypertension was defined as systolic blood pressure of ≥140 mm Hg and/or diastolic blood pressure of ≥90 mm Hg. Hyperlipidemia was described as a total cholesterol of >240 mg/dL, high-density lipoprotein cholesterol of <40 mg/dL, or the use of cholesterol-lowering medication.

Table 1: Characteristics of the patients (*n* = 4160)

Characteristics	Radiation-Related Group (No.) (%)	Control Group (No.) (%)	*P* Value
Male	24 (70.6)	1730 (41.9)	.001
Age (mean) (yr)	51.4 (SD, 15.0)	58.2 (SD, 13.5)	.003
Hyperlipidemia	3 (8.8)	348 (8.4)	NS
Hypertension	15 (44.1)	2187 (53.0)	NS
Diabetes	2 (5.9)	281 (6.8)	NS
Multiple aneurysms	7 (20.6)	470 (11.4)	NS
Presented with SAH	30 (88.2)	2979 (72.2)	.037

Note:—NS indicates not significant.

CTA Analysis

All patients underwent CTA with an FOV of 160 mm and a section thickness of 0.5 or 0.625 mm reconstructed at 0.5 or 0.625 mm. As previously described, the sites of the aneurysms were categorized by 4 locations: 1) the anterior cerebral artery (including the anterior communicating artery and anterior cerebral artery); 2) the MCA; 3) the ICA, including the ICA terminus, posterior communicating artery, cavernous ICA; and 4) the posterior circulation arteries (including the posterior cerebral artery and the vertebrobasilar system).[12,13] The aneurysm type was dichotomized into bifurcation aneurysms if they were located at the parent artery bifurcations in the cerebral vasculature based on CTA and sidewall aneurysms if they originated from only 1 parent vessel without an artery emerging from the top of the dome.[13] The aneurysm wall was defined as an irregular wall if the blebs, lobes, or protrusions were present on the wall. The size of the aneurysm was measured as in our previous report.[14] Two neuroradiologists reviewed CTA images and recorded the imaging characteristics independently. In case of disagreement, a consensus reading was performed with a third neuroradiologist on the classification parameters (including aneurysm location, type, and irregular wall); then, the values were used for statistical analyses afterward. Regarding the quantitative parameter (aneurysm size), the values were averaged for subsequent statistical analyses.

Statistical Analysis

SPSS 19.0 (IBM) was used for all statistical analyses. Quantitative data are presented as mean (SD) and were compared between the radiation-related group and the control group using an independent-samples *t* test. Categoric variables are presented in percentages and analyzed between groups using the χ^2 or Fisher exact test.

RESULTS

Of the 4160 patients, the average age was 57.9 (SD, 13.5) years (Table 1), 2406 (57.8%) were women, 477 (11.5%) had multiple aneurysms, 3009 (72.3%) had SAH, and 34 (0.8%) had radiation-related aneurysms. Of the 34 patients with radiation-induced aneurysms, 23 were diagnosed with nasopharyngeal carcinoma before radiation therapy; 2, with medulloblastomas; 2, with lymphomas; and 7, with other head and neck tumors. The average time interval of the 34 patients between radiation therapy and a diagnosis of an intracranial aneurysm was 6.8 (SD, 5.1) years. As Table 1 shows, the male-to-female ratio in the radiation-related group was significantly higher than in the control group (2.4:1 versus 0.72:1, P = .001). The mean age of the radiation-related group was

Table 2: Characteristics of the aneurysms (n = 4813)

Characteristics	Radiation-Related Group	Control Group	*P* Value
Aneurysm size (mean) (mm)	4.9 (SD, 2.3)	5.2 (SD, 2.2)	NS
Location of aneurysm (No.) (%)			.046
ICA	23 (53.5)	2015 (42.2)	
Anterior cerebral artery	6 (14.0)	1213 (25.4)	
MCA	6 (14.0)	1066 (22.3)	
Posterior circulation artery	8 (18.6)	476 (10.0)	
Type of aneurysm (No.) (%)			.048
Sidewall	20 (46.5)	1543 (32.3)	
Bifurcation	23 (53.5)	3227 (67.7)	
Irregular wall	12 (27.9)	1438 (30.1)	NS

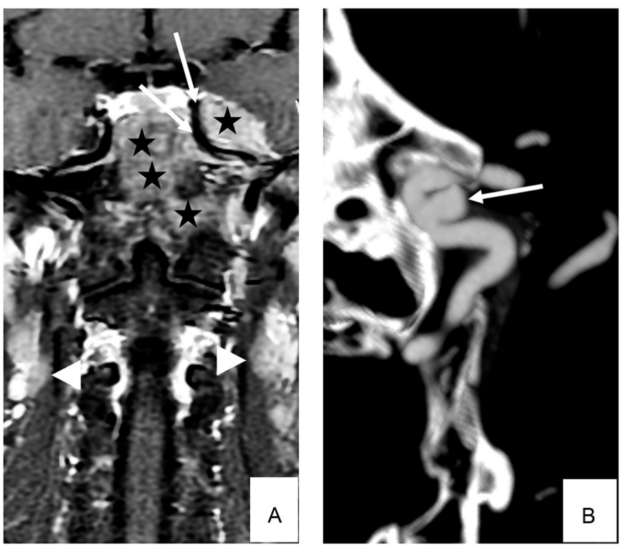

FIG 1. A 52-year-old man with nasopharyngeal cancer (T4N2M0, stage IVA). T1-weighted image (1.5T) with contrast shows that the tumor (*A, black stars*) has grown into the skull base and embraces the left ICA (*A, white arrows*) with swollen lymph nodes bilaterally (*A, white arrowhead*). Five years after irradiation, the patient presented with headache, and a sidewall aneurysm (5.1 mm) was detected at the left ICA using CTA (*B, white arrow*).

significantly younger than the control group (51.4 [SD, 15.0] years versus 58.2 [SD, 13.5] years, $P = .003$). The number of patients who presented with SAH in the radiation-related group was significantly higher than in the control group (88.2% versus 72.2%, $P = .037$), implying that radiation-related aneurysms may be more fragile and prone to rupture. For a subanalysis, we confirmed a 1:1 match in the age and sex of the radiation-related group and the controls. If >1 patient from the control group matched, to avoid possible selection bias, the patient used for comparison was randomly chosen by 1 neuroradiologist without knowledge of the participant's characteristics. The prevalence of SAH (88.2% versus 58.8%, $P = .006$) in the radiation-related group was significantly higher than in the age- and sex-matched controls.

Of the 4813 intracranial aneurysms (Table 2), only 43 (0.9%) aneurysms were categorized as in the radiation-related group, and the remaining 4770 (99.1%) aneurysms constituted the control group. The most frequent location for radiation-related aneurysms was the ICA (53.5%, Fig 1), followed by the posterior circulation arteries (18.6%, Fig 2), whereas aneurysms in the control group predominantly involved the ICA (42.2%) and anterior cerebral artery (25.4%) ($P < .05$). Compared with the control group, more sidewall aneurysms were found in the radiation-related group (46.5% versus 32.3%, $P < .05$). There was no difference in aneurysm size and wall irregularity between the 2 groups.

DISCUSSION

With improvement in comprehensive therapies, patients with head and neck cancer may have a reasonably long life expectancy, but they may have an increased risk of delayed complications resulting from radiation therapy. Most previous studies were case reports that lacked a comparison group due to the extremely low incidence of radiation-related aneurysms and the need for long-term follow-up after radiation therapy. The present study provided substantial insight into the demographic and clinical characteristics of patients with radiation-related aneurysms by comparing them with a cohort.

Unlike classic intracranial aneurysms, which are more common in women,[12] our study showed that radiation-related aneurysms were more common in men (the male-to-female ratio was 2.4:1). Previous literature reviews have documented that most patients with radiation-related aneurysms were men,[5,7,11] consistent with findings in our study. The percentage of men was even as high as 80%.[8] The average age of patients at the time of intracranial aneurysm diagnosis was 51.4 years, much younger than in the control group. This average age trend was similarly noted in the literature,[8,11] but our results are distinct from those in other literature.[5-7]

One possible explanation for the higher prevalence of radiation-induced aneurysms in men and younger patients could be because nasopharyngeal carcinoma and medulloblastoma, which are the main indications for radiation in our study, occur more often in men (male/female ratios were 2.5:1[1] and 1.8:1[15] for nasopharyngeal carcinoma and medulloblastoma, respectively) and are diagnosed at a relatively young age (incidence peaks in the fourth to sixth decades[1,16] and at 5–7 years[4,15] for nasopharyngeal carcinoma and medulloblastoma, respectively). One would postulate that younger patients and those with a favorable prognosis after treatment are most at risk of developing an aneurysm and potential rupture.[6,17]

Compared with the control group, radiation-related aneurysms had a significantly higher proportion of sidewall locations and a predilection for location in the ICA and posterior circulation arteries. A previous study revealed a similar result, with 53% of radiation-related aneurysms located at the ICA and 40% located at the posterior circulation arteries.[5] The exact mechanism is unknown, but vessel sensitivity to irradiation and hemodynamic factors may be responsible for the phenomenon. First, the CBF in each branch is different (ie, CBF in the ICA is significantly higher than in the basilar artery),[18] and the ICA is tortuous and transitions from elastic-to-muscular intracranial arteries.[19] The adverse effects of radiation on tissues are complex, including the possibility of inducing an inflammatory cascade and subsequently weakened blood vessels.[11,17,20] The combination of

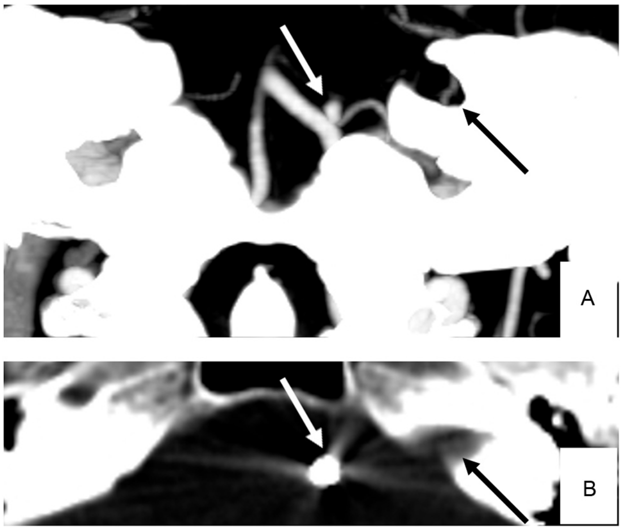

FIG 2. A 43-year-old woman with vestibular schwannoma. Eight years after irradiation, SAH and a ruptured bifurcation aneurysm (2.7 mm) were diagnosed by noncontrast CT and CTA (*A*, *white arrow*), which was treated with endovascular coiling (*B*, *white arrow*). Note a funnel-shaped enlargement of the left internal auditory canal (*A* and *B*, *black arrow*).

hemodynamic wall characteristics and a weakened vessel wall may affect hemodynamic force formation, which, in turn, affects aneurysm development.[14,21] Second, compared with the anterior cerebral artery and MCA, the posterior circulation has a relatively sparse sympathetic innervation.[22,23] However, cerebral autoregulation that depends on sympathetic nerve innervation may decrease and cause fibrosis after radiation,[24,25] leading to a passive overdistention of the vessel.[26] Recently, Pesce et al[7] reported that the posterior circulation is vulnerable even at low irradiation.

SAH was present in 88.2% of radiation-induced aneurysms, much higher than in the control group, implying that radiation-related aneurysms are more fragile and prone to rupture. Previous studies have shown that most patients with radiation-related aneurysms presented with SAH[5,11,17] and consequently had higher mortality and morbidity than patients with classic aneurysms.[5,6] Therefore, early detection of radiation-related aneurysms is crucial to allow monitoring or therapeutic intervention while the aneurysm is still unruptured. We think that it is reasonable to recommend dedicated screening for aneurysms after radiation therapy, but further studies are needed to determine the ideal timing to screen because the latency period remains highly variable (as early as 3 months[27] or as late as 37 years[28] after radiation therapy) and how to screen in terms of avoiding additional radiation exposure. The reasons for the high percentage of SAH in patients with radiation-related aneurysms should be cautiously interpreted. We postulate that the following reasons may contribute to this phenomenon: 1) the weakened and inflammatory vessel wall in the radiation-related aneurysm, as aforementioned, is vulnerable to rupture;[11,14,17,20,21] 2) as the longevity of treated patients increases (especially for young patients), the damaged blood vessels are correspondingly exposed to wall shear stress for an extended period, allowing a longer time for aneurysmal formation and rupture; and 3) radiation-related aneurysms are more likely to develop necrosis,[17] which is uncommon in classic intracranial aneurysms, and radiation-related aneurysms are associated more often with an inflammatory aneurysmal wall,[17] which is known to be a critical element of aneurysm rupture.[29]

Limitations

There are some limitations to our study: 1) The shape of an aneurysm may be affected by radiation therapy,[17] but we lost a chance to report this feature because the fusiform aneurysms were excluded in the first data collection, which was completed before January 2016, and the criteria of the second data collection followed the first one. 2) Because an intracranial aneurysm is a rare complication of radiation therapy, we included a small number of radiation-induced aneurysms. The gigantic difference in the sample size between groups, regardless of data types, might provide insufficient statistical power for analysis. 3) Clinically, we performed CT or/and MR imaging with contrast to evaluate the head and neck mass before radiation but did not regularly acquire CTA or TOF-MR angiography for those patients. Therefore, some radiation-related aneurysms could be coincidental because no vascular examination acquired before radiation therapy was available to prove the absence of the aneurysm. 4) CTA has a high sensitivity and specificity for the detection of intracranial aneurysms,[13,14] but we did not compare the results with the current criterion standard, DSA. Hence, we may have missed and/or misdiagnosed a fraction of smaller intracranial aneurysms. 5) Although the shortest time interval between delivery of radiation and the diagnosis of an aneurysm, to our knowledge, is 3 months,[27] the risk of a coincidental aneurysm may increase because the inclusion criterion of the latency interval (≥6 months) may not be long enough for aneurysm formation and development.

CONCLUSIONS

Compared with control group, patients with radiation-related aneurysms showed different characteristics related to their sex and age and the location and type of aneurysm. Furthermore, a higher percentage of these patients presented with SAH. Therefore, it is reasonable to recommend dedicated screening for aneurysms after radiation therapy, but further studies are needed to determine when to screen because the latency period remains highly variable and how to screen in terms of avoiding additional radiation exposure.

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Disclosure forms provided by the authors are available with the full text and PDF of this article at www.ajnr.org.

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