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ORIGINAL PAPER

Radiotherapy-related intracranial aneurysm: case presentation of a 17-year male and a meta-analysis based on individual patient data

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Abstract
Purpose The aim of this study was to investigate the incidence, clinical profiles, latency, and outcomes of radiotherapy (RT)-related intracranial aneurysms, rare but often fatal complications of cranial irradiation.
Methods We reviewed all published individual patient data regardless of language, using survival analysis to make statistical inferences.
Results We examined a total of 58 patients with RT-related intracranial aneurysms, including one unpublished case presented here, of whom 74.1 % presented with rupture. In the study, 29.3 % were younger than 18 years. The mean age at which patients received the first course of RT was 34.8 ± 22.8 years old. The mean latency between initiating RT and presenting with aneurysm was 10.4 ± 8.5 years. Rapid death ensured in 24 % shortly after presentation. The only significant predictor of death was rupture. In those with a single aneurysm, 43.1 % were located at the internal carotid artery, while 15.5 % of patients had multiple aneurysms. A male-to-female ratio of 1.87, 0.5, and 1.32 was found in patients younger than age 52, 52 years of age or older, and all 58 patients, respectively. Older age when receiving RT and presentation with ruptured aneurysm were significantly associated with shorter latency.
Conclusions RT-related intracranial aneurysms presented differently from classical ones based on age, sex, site, multiplicity, and type. Sex ratios differed with age. The younger age group showed a longer latency of occurrence of an aneurysm. Older patients and those who develop ruptured aneurysms presented earlier. Since rupture may affect outcome, early detection of aneurysms before rupture may save lives.

Keywords Vasculopathy · Radiation toxicity · Radiotherapy · Aneurysm

Introduction

Radiotherapy(RT) effectively relieves symptoms and prolongs survival in many cancer patients, but cranial irradiation may also increase stroke risk in cancer survivors. The estimated relative risk of stroke and transient ischemic attack (TIA) in pediatric cancer patients ever treated with cranial RT is 8, with

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an incidence of 548/100,000 person-years [1]. Besides these toxicities, cranial irradiation also can cause lacunar lesions, vaso-occlusive diseases including moyamoya syndrome, vascular malformations including aneurysms, and hemorrhage [2]. Among these complications, aneurysm is very rare. The crude incidence can be estimated from single-institution retrospective chart reviews. The Ottawa Regional Cancer Clinic in Canada reviewed the data from 244 pediatric cancer patients who had received brain irradiation and found that postradiation cerebral vascular disease occurred in 11 (5 %) patients, one (0.4 %) of whom developed a ruptured aneurysm [3]. To the best of our knowledge, only 57 cases of postirradiation aneurysm have been published [4–51]. Of 529 pediatric brain tumor patients treated with RT between 1975 and 2004 at Taipei Veterans General Hospital (TVGH), Taipei, Taiwan, only one (0.19 %) developed an RT-related aneurysm [52]. To understand the characteristics of this rare complication and to analyze factors affecting the outcomes and latency of RT-related intracranial aneurysms, we performed a literature review of all patient data ever published describing intracranial aneurysms presenting in-field after cranial RT. One unpublished case from TVGH was added into the reviewed, published cases for statistical inference.

Materials and methods

The study followed the PRISMA guideline for meta-analyses [53]. We searched the PubMed, OVID, and Google Scholar databases using the keywords “aneurysm,” “radiotherapy,” “radiation,” and “RT,” including non-English language publications. Publications that did not provide the age at which RT was given were excluded. The date of last search was December 31, 2015. Two radiation oncologists reviewed the literature independently. Intracranial aneurysm(s) identified within prior radiation fields after cranial RT were deemed RT related, and the publications describing them, whether case series or single case reports, were included in the analysis. Data from patients that fulfilled the above criteria were pooled with an additional data from one unpublished case from the TVGH.

We set out to investigate the effect of all potential predictors on clinical outcomes and the latency between initiation of RT and presentation of intracranial aneurysm. We first performed univariate survival analysis for each factor, including age at first RT course, patient sex, cumulative conventional external beam RT (EBRT) dose, RT mode, aneurysm site, underlying diagnosis, type of aneurysm, whether the patient had ever received repeated RT or not, whether the aneurysm had ruptured or not, and the presence or absence of other clinical symptoms.

Conventional EBRT includes involved-field RT (IFRT) or whole-brain RT (WBRT) with a stated daily fraction size of 1.8–2.0 Gy as well as RT described as fractionated without an indication of fraction size. RT modes were categorized into hypofractionated EBRT, WBRT, conventional IFRT, brachytherapy, combined, and unknown. Patients who received more than one mode were listed as combined. Stereotactic radiosurgery (SRS), gamma knife radiosurgery (GKRS), and hypofractionated IFRT were all included in hypofractionated EBRT.

The mean cumulative dose for all patients was calculated, excluding SRS, hypofractionated radiotherapy, and brachytherapy, since their biological effects differ.

The sites of aneurysms were categorized as the internal carotid artery (ICA), anterior communicating artery (ACoA), posterior circulation (PC), multiple, and others. PC included the posterior cerebral artery (PCA), posterior communicating artery (PcoA), anterior inferior cerebellar artery (AICA), posterior inferior cerebellar artery (PICA), basilar artery (BA), and vertebral artery (VA). The categorization was based on our observation that the ICA, ACoA, PCoA, and PC might have a higher risk of rupture, while there were no solitary RT-related aneurysms reported over the PCoA [54, 55].

Given the high heterogeneity of diagnoses, patients were categorized only as nasopharyngeal carcinoma (NPC) or non-NPC patients. Types of aneurysm were categorized as saccular, fusiform, saccular and fusiform, giant, and dissecting. Those described as giant or with a diameter ≥25 mm were considered giant. Patients who received 1 course of RT were considered to have received repeated RT, but those receiving different RT modes within the same course of RT, e.g., brachytherapy after EBRT for patients with NPC, were not considered to have received repeated RT.

The significant predictor(s) in univariate analysis of the development of an aneurysm were included in multivariate Cox proportional hazard model. Potential predictors of aneurysmal fatality were analyzed by two-tailed Fisher’s exact test. To analyze the effect of menopause, we compared the sex ratios across the age of 52, while the median age of menopause in Western countries was 51.3 years [56]. All analyses were performed using SAS 9.3 software (Cary, NC). All p values less than 0.05 were considered significant, and no adjustments were made for multiple comparisons.

Results

Patient characteristics

Fifty-seven cases of RT-related intracranial aneurysm were found in 48 publications between 1984 and 2015. By combining these cases with one unpublished case from TVGH, individual patient data from 58 cases were analyzed. Characteristics of the patients and RT-related intracranial aneurysms are listed in Table 1.

Table 1 Characteristics of patients and their RT-related intracranial aneurysms

Authors and year	Age, year; sex	Cancer		RT			Post-RT interval, year	Aneurysm			
		Diagnosis	CT	Dose, Gy	Mode	Repeat		Site; type	Ruptures	Symptomatic	Outcome
Gonzales-Portillo et al., 2006 [32]	0; M	Retinoblastoma	N.R.	NA + 49 + 50	Brachy (^{125}I plaques) + hyperfractionated IFRT	Yes	12	ACA; saccular	Yes	Yes	Stable
Maruyama et al., 2000 [17]	0.4; F	Optic glioma	ACNU	70 + 40	IFRT + IFRT	Yes	15	ICA, ACA; NA	Yes	Yes	Stable
Aoki et al., 2002 [22]	1; F	Optic glioma	N.R.	50 + 40	IFRT + IFRT	Yes	19	ICA; NA	Yes	Yes	NA
Aichholzer et al., 2001 [18]	1.1; M	Pilocytic astrocytoma	N.R.	54	IFRT	Yes	9	ACoA; fusiform	Yes	Yes	Stable
Pavlisa et al., 2010 [40]	2; F	Craniopharyngioma	N.R.	NA	Brachy (^{90}Y seed)	No	21	PCA; fusiform	Yes	Yes	Stable
Benson et al., 1989 [7]	2; M	Medulloblastoma	N.R.	30.66 + 16.56 + NA	WBRT + IFRT + IT ^{198}Au colloid	No	19	PCA; saccular	Yes	Yes	Death
Benson et al., 1989 [7]	5; M	Medulloblastoma	N.R.	35.04 + 15 + NA	WBRT + IFRT + IT ^{198}Au colloid	No	9	PCA; saccular	Yes	Yes	Death
Vogel et al., 2011 [42]	5; F	Optic glioma	Carboplatin, vincristine, bevacizumab	54+ NA + NA + NA	IFRT+ brachy + GKRS+ Proton	Yes	11	ICA bifurcation; NA	Yes	Yes	Stable
Nanney et al., 2014 [50]	5; M	Medulloblastoma	N.R.	30.6 + 24.06	IFRT + WBRT	No	33	PICA; saccular	Yes	Yes	Stable
Current	5; M	Medulloblastoma	PVP16, IT ACNU	31.5 + 24	WBRT + IFRT	No	13	AICA, PICA; dissecting	Yes	Yes	Deteriorated
Liu et al., 2009 [37]	5.6; M	Craniopharyngioma	Intracystic bleomycin	58.8	IFRT	No	0.7	ICA; NA	Yes	Yes	Stable
Jensen et al., 1997 [15]	9; M	Medulloblastoma	VP-16, cyclophosphamide, carboplatin	40 + 8	WBRT + IFRT	No	0.8	ACA; saccular	Yes	Yes	NA
Sciubba et al., 2006 [33]	9; M	Medulloblastoma	N.R.	55.8	WBRT + IFRT	No	15	MCA; fusiform	No	No	Stable
Murakami et al., 2002 [23]	11; M	Craniopharyngioma	N.R.	60	IFRT	No	19	PcoA, BA; NA	No	No	Stable
Azzarelli et al., 1984 [4]	12; F	Suprasellar germinoma	N.R.	40 + 12.2	WBRT + IFRT	No	5	ICA, BA, VA/BA junction, ACA; NA	Yes	Yes	Death
Benson et al., 1989 [7]	13; F	Medulloblastoma	N.R.	35 + 15 + NA	WBRT + IFRT + IT ^{198}Au colloid	No	18	PCA at PcoA junction; saccular	Yes	Yes	Death
Pereira et al., 2002 [24]	14; F	Craniopharyngioma	N.R.	54	IFRT	No	5	ICA bifurcation; saccular	No	No	Stable
Huang et al., 2001 [20]	19; F	AVM	N.R.	25[a]	GKRS	No	0.75	Pericallosal; NA	No	Yes	Stable
	22; M	NPC	N.R.	60	IFRT	No	8	ICA, ACA, MCA, OA, PCOM, PCA; NA	Yes	Yes	Stable

Table 1 (continued)

Authors and year	Age, year; sex	Cancer		RT			Post-RT interval, year	Aneurysm			
		Diagnosis	CT	Dose, Gy	Mode	Repeat		Site; type	Ruptures	Symptomatic	Outcome
Gulati et al., 2014 [48]											
Thun et al., 1991 [9]	23; F	Pituitary adenoma	N.R.	NA	Brachy (^{90}Y seed)	No	7	ICA; giant	No	Yes	NA
Casey et al., 1993 [11]	23; M	AVM	N.R.	45	WBRT	No	21	MCA; NA	Yes	Yes	Stable
Ghoshhajra et al., 2006 [31]	23; M	Suprasellar mass	N.R.	NA	NA	No	37	Multiple; NA	No	Yes	Stable
Tamura et al., 2013 [46]	25; M	PNET	VDC, IE, melphalan, TEPA	$54.9^b + 62.3^b + 60^b$	Hypofractionated IFRT x3	Yes	4	ICA; NA	Yes	Yes	Stable
Auyeung et al., 2003 [25]	31; F	NPC	N.R.	NA	IFRT + Brachy (gold grain)	Yes	21	ICA; dissecting	Yes	Yes	Stable
Gabriel et al., 2004 [28]	31; F	Pituitary adenoma	N.R.	NA	Brachy (Yttrium implant)	No	29	ICA; giant	Yes	Yes	Stable
Cheng et al., 2001 [35]	33; M	NPC	N.R.	60 + 60	IFRT + IFRT	Yes	2	ICA; NA	Yes	Yes	Stable
McConachie et al., 1994 [13]	34; F	Pituitary adenoma	N.R.	NA	Brachy (^{90}Y seed)	No	20	ICA; NA	No	Yes	Stable
Louis et al., 2003 [26]	34; M	Hodgkin disease	MOPP	43.5	IFRT	No	27	ICA; NA	No	Yes	NA
Gross et al., 2013 [45]	36; M	AVM	N.R.	NA	SRS	No	14	Pericallosal; dissecting	Yes	Yes	NA
Lam et al., 2001 [21]	39; M	NPC	N.R.	66 + 50	IFRT + IFRT	Yes	8	ICA; dissecting	Yes	Yes	Stable
Lau et al., 2005 [30]	41; M	NPC	N.R.	60	IFRT	No	12	ICA; dissecting	Yes	Yes	Stable
Thun et al., 1991 [9]	42; M	Pituitary adenoma	N.R.	NA	Brachy (^{90}Y seed)	No	11	ICA; NA	No	Yes	NA
Yucesoy et al., 2004 [29]	42; F	Optic nerve glioma	N.R.	NA	NA	No	6	AcoA; NA	Yes	Yes	Stable
Gomori et al., 1987 [5]	44; M	NPC	N.R.	60	IFRT	No	3	BA; fusiform	Yes	Yes	Death
Endo et al., 2011 [41]	45; F	Pituitary prolactinoma	N.R.	$35^a + 55.2$	GKRS + IFRT	Yes	17	ICA; NA	Yes	Yes	Stable
Scodary et al., 1990 [8]	47; M	Astrocytoma	N.R.	65	WBRT	No	15	ACA, pericallosal; NA	Yes	Yes	Death
Cheng et al., 2001 [19]	47; M	NPC	N.R.	60 + 60	IFRT + IFRT	Yes	7	ICA; NA	Yes	Yes	Stable
	48; M	Pituitary adenoma	N.R.	50	IFRT	No	9	ICA; saccular	No	Yes	Stable

Table 1 (continued)

Authors and year	Age, year; sex	Cancer		RT			Post-RT interval, year	Aneurysm			
		Diagnosis	CT	Dose, Gy	Mode	Repeat		Site; type	Ruptures	Symptomatic	Outcome
Nishi et al., 1987 [6]											
Lam et al., 2001 [21]	48; 7	NPC	N.R.	66	IFRT	No	7	ICA; NA	Yes	Yes	Death
Moriyama et al., 1992 [10]	50; F	Pituitary adenoma	N.R.	50	IFRT	No	1	MCA, PCA; NA	Yes	Yes	NA
John et al., 1993 [12]	50; M	NPC	N.R.	66	IFRT	No	5	ICA; NA	Yes	Yes	Death
Fujita et al., 2014 [47]	50; M	Meningioma	N.R.	12[a] + 47.6[b]	SRS + hypo-fractionated IFRT	Yes	11	ICA; NA	Yes	Yes	Stable
Auyeung et al., 2003 [25]	51; M	NPC	N.R.	NA	IFRT + SRS	Yes	0.66	ICA; dissecting	Yes	Yes	Stable
Lam et al., 2001 [21]	53; M	NPC	N.R.	60 + 51	IFRT + IFRT	Yes	12	ICA; dissecting	Yes	Yes	Death
Cheng et al., 2008 [35]	54; M	NPC	PF	70.4 + 40 + 18[c]	IFRT + IFRT+ Brachy	Yes	3	ICA; dissecting	Yes	Yes	Stable
Chen et al., 2004 [27]	55; M	NPC	PF	73.8 + 8[c]	IFRT + brachy	No	0.33	ICA; dissecting	Yes	Yes	Stable
Yoon et al., 2011 [43]	57; M	GBM	PCV	59.4	IFRT	No	0.83	ACA; saccular	Yes	Yes	Stable
Kellner et al., 2014 [49]	58; F	Meningioma	N.R.	16[a]	SRS	No	10	Superior cerebellar artery; saccular + fusiform	No	No	Stable
Huh et al., 2012 [44]	61; F	Chondrosarcoma	N.R.	59.4	IFRT	No	8	AcoA; NA	Yes	Yes	Deteriorated
Casey et al., 1993 [11]	62; F	Astrocytoma	N.R.	60	IFRT	No	3.5	MCA bifurcation; giant	Yes	Yes	Deteriorated
Holodny et al., 1996 [14]	62; F	Breast cancer, brain metastasis, with Ehlers-Danlos syndrome	N.R.	21 + 10.8	WBRT + WBRT	No	0.6	BA, circle of Willis; NA	Yes	Yes	Death
Takao et al., 2006 [34]	63; F	Acoustic neuroma	N.R.	12[a]	GKRS	No	6	AICA; dissecting	Yes	Yes	Stable
Wu et al., 2014 [51]	65; F	Bladder cancer, clival metastasis	N.R.	60	IFRT	No	3	ICA; giant	No	Yes	Stable
Mak et al., 2000 [16]	66; F	NPC	N.R.	NA + NA	IFRT + IFRT	Yes	9	ICA; dissecting	Yes	Yes	Stable
Yamaguchi et al., 2009 [39]	67; F	Vestibular schwannoma	N.R.	50	IFRT	No	6	AICA; dissecting	Yes	Yes	Stable
	69; F		N.R.	12[a]	GKRS	No	5	AICA; dissecting	Yes	Yes	Stable

Table 1 (continued)

Authors and year	Age, year; sex	Cancer	CT	RT			Post-RT interval, year	Aneurysm			
		Diagnosis		Dose, Gy	Mode	Repeat		Site; type	Ruptures	Symptomatic	Outcome
Park et al., 2009 [38]		Vestibular schwannoma									
Gross et al., 2013 [45]	73; M	AVM	N.R.	17[a]	SRS	No	1.25	Pericallosal; dissecting	Yes	Yes	Death
Akamatsu et al., 2009 [36]	75; F	Vestibular schwannoma	N.R.	12[a]	GKRS	No	8	AICA; dissecting	Yes	Yes	NA

[a] Physical dose of SRS

[b] Physical dose of hypofractionated radiotherapy

[c] Physical dose of brachytherapy

CT chemotherapy, *N.R.* not reported, *IFRT* involved-field RT, *WBRT* whole-brain RT, *SRS* stereotactic radiosurgery, *GKRS* gamma knife radiosurgery, *IT* intrathecal, *ICA* internal carotid artery, *MCA* middle cerebral artery, *PCA* posterior cerebral artery, *AcoA* anterior communicating artery, *PCoA* posterior communicating artery, *AICA* anterior inferior cerebellar artery, *PICA* posterior inferior cerebellar artery, *OA* ophthalmic artery, *VA* vertebral artery, *BA* basilar artery, *GBM* glioblastoma, *AVM* arteriovenous malformations, *NPC* nasopharyngeal carcinoma, *PNET* primitive neuroectodermal tumor, *NA* not available

Inferential statistics of the potential predictors and the results of univariate analysis for latency are listed in Table 2.

The mean latency between the first course of RT and presentation of radiotherapy-related intracranial aneurysm is 10.4 ± 8.5 years, with a median of 8.5 years. The mean ages of presenting with an aneurysm were 45.8 ± 20.6 years old, with a median of 52 years old. The mean cumulative dose of conventional EBRT was 66 ± 24 Gy, with a median dose of 59.4 Gy. Our study included 29.3 % pediatric patients who received RT at age 18 or younger. The mean age at the first course of RT was 34.8 ± 22.8 years old, with a median of 37.5 years old. In the study, the male-to-female ratio was 1.38 (25 men and 18 women) among those with ruptured aneurysms. The male-to-female ratio of all 58 patients was 1.32. By grouping the 58 patients in the present study into those less than 52 years of age versus 52 years of age or older, the sex ratios would be 1.87 and 0.5, respectively; multiple aneurysms were found in 15.5 % of the patients. For those presenting with a single aneurysm in the study, 43.1 % were located in the ICA. We also found that dissecting aneurysms were the most common type identified, accounting for 25.9 % of all cases.

Case presentation

A 17-year-old boy presented with sudden-onset left hemiplegia in January 2011. Emergency brain computerized tomography (CT) revealed intracranial hemorrhage (ICH) at the pons, with subarachnoid hemorrhage (SAH) at the circle of Willis and the pre-pontine cistern. There was no focal neurological sign except a fixed right pupil, 5–6 mm in size. No obvious increased intracranial pressure (IICP) signs nor hydrocephalus was observed to support placement of a ventriculoperitoneal (V-P) shunt. Angiography identified an arterial segment with an irregular lumen near the origin of the right AICA, compatible with a ruptured aneurysm, and another aneurysm at the right P1 section (from the termination of the BA to the PCA, within the interpeduncular cistern) of the PCA with a 1.8-mm sac and a 1.5-mm neck (Fig. 1). Coils were used to embolize the right AICA aneurysm. His symptoms, except for the left hemiparesis, improved after the embolization. This aneurysm was determined to be RT related, since the patient was extremely young for an aneurysm and the aneurysms were located outside the common sites of arterial branch points but within the radiation field and were dissecting in type.

The patient developed blood-tinged stool 15 months after the aneurysm ruptured. Sigmoidoscopy revealed a 1.5-cm polyp 20 cm from the anal verge. Polypectomy was performed, which identified signet ring cell adenocarcinoma.

He had a history of classic medulloblastoma with spinal seeding at the C6–7 level diagnosed at age 5. He underwent subtotal tumor resection in 1998. Subsequently, he received adjuvant chemotherapy with ifosfamide, cisplatin, and etoposide, followed by postoperative RT, including

Table 2 Inferential statistics of potential factors affecting latency of RT-related aneurysms

Potential factors		Latency		
		Mean, year	*P*	HR (95 % CI)
Age at first RT course				
Mean (range), year	34.8 (0–75)	10.4	0.0009	1.025 (1.010–1.040)
≤18, *n* (%)	17 (29.3 %)	13.2*	0.0022	0.334 (0.166–0.674)
19–51, *n* (%)	26 (44.8 %)	13.8*	0.0010	0.284 (0.134–0.600)
>51, *n* (%)	15 (25.9 %)	5.7		Ref.
Sex				
Male, *n* (%)	33 (56.9 %)	10.6	0.76	1.091 (0.630–1.888)
Female, *n* (%)	25 (43.1 %)	10.2		Ref.
Physical dose[a]				
Mean (range), Gy	69.5 (31.8–177.2)		0.77	1.002 (0.986–1.019)
>60, *n* (%)	9 (15.5 %)	9.9	0.388	1.318 (0.704–2.469)
≤60, *n* (%)	22 (37.9 %)	9.2		Ref.
Not included, *n* (%)	27 (46.6 %)			
RT mode, *n* (%)				
Brachytherapy	5 (8.6 %)	17.6	0.032	0.318 (0.111–0.906)
Conventional IFRT	24 (41.4 %)	8.3		Ref.
WBRT	3 (5.2 %)	12.2	0.26	0.475 (0.130–1.734)
Hypofractionated EBRT[b]	9 (15.5 %)	6.7	0.37	1.448 (0.641–3.272)
Combined	15 (25.9 %)	11.9	0.09	0.542 (0.266–1.103)
Except brachytherapy only	51 (87.9 %)	9.3	0.08	0.425 (0.161–1.122)
Unknown	2 (3.4 %)			
Site, *n* (%)				
ICA	26 (44.8 %)	10.0		Ref.
PC	11 (19.0 %)	12.5	0.52	0.660 (0.187–2.333)
Others	9 (15.5 %)	7.7	0.3108	0.2480 (0.128–1.923)
ACoA	3 (5.2 %)	7.7	0.7758	0.818 (0.205–3.268)
Multiple	9 (15.5 %)	12.6	0.2701	0.453 (0.111–1.852)
Diagnosis, *n* (%)				
NPC	14 (24.1 %)	7.0	0.0609	1.867 (0.972–3.586)
Other than NPC	44 (75.9 %)	11.5		Ref.
Pituitary adenoma	7 (12.1 %)	13.4		
Medulloblastoma	7 (12.1 %)	15.4		
Optic glioma	5 (8.6 %)	11.9		
AVM	4 (6.9 %)	9.25		
Craniopharyngioma	4 (6.9 %)	11.7		
Vestibular schwannoma	4 (6.9 %)	6.25		
Astrocytoma	2 (3.4 %)	9.25		
Meningioma	2 (3.4 %)	10.5		
Others[c]	9 (15.3 %)	10.8		
Symptomatic, *n* (%)				
Symptomatic	52 (89.7 %)	10	0.407	1.452 (0.601–3.509)
Asymptomatic	6 (10.3 %)	13.8		Ref.
Ruptured, *n* (%)				
Ruptured	43 (74.1 %)	8.8*	0.019	2.327 (1.149–4.713)
Non-ruptured	15 (25.9 %)	15.1		Ref.
Repeated RT, *n* (%)				
Repeated	15 (30 %)	10	0.7575	1.103 (0.592–2.054)
Non-repeated	43 (70 %)	10.5		Ref.
Type, *n* (%)				
Dissecting	15 (25.9 %)	7.9	Ref.	Ref.
Saccular	9 (15.5 %)	11.8	0.1930	0.539 (0.212–1.367)
Giant	4 (6.9 %)	10.6	0.3055	0.539 (0.165–1.758)
Fusiform	4 (6.9 %)	12	0.5499	0.688 (0.201–2.347)
Unknown/multiple	26 (44.8 %)			

[a] Doses of SRS, hypofractionated IFRT, and brachytherapy are not included

[b] Including SRS, GKRS, and hypofractionated IFRT

[c] Including 1 (1.7 %) retinoblastoma, 1 (1.7 %) germinoma, 1 (1.7 %) GBM, 1 (1.7 %) chondrosarcoma, 1 (1.7 %) brain metastasis, 1 (1.7 %) Hodgkin's disease, 1 (1.7 %) unspecified suprasellar mass, 1 (1.7 %) PNET, and 1 (1.7 %) clivus metastasis

The asterisk indicated that "rupture" is a significant factor for latency, which corresponds to the p-value of 0.019 (<0.05) on the right column. The asterisk indicated that "rupture" is a significant factor for latency, which corresponds to the p-value of 0.019 (<0.05) on the right column

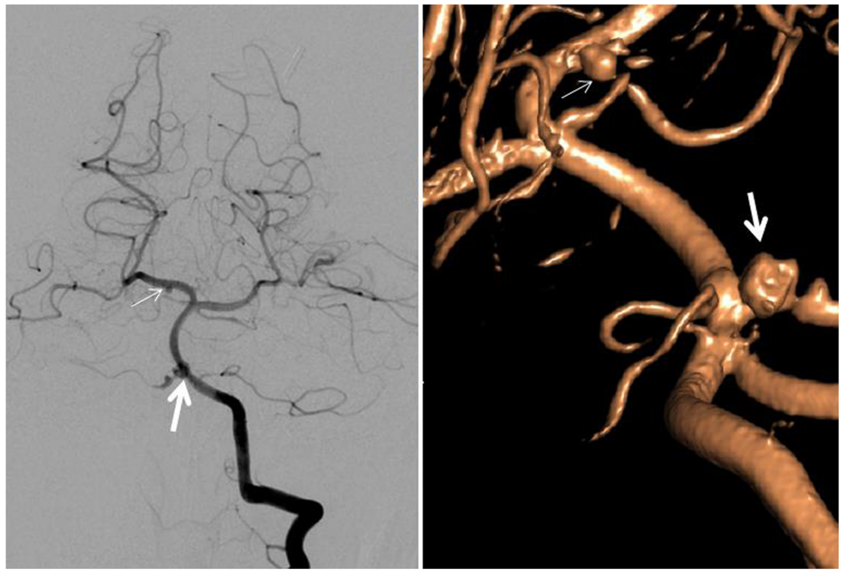

Fig. 1 Angiography identified a segment with irregular lumen in the proximal right AICA, compatible with dysplastic aneurysm, as marked by a *thick arrow*. Another aneurysm was noted at the right P1 segment of the posterior cerebral artery, as marked by a *thin arrow*

5550 cGy in 34 fractions to the residual tumor, 4550 cGy in 29 fractions to the posterior fossa and C6–7 spinal canal, and 3150 cGy in 21 fractions to the craniospinal axis. After RT, chemotherapy continued for 1 year with 6 courses of intravenous ifosfamide, cisplatin, and etoposide and 10 courses of intrathecal nimustine hydrochloride (ACNU). Regular follow-up brain magnetic resonance imaging (MRI) through December 2010 was stable.

Both of his paternal grandparents died from strokes. His paternal grandfather's stroke occurred in his sixth decade while his paternal grandmother's occurred at the age of 40 and was rapidly fatal. There was no other family history of cerebral artery accident or cancer.

Statistical analysis

Fisher's exact test revealed that the presence or absence of rupture at presentation was the only significant predictor of death shortly after aneurysm presentation with $p = 0.047$.

Univariate analysis identified age at first course of RT and whether or not the aneurysm had ruptured at presentation as the only two significant predictors for latency. These factors were included in a Cox proportional hazard model, and both were significant in multivariate regression (Table 3). An HR of 1.024 was noted for age. Increasing age at initiation of RT increased the chance of developing an intracranial aneurysm by approximately 2.4 % for each additional year in age, thus shortening the interval between RT and the presentation of RT-related aneurysm. The estimated HR for rupture as the presentation of RT-related aneurysm was 2.3, implying that those aneurysms that eventually rupture, compared with those that presented without rupture, i.e., that were identified by mass effect or follow-up imaging, were more likely to be identified and thus might be developed earlier after RT. As shown in Table 2, the mean latency between the first course of RT and RT-related aneurysm in those ruptured and not ruptured was 8.8 and 15.1 years, respectively.

The effect of age on aneurysm presenting with rupture was checked by mediation analysis (Table 4). The effects of age among models with rupture versus without rupture were similar (HR = 1.024 vs. 1.025), which indicated that the mediated effect of age in the path to rupture for aneurysm hazard is limited.

Table 3 Multivariate analysis of factors affecting the interval between the first RT course and presentation of intracranial aneurysm

Factor	*P*	HR (95 % CI)
Age	0.0011	1.024 (1.010–1.039)
Sex	0.6631	0.882 (0.500–1.555)
Rupture	0.0216	2.333 (1.132–4.805)

Discussion

In this study, we found RT-related intracranial aneurysms are different from classical ones in age, sex, multiplicity, site, and type. For classical aneurysms, the mean age of patients with aneurysmal subarachnoid hemorrhage is around 50 years [57]. The mean age of presentation of RT-related intracranial aneurysms is about 5 years younger. Male-to-female sex ratio of classical aneurysmal subarachnoid hemorrhage was found to

Table 4 Mediation analysis by difference method

Factor	*P*	HR (95 % CI)
Age	0.0010	1.025 (1.010–1.041)
Sex	0.7973	0.928 (0.527–1.636)

be around 0.5 [58]. But a male dominance sex ratio was found in our study in RT-related intracranial aneurysms. Sex ratios reversed in elder patients. Multiplicity was found to be less frequent in RT-related than classical intracranial aneurysms, while multiple intracranial aneurysms, usually two or three in number, are found in 20–30 % of patients with classical aneurysms [57]. For those with a single lesion, our study found that RT-related intracranial aneurysm located at ICA about 6 times often than classical one [59]. Those with older age at receiving RT and presentation with aneurysmal rupturing had a shorter latency between RT and diagnosis of RT-related aneurysms with shorter latency. Rupture is the only predictor found to be associated with higher fatality after the diagnosis of RT-related aneurysm.

As a rare complication of RT, intracranial aneurysms were published mostly in forms of case reports or case series. This study is the first meta-analysis to investigate predictors of latency with multivariate analysis, to analyze predictor(s) of clinical outcome, and to investigate how age might affect sex ratios.

There are still many unknowns regarding the pathophysiology of this rare complication. Even in people without radiation exposure, little is known about the causes of intracranial aneurysms, although hypertension and smoking-induced vascular changes are thought to play a role [59]. Radiation causes cell death, induces inflammation, and damages arterial endothelial cells [60]. These effects might cause a decrease of the middle muscular layer of the artery, causing structural defects. Under hemodynamic shear force, an outpouching of the arterial wall is thus formed. Besides the direct insult of RT to the artery, indirect host factors, including obesity, metabolic syndrome, and atherosclerosis, may also contribute to aneurysm formation [61–64].

Early radiation exposure may explain the younger age at aneurysm presentation. The sex ratio appeared higher than that reported for classical intracranial aneurysms in younger patients but the same in older patients, perhaps related to a disturbance of sex hormones caused by irradiation to hypothalamus-pituitary axis [65].

The median radiation dose in patients with radiation-related intracranial aneurysms was nearly identical to the highest dose (60 Gy) generally prescribed for brain irradiation. Repeated RT did not shorten the interval of aneurysm presentation in univariate analysis (10 vs. 10.5 years) as in this study results. These findings imply that aneurysm development may be more due to individual conditions of the patients being treated rather than being caused by high RT doses. Several genetic conditions, including autosomal dominant polycystic kidney disease, fibromuscular dysplasia, Marfan's syndrome, Ehlers-Danlos syndrome type IV, and AVM, are associated with the development of intracranial aneurysms [59]. Four patients with AVM and one with Ehlers-Danlos syndrome were identified in the literature review [11, 14, 20, 45]. Familial intracranial aneurysms are not rare, accounting for 7–20 % of patients with aneurysmal subarachnoid hemorrhage, and generally are not associated with any of the known heritable connective tissue disorders [66].

Regardless of a patient's genetic predisposition, the RT dose still plays a role in aneurysm development: high doses of RT are more likely to cause intracranial aneurysms. Intrathecal gold isotopes (IT-Au) were administered together with EBRT in the 1960s to treat medulloblastoma, to increase the radiation dose in leptomeningeal sites. In a case series of 14 patients treated in this manner, six died of the disease while three of the remaining eight that survived more than 2 years developed ruptured intracranial aneurysms [67]. It was later learned that intrathecal isotopes tend to pool in the basal cisterns and cause radiation hot spots, which might explain the unusually high incidence of aneurysms in these patients. In contrast, our study did not show the association between the RT dose and the latency of the diagnosis of RT-related aneurysm. However, our study still found that those who received brachytherapy only, which would have delivered minimal radiation to adjacent arteries, presented with aneurysms later than those who received conventional IFRT.

Rupture of the aneurysm was a significant predictor for mortality from aneurysm. This suggests that early detection of RT-related aneurysms, prior to rupture, may save lives.

This study found that the latency between administration of RT and diagnosis of aneurysms was inversely proportional to age. Age per se has been recognized as a risk factor for aneurysmal rupture [54]. Other known risk factors, such as hypertension and smoking, may also be more prevalent in older patients. However, the increased risk of death with advancing age as a confounding factor, i.e., younger patients receiving cranial RT usually survive longer, may also contribute to this finding. Those with ruptured aneurysms presented sooner after RT. The chance of aneurysmal rupture thus decreases with time. The necessity to screen for intracranial aneurysms in patients who have received cranial RT may decrease years after treatment.

Limitation of the study

For this rare complication, we only were able to evaluate cases reported in the literature. Reporting bias is inevitable [68]. The actual RT doses to the involved arteries could not be evaluated, because the prescribed RT dose published typically is the dose given to the target volume rather than that of the affected artery. Evaluating biologically equivalent doses is difficult. The fraction size is often unavailable. Some publications did not provide the total dose of RT. The interval between repeated RT treatments is usually several years. There is no reliable way to sum up these treatments. For single fraction irradiation, brachytherapy, and IT-Au, there is also no generally accepted method to convert these treatments to biologically equivalent doses. More detailed analyses were not likely, since the known risk factors, such as hypertension, smoking, and menopause, were not described in the publications examined. The effect of chemotherapy could not be analyzed, since many of the searched articles did not indicate whether or not the patient received chemotherapy, although, from the history, we suspect some patients should have received it.

Conclusions

RT-related aneurysms present at a younger age, more frequently in the ICA, less frequently with multiplicity, more often in men, and more often with dissection, than classical aneurysms. The male-to-female ratio was significantly higher in younger patients. The only predictor for survival was whether or not the aneurysm presented with rupture. Early detection of RT-related aneurysms prior to rupture may save lives. Older age at treatment with RT and presentation with ruptured aneurysm were associated with a shorter latency. Follow-up imaging for aneurysm may be less necessary years after RT.

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Compliance with ethical standards

Conflict of interest The authors declare that there are no conflicts of interest.

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