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Original Article

# The angiographic and clinical outcomes of intracranial aneurysms following irradiation in patients with nasopharyngeal carcinoma: A 13-year experience and literature review

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ARTICLE INFO

Article history:  
Available online xxx

Keywords:  
Radiotherapy  
Intracranial aneurysms  
Nasopharyngeal carcinoma  
Screening

ABSTRACT

**Background and purpose.** – Intracranial aneurysms are a known but rare complication of radiotherapy (RT). We reviewed the angiographic and clinical outcomes of intracranial aneurysms following RT in patients with nasopharyngeal carcinoma (NPC), a malignancy endemic in Hong Kong.

**Materials and methods.** – The clinical, angiographic and laboratory data was collected for nine NPC patients harboring fifteen intracranial aneurysms following RT, diagnosed between 1st January 2000 and 31st December 2012.

**Results.** – The median age at aneurysm diagnosis was 56 years with a male predilection (67%). The median latent period to diagnosis was nine years (0.3–30). Eight patients (89%) presented with aneurysmal subarachnoid hemorrhage. Nine aneurysms were located at the anterior circulation, and 14 were saccular in morphology. Of the treated aneurysms, eight underwent endovascular intervention and two were surgically clipped. Within a year, 50% of the treated aneurysms had recurred. Poor neurological outcome was noted. At two-year follow-up, the median score for modified Rankin score and Glasgow Outcome score was 5 and 2 respectively. The two-year mortality rate of patients with treated ruptured intracranial aneurysms was 50%.

**Conclusion.** – Compared to previous studies, our irradiated NPC patients had higher mortality and morbidity rates after aneurysm rupture and a higher angiographic recurrence rate following treatment. Greater vigilance is required in the detection of post-treatment recurrence of these aneurysms due to the higher risk of rupture. The authors recommend dedicated screening of intracranial aneurysms by active surveillance in routine CT protocols or the addition of three-dimensional time-of-flight magnetic resonance angiography in MR protocols.

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## Introduction

Intracranial aneurysms following irradiation are uncommon. Only 58 such aneurysms have been reported in the medical literature [1]. In spite of the paucity of affected patients, the histopathological effects of radiation on the cerebral arterial vasculature have been well documented [2]. Microscopic and ultrastructural vessel examinations of aneurysms following radiotherapy (RT) reveal a fragmented endothelium, disintegration of the internal elastic lamina, scarcity of smooth muscle cells and the formation of a dense collagen coat in the absence of arteriosclerosis [3].

Nasopharyngeal carcinoma (NPC) is the 10th most common cancer in Hong Kong with an incidence of 834 patients in 2014 alone [4]. Although endemic in South-East China, it remains uncommon elsewhere. The malignancy is strongly associated with Epstein-Barr virus (EBV) infection [5], whereby complex interactions between

**Abbreviations:** 2DRT, two-dimensional radiotherapy; 3D-TOF, three-dimensional time-of-flight; CT, Computed tomography; EBV, Epstein-Barr virus; GCS, Glasgow Coma Scale; GOS, Glasgow Outcome Score; IMRT, intensity-modulated radiotherapy; MR, magnetic resonance; mRS, modified Rankin Scale; NPC, nasopharyngeal carcinoma; RROC, Raymond-Roy occlusion classification; RT, radiotherapy; SAH, subarachnoid hemorrhage; WFNS, World Federation of Neurological Surgeons.

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<https://doi.org/10.1016/j.neurad.2018.01.056>

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Please cite this article in press as: Victor CSH, et al. The angiographic and clinical outcomes of intracranial aneurysms following irradiation in patients with nasopharyngeal carcinoma: A 13-year experience and literature review. J Neuroradiol (2017), <https://doi.org/10.1016/j.neurad.2018.01.056>

the oncogenic herpes virus, environmental and genetic factors exist [6]. RT is the primary curative treatment modality for NPC. Together with early diagnosis, the relative five-year survival rate for stage I patients is as high as 72% [7]. When the disease is locally infiltrative, irradiation fields often encompass critical areas of the skull base such as the arteries at the skull base [8].

As NPC patients experience improved survival, the clinician should be cognizant of the potential delayed complications of RT. Due to their unique histopathology, the authors believe that the natural history of aneurysms following RT regarding their clinical outcomes and treatment response deserves special attention.

## Materials and methods

A single-center review was performed for selected patients over a 13-year study period from the 1st of January 2000 to the 31st of December 2012. Clinical, radiological and laboratory data were retrieved from patient records and all cerebral angiograms were reviewed. The inclusion criteria were: (i) age of 18 years and above, (ii) a pre-existing diagnosis of NPC with a history of RT, (iii) a diagnosis of an intracranial aneurysm following RT, and (iv) a minimum follow-up duration of two years after aneurysm diagnosis. We excluded internal carotid artery pseudo-aneurysms following RT that presented as carotid blowout and considered them as a distinct disease entity with a different treatment strategy. In total, nine patients with fifteen intracranial aneurysms were identified. Institutional review board approval was obtained.

In addition to patient demographics and vasculopathic risk factors, we also reviewed medical comorbidities including hypertension, diabetes mellitus and hyperlipidemia. Important clinical parameters were documented, including the Glasgow Coma Score (GCS) upon presentation, and the subarachnoid hemorrhage (SAH) grade in accordance to the World Federation of Neurological Surgeons (WFNS) score. WFNS grades of I to III were considered as good clinical grade SAH, while grades IV to V were considered as poor grade hemorrhage. Radiological features such as aneurysm location, morphology and immediate angiographic outcome after treatment were reviewed. Treatment modalities adopted, mortality rates, and the length of inpatient hospitalization were also studied. Clinical outcomes of the patients were assessed via the Glasgow Outcome Score (GOS), and modified Rankin Score (mRS). Poor clinical outcomes were defined as GOS of 1–3, and mRS of 3–6. The primary endpoint of this study was angiographic aneurysm recurrence; secondary endpoints were mortality and functional outcome.

## Results

The clinical characteristics of the subjects and their intracranial aneurysms are summarized in Table 1. The median age at the time of aneurysm diagnosis was 56 years (range: 50–85 years). Six patients were male (67%) and three were female (33%). Two patients (22%) were smokers and none were regular alcohol drinkers. Four were hypertensive (44%) and one had hyperlipidemia. All patients were functionally independent prior to aneurysm diagnosis.

All NPC patients were treated by external beam RT. None underwent brachytherapy. The median latent period between the initiation of RT and the diagnosis of an intracranial aneurysm was nine years (4 months to 30 years). No underlying history of cerebral vascular pathology such as arteriovenous malformation was noted prior to aneurysm diagnosis. This was established by means of contrast-enhanced computed tomography (CT) performed prior to irradiation.

Apart from a single patient presenting with non-specific chronic headache not likely attributed to the aneurysm, the majority of

patients presented with SAH (eight patients, 89%). The median admitting GCS was 9/15, while the median WFNS grade was IV. Over half (five patients, 56%) presented with poor clinical grade SAH. Nine aneurysms were located at the anterior circulation; of which eight arose from the internal carotid artery, and one at the middle cerebral artery. Of the posterior circulation aneurysms, three were located at the vertebral artery, two at the basilar artery and one from the posterior inferior cerebellar artery. Fourteen aneurysms were saccular in morphology and only one aneurysm was fusiform. Multiple aneurysms, with concomitant parent artery stenosis, were diagnosed in three patients (33%). The size, aspect ratio and bottle-neck ratio of the studied aneurysms are included in Table 1. The aspect ratio is defined by the height/neck measurement of the aneurysm. The bottle-neck ratio is defined by the width/neck measurement of the aneurysm. A wide-necked aneurysm is defined as the aneurysm having a width of  $\geq 4$  mm or a bottle-neck ratio of  $< 2$ .

Of the 15 aneurysms included in our study, three were treated with flow diverters via the Pipeline<sup>®</sup> embolization device (PED, ev3, Irvine, CA, USA); another three were treated with primary endosaccular coil embolization; and two aneurysms were treated with stent-assisted coiling using the Neuroform EZ<sup>®</sup> Stent System (Boston Scientific Neurovascular, Fremont, CA, USA). The remainder two aneurysms were surgically clipped. Conservative management was adopted for a patient who was diagnosed with multiple intracranial aneurysms with poor clinical grade SAH and fulminant neurological deterioration.

The first modality of surveillance imaging for treated intracranial aneurysms was either CT angiography (CTA) for clipped aneurysms or magnetic resonance angiography (MRA) for aneurysms treated by endovascular intervention at six to nine months. Complete obliteration was observed in six aneurysms while the remaining four treated aneurysms demonstrated a residual neck on serial imaging. The Raymond-Roy occlusion classification (RROC) scheme for grading the occlusion of endovascular treatment of intracranial aneurysms has been included in Table 1. RROC I is defined by complete obliteration; RROC II with the presence of a residual neck; and RROC III is defined by the presence of a residual aneurysm.

Within a year of diagnosis, five of the treated aneurysms had recurred, presenting with rupture in three patients (38% of treated patients), and asymptomatic radiological recurrence with aneurysm regrowth in two patients (25% of treated patients). The median length of hospitalization was 43 days (range: 5–445 days). A single patient (patient 4) had a prolonged hospitalization of up to 15 months due to complications of severe neurological sequelae including dysphagia and aspiration pneumonia.

A poor clinical grade hemorrhage tended to reflect poor neurological outcome. The median modified Rankin Scale (mRS) at both one-year and two-years of follow-up was 5, reflecting that most patients were severely disabled, requiring constant caregiver attention. The median Glasgow Outcome Score (GOS) at both of these follow-up time points was 2, with most SAH survivors being in a persistent vegetative state. The overall 1-month all-cause mortality rate was 13%. Four out of the eight patients (50%) with ruptured intracranial aneurysms died within two years of aneurysm diagnosis (range: 4 days to 23 months).

## Discussion

*The pathogenesis of intracranial aneurysms following radiotherapy*

This case series is the first to review intracranial aneurysms following RT within a defined cohort of NPC patients. Although the

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