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ORIGINAL ARTICLE

CME

Radiotherapy for Nasopharyngeal Carcinoma as a Risk Factor for Extracranial Carotid Stenosis. Is It Also a Risk Factor for Intracranial Arteries? A Retrospective Case-control Study

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ABSTRACT

Objective: *Carotid duplex ultrasound has revealed that radiotherapy is associated with stenosis of the extracranial carotid arteries in patients with nasopharyngeal carcinoma (NPC). The objective of the study was to determine the relationship between intracranial and extracranial arterial stenosis and radiation therapy using computed tomographic angiography (CTA) in patients with NPC and a history of symptomatic cerebral ischaemia.*

Methods: *This was a retrospective case-control study conducted in Pok Oi Hospital, Hong Kong. All consecutive CTA scans of the head and neck from January 2008 to December 2009 in patients with a history of transient ischaemic attack or ischaemic stroke were included. Intracranial arterial (including intracranial internal carotid artery, M1 segment of middle cerebral artery, and intracranial vertebral artery) and extracranial arterial stenosis was defined as a diameter reduction of ≥50%. Patient demographics, history of radiotherapy for NPC, smoking history, medical history of diabetes mellitus, hypertension, and hyperlipidaemia were recorded.*

Results: *A total of 152 patients (105 men and 47 women; mean [standard deviation] age, 64.9 [11.6] years) were enroled. Of them, 19 (12.5%) had a history of NPC and treatment by radiotherapy; 133 (87.5%) patients did not receive any head and neck radiotherapy. A statistically significantly increased risk of common carotid artery stenosis ($p < 0.001$; adjusted odds ratio = 34.510) and extracranial arterial stenosis ($p = 0.001$; adjusted odds ratio = 6.607) was observed in patients with NPC treated with radiotherapy compared with those without irradiation. Radiotherapy did not increase the risk of intracranial arterial stenosis (10/19 [52.6%] vs. 75/133 [56.4%]; $p = 0.710$).*

Conclusion: *Radiotherapy for NPC is associated with an increased risk for stenosis of the extracranial arteries, particularly the common carotid artery. Radiotherapy for NPC was not shown to increase the risk of intracranial artery stenosis based on CTA findings in patients with symptomatic cerebral ischaemia.*

Key Words: *Angiography; Carotid stenosis; Nasopharyngeal carcinoma; Radiotherapy; Tomography, X-ray computed*

中文摘要

鼻咽癌放射治療作為誘發顱外頸動脈狹窄的危險因素之一，是否也為顱內動脈的危險因素？回顧性病例對照研究

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目的：頸動脈多普勒超聲顯示放射治療與鼻咽癌（NPC）患者的顱外動脈狹窄有關。本研究的目的

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在於運用電腦斷層血管造影術（CTA）確定鼻咽癌以及有症狀性腦缺血病史的人群中，其顱內外動脈狹窄與放射治療的關係。

方法：本回顧性病例對照研究在香港博愛醫院進行。2008年1月至2009年12月期間接受CTA掃描的短暫性腦缺血發作或缺血性中風患者被陸續納入研究。顱內動脈（包括顱內頸內動脈、大腦中動脈M1段和顱內椎動脈）和顱外動脈狹窄的定義為50%或以上的直徑減小。本研究記錄了患者的人口學數據、NPC的放射治療病史、吸煙史、糖尿病史、高血壓和高血脂。

結果：總計152名患者納入研究（105名男性和47名女性；平均年齡64.9歲，標準差11.6歲）。其中19人（12.5%）曾因NPC而接受放射治療，133人（87.5%）未接受任何頭頸部放射治療。與沒有接受放射治療的患者比較，接受放射治療的NPC患者的頸總動脈狹窄（調整後比值比=34.510；p<0.001）和顱外動脈狹窄（調整後的比值比=6.607；p=0.001）的風險顯著增加。然而放射治療沒有增加顱內動脈狹窄的風險（10/19〔52.6%〕比75/133〔56.4%〕；p=0.710）。

結論：NPC放射治療與顱外動脈狹窄的風險增加有關，尤其是頸總動脈。根據症狀性腦缺血患者的CTA掃描結果，NPC放射治療不會增加顱內動脈狹窄的風險。

INTRODUCTION

Nasopharyngeal carcinoma (NPC) is a unique disease in terms of its geographical distribution, and biological association with the Epstein-Barr virus.[1] Endemic to China and South-East Asia, this cancer reaches an annual incidence rate of about 14 per 100,000 person-years in Hong Kong. NPC is also the fifth leading cause of cancer among males in Hong Kong.[2]

External irradiation is the treatment of choice for early NPC, as well as adjuvant treatment of local and cervical lymph node recurrences.[3]

Delayed complications resulting from radiotherapy for NPC, a cancer treated with a high dose of radiation to a fairly large region, are common and well-recognised. Temporal lobe necrosis, one of the most notorious post-radiation complications, has an incidence that ranges from 3% to 20% but can be as high as 40% when hyperfractionated radiotherapy is employed.[4-7]

The extracranial carotid artery and intracranial arteries such as intracranial internal carotid artery (ICA), and M1 segment of middle cerebral artery (MCA), which lie in close proximity to the temporal lobe and the intracranial vertebral arteries, are all within or near the irradiation field for treatment of NPC. Radiation-induced injury either causing or accelerating atherosclerotic changes in the carotid arteries has been well-documented in both experimental animal and human subjects.[8-17]

Thus the possibility of post-irradiation intracranial arterial stenosis due to atherosclerosis is a particular concern. Intracranial atherosclerotic stenosis is a significant risk factor for stroke and is postulated to cause approximately 15% of all ischaemic events.[18] We hypothesise that there may be an increased rate of intracranial arterial stenosis in patients with NPC who have undergone radiotherapy.

METHODS

Patients

This was a retrospective case-control study conducted at Pok Oi Hospital in Hong Kong, a collaborative hospital of Tuen Mun Hospital. The study was approved by the Clinical and Research Ethics Committee of New Territories West Cluster of Hospital Authority, Hong Kong. Consecutive computed tomographic angiography (CTA) scans of the head and neck performed from January 2008 to December 2009 were selected. The inclusion criteria were patients with symptomatic cerebral ischaemia, and transient ischaemic attack (TIA) or ischaemic stroke. The demographics, clinical history of TIA or stroke, history of radiotherapy for NPC, history of smoking, medical history of diabetes mellitus (DM), hypertension, and hyperlipidaemia were retrieved from the electronic Patient Record.

Image Acquisition

CTA was acquired with a 64-detector row scanner (Aquilion 64; Toshiba Medical Systems, Otawara, Japan). Intravenous iohexol (Omnipaque 300; GE Healthcare Inc., Buckinghamshire, UK) or iopamidol (Iopamiro 300; Bracco SpA, Milan, Italy) was injected with a power injector via the venous access preferably via the right arm at a rate of 4 ml/s. Subsequent contrast computed tomography (CT) scans of the neck and circle of Willis (CoW) were acquired separately. For the CTA of the neck region, the region of interest (ROI) for the bolus chasing was placed over the descending aorta at the start level with a scan trigger attenuation of 170 Hounsfield unit. Data were acquired from the aortic arch to the external auditory meatus. The scan parameters were as follows: 120 kV, automatically modulated mA; thickness 0.5 mm; increment 0.4 mm. For the CT of the CoW, the ROI for the bolus chasing was placed over the carotid artery at C1 level by the operator (manual tracker). This had the advantage of ensuring optimal enhancement of the vessels. Data were acquired from C1 level to midbrain level. The scan parameters for CTA of the CoW were as follows: 120 kV, automatically modulated mA; thickness 0.5 mm; increment 0.3 mm. Subtraction would be performed. Various post-processing techniques including two-dimensional (2D) cross-sectional multiplanar reformation (MPR), 3D volume rendering (VR), and 2D curve planar reformation (CPR) were made on a Vitrea workstation (Vitrea3; Toshiba Medical Systems, Otawara, Japan). Non-contrast CT of the brain and neck were also obtained.

Image Analysis

The source images, 3D VR, cross-sectional MPR and CPR images were reviewed at a Vitrea workstation by

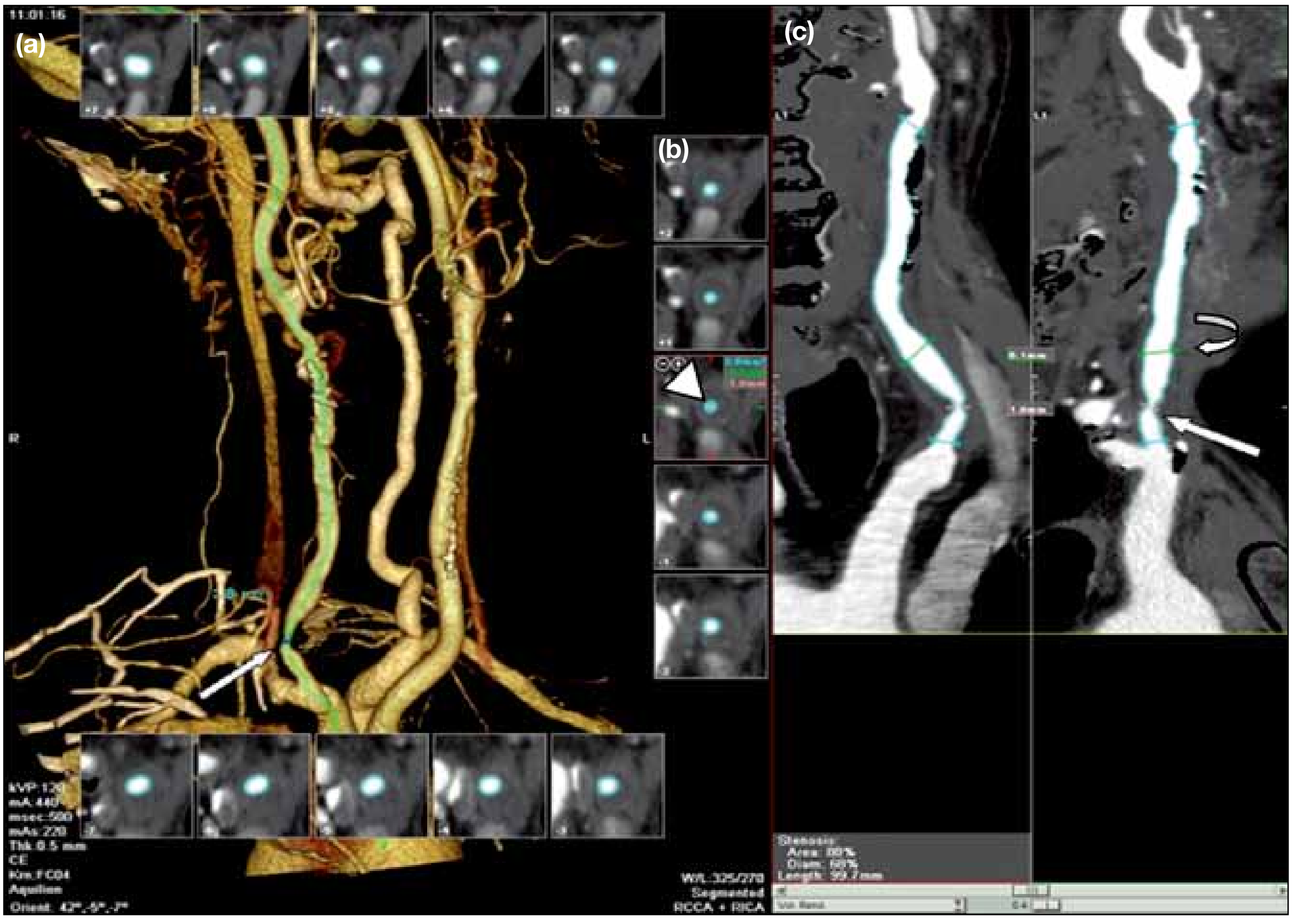

Figure. Stenosis of right common carotid artery (CCA) in a 75-year-old man with cerebrovascular accident who presented with left hemiparesis. The patient had a history of nasopharyngeal carcinoma treated with radiotherapy more than 20 years ago. He also had a history of smoking, hypertension, diabetes mellitus, and hyperlipidaemia. The reformed images were generated from multidetector row computed tomography data for vascular analysis. (a) A 3-dimensional volume-rendering image provides an overview of the stenotic lumen (arrow) in the proximal third of the CCA. (b) Cross-sectional multiplanar reformation images at different levels demonstrate varying degrees of luminal enhancement. The narrowest level (arrowhead) had a diameter of 1.9 mm and was defined as the lesion site (L). (c) Curve planar reformation images show the corresponding lesion site (arrow). The normal-looking level of the CCA (curved arrow) distal to the lesion site had a diameter of 6.1 mm and was defined as the reference site (R). The calculated degree of diameter stenosis by the NASCET criteria was 68%. It was defined as significant stenosis by our criteria as the luminal diameter reduction was ≥50%.

two dedicated fellow radiologists. A consensus was reached after discussion if findings were debatable. The window setting of the source and reformed images could be individually adapted by the readers if deemed appropriate. The lesion site (L) was defined as the residual lumen of minimum diameter along the artery. The reference site (R) was defined as the normal-looking portion of the stenotic vessel distal to the lesion. The degree of diameter stenosis was calculated by the NASCET (North American Symptomatic Carotid Endarterectomy Trial) criteria: degree of stenosis = (1-L/R) x 100% (Figure). Intracranial arterial stenosis (including intracranial segment of ICA, M1 segment of MCA and intracranial segment of vertebral artery) and extracranial arterial stenosis (including common carotid artery, and extracranial ICA) was defined as a luminal diameter reduction of ≥50%.

Statistical Analysis

Statistical analysis was performed using the Statistical Package for the Social Sciences (SPSS version 18.0, SPSS Inc., Chicago [IL], USA). Descriptive statistics were provided when appropriate. The presence of arterial stenosis was determined in the common carotid artery, extracranial ICA, intracranial ICA, M1 segment of MCA, and intracranial vertebral artery. The relationship between age and presence of arterial stenosis was analysed by independent sample *t*-test. The relationship between gender, history of radiotherapy for NPC, smoking history, medical history of DM, hypertension, hyperlipidaemia, and the presence of arterial stenosis was analysed with Pearson Chi-square test. Binary logistic regression forward step likelihood ratio analysis was used to determine the association between radiotherapy, vascular risk factors, and the presence of arterial stenosis. Independent variables with $p < 0.2$ were put into the regression model one in each time in a forward stepwise fashion. A p value of <0.05 was taken as statistically significant.

RESULTS

There were 152 consecutive patients who fulfilled the inclusion criteria (105 men, 47 women; mean age of 64.9 years). Among the 152 patients, 19 (12.5%) patients had radiotherapy for NPC. The mean duration between time of radiotherapy and CTA was 14.8 years (range, 2-30 years). DM was present in 52 (34.2%) patients. Over 50% of the study population had a positive history of smoking (57.9%), hypertension (78.3%), and hyperlipidaemia (73.0%). The basic demographic characteristics, radiation therapy for NPC, and vascular risk factors of the study population are shown in Table 1.

Of the 152 patients, 60 (39.5%) had stenosis of the extracranial arteries. Among these, 17 had common carotid artery stenosis; 52 had extracranial ICA stenosis; and 9 had both common carotid and extracranial ICA stenosis.

More than half of the patients had intracranial arterial stenosis (85/152, 55.9%). Among the 19 NPC patients with radiotherapy, 10 (52.6%) had intracranial arterial stenosis. In the 133 patients without irradiation, 75 (56.4%) patients had intracranial arterial stenosis.

Table 2 summarises the number of patients with significant stenosis of the extracranial and intracranial arteries. Radiotherapy was significantly associated with

Table 1. Patient demographic characteristics, radiation therapy for NPC, and associated vascular risk factors.

Characteristics	Data*
Gender	
Male	105 (69.1%)
Female	47 (30.9%)
Age (years)	64.9 ± 11.6
Radiation therapy for NPC	19 (12.5%)
Duration between RT and CTA (years)	14.8 (2-30)
Smoking	88 (57.9%)
Diabetes mellitus	52 (34.2%)
Hypertension	119 (78.3%)
Hyperlipidaemia	111 (73.0%)

Abbreviations: CTA = computed tomographic angiography; NPC = nasopharyngeal carcinoma; RT = radiotherapy.
* Data are shown as No. (%), mean ± standard deviation, or mean (range).

Table 2. Summary of presence of significant stenosis of the extracranial and intracranial arteries.

Arteries	No. (%) of patients	
	Significant stenosis	No significant stenosis
Extracranial arteries	60 (39.5)	92 (60.5)
CCA	17 (11.2)	135 (88.8)
Extracranial ICA	52 (34.2)	100 (65.8)
Intracranial arteries	85 (55.9)	67 (44.1)
Either extracranial or intracranial arteries	106 (69.7)	46 (30.3)
Both intracranial and extracranial arteries	38 (25.0)	114 (75.0)

Abbreviations: CCA = common carotid artery; ICA = internal carotid artery.

common carotid artery stenosis (p<0.001, adjusted odds ratio [OR] = 34.510) in patients with symptomatic cerebral ischaemia (Table 3). It was also associated with stenosis of the extracranial arteries (p=0.001, adjusted OR = 6.607), either the intracranial/extracranial arteries (p=0.035, adjusted OR = 4.522), and both intracranial and extracranial arteries (p=0.026, adjusted OR = 3.650) [Table 4]. No statistically significant association was demonstrated between radiotherapy and the incidence of significant stenosis of the extracranial

Table 3. Binary logistic regression forward step likelihood ratio analysis for extracranial artery, common carotid artery, and extracranial internal carotid artery stenosis with radiotherapy and vascular risk factors.

Stenosis	Risk factor	p Value	Adjusted OR	95% CI
Extracranial arteries	RT	0.001	6.607	2.060-21.188
	Smoking	<0.001	4.472	2.057-9.725
	Gender	0.391		
	DM	0.429		
	Hypertension	0.671		
	Hyperlipidaemia	0.614		
	Age	0.087		
CCA	RT	<0.001	34.510	7.999-148.885
	Smoking	0.006	12.958	2.087-80.460
	Gender	0.529		
	DM	0.092		
	Hypertension	0.309		
	Hyperlipidaemia	0.745		
	Age	0.508		
ExCr_ICA	Smoking	0.003	3.122	1.490-6.545
	RT	0.423		
	Gender	0.602		
	DM	0.306		
	Hypertension	0.566		
	Hyperlipidaemia	0.534		
	Age	0.176		

Abbreviations: CCA = common carotid artery; CI = confidence interval; DM = diabetes mellitus; ExCr_ICA = extracranial internal carotid artery; OR = odds ratio; RT = radiotherapy.

Table 4. Binary logistic regression forward step likelihood ratio analysis for intracranial arteries, either intracranial / extracranial arteries, and both intracranial and extracranial arteries stenosis with radiotherapy and vascular risk factors.

Stenosis	Risk factor	p Value	Adjusted OR	95% CI
Intracranial arteries	Age	<0.001	1.090	1.052-1.113
	RT	0.710		
	Gender	0.457		
	Smoking	0.388		
	DM	0.716		
	Hypertension	0.435		
	Hyperlipidaemia	0.984		
Either intracranial or extracracranial arteries	RT	0.035	4.522	1.110-18.419
	Age	<0.001	1.106	1.062-1.152
	Gender	0.647		
	Smoking	0.087		
	DM	0.850		
	Hypertension	0.579		
	Hyperlipidaemia	0.576		
Both intracranial and extracranial arteries	RT	0.026	3.650	1.169-11.395
	Smoking	0.001	5.608	2.112-14.889
	Age	0.017	1.047	1.008-1.008
	Gender	0.704		
	DM	0.285		
	Hypertension	0.789		
	Hyperlipidaemia	0.534		

Abbreviations: CI = confidence interval; DM = diabetes mellitus; OR = odds ratio; RT = radiotherapy.

ICA or intracranial arteries. Age was associated with an increased incidence of stenosis of the intracranial arteries ($p<0.001$, adjusted OR = 1.090). Smoking was associated with an increased incidence of extracranial artery stenosis ($p<0.001$, adjusted OR = 4.472).

DISCUSSION

Extracranial carotid artery stenosis has been shown by multiple studies using duplex sonography to occur following radiotherapy in patients with NPC.[19-26] The effects of radiotherapy on intracranial arteries is less clear. Use of transcranial Doppler (TCD) to assess the intracranial arteries was reported by Tai et al.[26] It demonstrated an increased incidence of stenosis of the extracranial carotid arteries in NPC patients treated with radiotherapy. Nonetheless, radiotherapy was not shown to increase the risk of intracranial arterial stenosis.

We have shown by CTA that NPC patients treated with radiotherapy have a significantly increased risk of stenosis of the common carotid artery. This finding is in agreement with prior studies.[16,17,19-26]

Radiotherapy for NPC did not increase the risk for extracranial ICA stenosis in our study. This finding is in keeping with a previous study by Lam et al.[24] On the contrary, some studies have suggested extracranial ICA involvement.[16,17,20-22] This discrepancy may be related to differences in the imaging modalities used in the assessment of stenosis (CTA versus sonography), and differences in the radiation fields and dosages.[26]

Radiation-induced or accelerated atherosclerotic changes in the carotid arteries have been well documented.[10-17] Arterial stenosis was localised to the common carotid artery in our study, and there was no increased incidence of intracranial arterial stenosis. This may be explained by the fact that the intracranial arteries are not directly within the centre of radiation port, and there is bone surrounding the vessels, thus they are not exposed to the same radiation dosage as the extracranial arteries.

The findings of this study may have an important bearing on treatment planning because when the intracranial ICA or the MCA is involved, any kind of interventional procedure like carotid endarterectomy or stenting on the extracranial carotid arteries may not be beneficial.

It may be argued that our study included patients with a history of TIA or ischaemic stroke, who have an increased atherosclerotic risk. The additional effect of radiotherapy on the incidence of intracranial arterial stenosis may not be significant. Tai et al[26] compared the rate of intracranial arterial stenosis using TCD in 47 NPC patients who were treated with radiation and 47 healthy controls. They also demonstrated no increased risk from radiotherapy on the rate of intracranial stenosis.

Carotid duplex and TCD ultrasonography is the initial non-invasive screening tool for neurovascular disease.[27] They are operator-dependent and require skilled sonographers or radiologists and specific technical equipment.

Nonetheless, CTA was very accurate in assessing the degree of carotid stenosis. A meta-analysis of the diagnostic accuracy of CTA for the assessment of carotid stenosis by Koelemay et al[28] reported an overall sensitivity of 97% and specificity of 99%. CTA was also found to be reliable for severe stenosis with a sensitivity of 85% and specificity of 93% in the meta-analysis.

To the best of our knowledge, this is the first study to use CTA to determine the relationship between intracranial and extracranial arterial stenosis and radiation therapy in patients with NPC and a history of symptomatic cerebral ischaemia.

There were several limitations of our study. First, it was a small-scale study consisting of 19 patients with NPC treated by radiotherapy. Second, as a retrospective study, length of time bias may arise because patients with NPC may die from the malignancy or cerebrovascular events before the CTA examination. Selection bias may also occur because those who were severely debilitated might not have been referred for CTA and therefore were not included in this study.

Larger-scale, prospective, cross-sectional, or conventional angiographic studies are important to provide information about the relationship of stenosis of the intracranial arteries and radiation therapy.

CONCLUSION

We have shown by CTA that radiotherapy for NPC is a significant risk factor for common carotid artery stenosis. Radiotherapy was not shown to increase the risk of stenosis to the intracranial arteries. Our results are in agreement with most prior studies. This finding has an important bearing on treatment planning because when the intracranial ICA or the MCA is involved, any kind of interventional procedure on the extracranial carotid arteries may not be beneficial.

DECLARATION

No conflicts of interest were declared by authors.

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