Received:
5 October 2015

Revised:
17 February 2016

Accepted:
1 March 2016

<http://dx.doi.org/10.1259/bjr.20150815>

Cite this article as:

Zhou L, Xing P, Zou L, Shen J, Tian Y, Lu X. Middle cerebral artery stenosis in patients with nasopharyngeal carcinoma after radiotherapy: the incidence of stenosis and the risk factors. *Br J Radiol* 2016; **89**: 20150815.

FULL PAPER

Middle cerebral artery stenosis in patients with nasopharyngeal carcinoma after radiotherapy: the incidence of stenosis and the risk factors

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Objective: The purpose of the present study was to investigate the incidence of middle cerebral artery (MCA) stenosis by contrast-enhanced MR angiography (CE-MRA), and to evaluate the risk factors for significant (>50%) MCA stenosis in patients with nasopharyngeal carcinoma (NPC) after radiotherapy.

Methods: 116 patients with NPC after radiotherapy were recruited into the irradiation group to investigate the incidence and degree of MCA stenosis by CE-MRA. The results were compared with those of the control group, which comprised 57 newly diagnosed patients with NPC who did not receive radiotherapy. Furthermore, the risk factors for significant MCA stenosis were evaluated.

Results: There was a higher incidence of MCA stenosis in the irradiation group than in the control group in terms of patient number ($p = 0.000$) and vessel involvement ($p = 0.000$), respectively. The incidence of significant MCA stenosis in the irradiation group was 8.6%

(10/116 patients) and 5.2% (12/232 patients) in terms of patient number and vessel involvement, respectively. However, no significant MCA stenosis was found in the control group. Univariate analysis showed that hypercholesterolaemia, T₃₋₄ stage and longer time interval from radiotherapy were the risk factors related to significant MCA stenosis. Multivariate analysis demonstrated that only T stage was the independent risk factor for significant MCA stenosis development.

Conclusion: The results showed that radiation can cause MCA stenosis in patients with NPC after radiotherapy, especially in those with T₃₋₄ stage, and further study is needed.

Advances in knowledge: Radiation-induced MCA stenosis exists in patients with NPC after radiotherapy, and its prevalence is more common in patients with clinical T₃₋₄ stage.

INTRODUCTION

Definitive radiotherapy remains the mainstay treatment for nasopharyngeal carcinoma (NPC). Currently, the standard treatment modality for these patients consists of intensity-modulated radiotherapy and concurrent chemoradiotherapy with cisplatin-based regimens, which has been shown to improve clinical outcomes, even in those with locally advanced disease.¹ However, the issue of late complications after radiotherapy has become increasingly concerning for these long-term survivors, because radiation-induced complications have a significant adverse effect on health-related quality of life.²

Radiation-induced vascular injury has been well described previously.³ The vascular injury caused by radiotherapy may result in carotid artery stenosis and increase the risk of

neurological sequelae, such as stroke and transient ischaemic attack, because carotid arteries frequently receive high irradiation doses during the treatment of head and neck cancers, including NPC.³ To our knowledge, most of the previous studies in this field have focused on extracranial carotid artery stenosis.⁴⁻⁷ Our previous study suggested a wider range of the incidence of stenosis of the carotid and vertebral arteries in patients with NPC after radiotherapy compared with patients who did not receive radiotherapy.⁸ However, there are few studies that have assessed intracranial carotid artery stenosis in patients with NPC after radiotherapy by modern imaging diagnostic methods, including digital subtraction angiography, CT angiography and MR angiography (MRA). The middle cerebral artery (MCA), as the direct continuation of the intracranial carotid artery, may

also receive high radiation doses during the treatment course in patients with NPC. Therefore, we undertook the present study on patients with NPC after radiotherapy and investigated the incidence and degree of MCA stenosis by CE-MRA. Furthermore, the risk factors for significant MCA stenosis were evaluated.

METHODS AND MATERIALS

Patients

The study was approved by the ethics committee of the Second Affiliated Hospital of Soochow University. Contrast-enhanced MR angiography (CE-MRA) is routinely used to evaluate vascular diseases in the hospital; therefore, only verbal informed consent was required from patients before CE-MRA in addition to concurrent routine follow-up MRI scanning. During the 24-month period between January 2013 and December 2014, patients with NPC after radiotherapy were recruited from a follow-up clinic at the Department of Radiation Oncology. The irradiation group included 116 patients (79 males and 37 females), with a median age of 57 years (range, 19–82 years), and the control group comprised 57 patients with newly diagnosed NPC who did not receive radiotherapy (33 males and 24 females), with a median age of 55 years (range, 18–85 years).

57 of the 116 patients in the irradiation group received two-dimensional conventional radiotherapy and 59 patients received intensity-modulated radiotherapy. The radiotherapy fields covered the nasopharynx and adjacent tissues at risk and both sides of the neck. Definitive-intent radiotherapy was administered to all patients using conventional 1.8–2.2-Gy daily fraction. The median total dose to the primary tumour was 70.3 Gy (range, 66.0–76.0 Gy), and the median accumulated doses were 66.4 Gy (range, 60.0–75.0 Gy) to the involved areas of the neck and 52.0 Gy (range, 45.0–57.8 Gy) to the uninvolved areas of the neck. Systemic concurrent, neoadjuvant and/or adjuvant chemotherapy was administered to 85 patients, with 68 patients receiving concurrent chemoradiotherapy.

Contrast-enhanced MR angiography and brain MRI scanning

All examinations were performed on a 1.5-T MRI scanner (Philips Achieva®; Philips Healthcare, Best, Netherlands) using a 16-channel sensitivity encoding head and neck phased-array coil.

For the CE-MRA series, a three-dimensional fast field echo sequence was acquired before (*i.e.* mask) and after the intravenous injection of the contrast agent in the coronal plane with the following parameters: repetition time (TR)/echo time (TE)/flip angle, 4.70 ms/1.72 ms/35°; matrix, 492 × 492; field of view (FOV), 320 × 320 mm²; slab thickness, 80 mm; section thickness, 1.30 mm with 0.65 mm overlap; 123 sections. The acquired voxel size was 0.65 × 0.65 × 1.30 mm³ and was reconstructed to a matrix of 640 × 640 with interpolation, yielding a spatial resolution of 0.5 × 0.5 × 0.65 mm. K-space was acquired using elliptic centric view ordering, and the scanning time was 1 min 4 s per acquisition. The contrast agent (gadopentetate dimeglumine) (Magnevist®; Bayer Schering Pharma AG, Berlin, Germany) was injected *via* the antecubital vein with a power injector (Mississippi XD 2000 CT/MRI, Ulrich Medical, Ulm, Germany) at a rate of 2.5 ml s⁻¹, followed by a saline (0.9%)

bolus of 30 ml at 2.5 ml s⁻¹. The contrast agent was given at a dose of 0.2 ml kg⁻¹ (or 0.4 mg kg⁻¹) bodyweight. The Bolus-Trak™ technique was used to track the bolus, and the post-contrast scan was immediately started at bolus arrival in the aortic arch.

For the brain series, *T*₂ weighted turbo spin-echo (TSE) images and *T*₁ weighted spin-echo (SE) images in the axial planes were obtained before injection of the contrast agent. After intravenous injection of the contrast agent, *T*₁ weighted SE axial and sagittal sequences and *T*₁ weighted SE fat-suppressed coronal sequences were performed. The *T*₂ weighted TSE image parameters included: TR, 4847 ms; TE, 100 ms; flip angle, 90°; matrix, 512 × 512; FOV, 230 × 230 mm²; TSE factor, 15. The *T*₁ weighted SE image parameters included: TR, 650 ms; TE, 15 ms; flip angle, 90°; matrix, 256 × 256; FOV, 230 × 230 mm². In the axial plane, the section thickness was 6.0 mm, with a 1.2-mm interslice gap, while in other planes, the section thickness was 4.5 mm, with a 1.0-mm interslice gap.

The CE-MRA image data were sent to a dedicated workstation (Extended MR Workspace 2.6.3.2; Philips Medical Systems, Best, Netherlands), and a vessel analysis software (vessel explorer; Philips Medical Systems) was used to assess MCA stenosis. Two neuroradiologists (LZ and JS) performed digital image processing to obtain both the maximum intensity projection and multiplanar reformation images for the identification of the MCA stenosis site. In addition, they defined the key anatomic points of interest, namely the point of maximal stenosis and the reference point according to the Warfarin–Aspirin Symptomatic Intracranial Disease criteria. The software automatically detects the vessel centreline and computes the cross-sectional area and minimum diameter at each point. The degree of MCA stenosis was evaluated by measuring the percentage reduction in the area of the true lumen, which was calculated according to the Warfarin–Aspirin Symptomatic Intracranial Disease criteria using the following equation: degree of stenosis (%) = [1 – area of minimal residual lumen (mm²)/area of the reference lumen (mm²)].⁹ According to Ahn's description, significant stenosis was defined as stenosis of >50% or occlusion.¹⁰

Data analysis

Statistical analysis was performed using a commercially available software package (SPSS®, v. 10 for Windows; IBM Corp., New York, NY; formerly SPSS Inc., Chicago, IL). Categorical variables were expressed as numbers (percentage) and χ^2 test was used to identify the difference between the two groups. Univariate and multivariate analyses of the risk factors for significant MCA stenosis were evaluated by a logistic regression model. For all tests, two-sided $p < 0.05$ was considered significant.

RESULTS

Patients

The follow-up time of all patients in the irradiation group was 12–191 months. There was no statistically significant difference in the median age or in the male-to-female ratio between the irradiation and control groups. No significant differences were found between the groups in terms of the number of patients who were smokers or with diabetes, hypercholesterolaemia,

hypertension, history of ischaemic heart disease and cerebrovascular disease or clinical stage. Patient characteristics are summarized in Table 1.

The incidence of middle cerebral artery stenosis

The incidence of MCA stenosis was 88.8% (103/116 patients) and 50.9% [(29/57 patients)] in the irradiation group and the control group in terms of patient number, respectively ($p = 0.000$). In terms of vessel involvement, the incidence of MCA stenosis was 77.6% (180/232 patients) and 33.3% (38/114 patients) in the irradiation group and the control group, respectively ($p = 0.000$). The incidence of significant MCA stenosis in the irradiation group was 8.6% (10/116 patients) and 5.2% (12/232 patients) in terms of patient number and vessel involvement, respectively. However, no significant MCA stenosis was found in the control group (Figure 1; Table 2).

Univariate analysis showed that hypercholesterolaemia, T_{3–4} stage and longer time interval from radiotherapy were the risk factors for the incidence of significant MCA stenosis. Patient age at receiving the CE-MRA scan, smoking, diabetes, hypertension, history of ischaemic heart disease and cerebrovascular disease, different radiotherapeutic techniques and chemotherapy were not significant variables (Table 3). Multivariate analysis demonstrated that only T stage was the independent risk factor for significant MCA stenosis development (Table 3).

DISCUSSION

Radiation-induced cerebrovasculopathy has been attracting more attention in long-term survivors who received cranial radiotherapy to treat their brain tumours, especially in children after cranial radiation.^{11,12} Involvement of the Willis' circle and MCA in the radiation fields in patients with NPC is unavoidable,

Table 1. Patient characteristics

Characteristics	Control group $n = 57$ (%)	Irradiation group $n = 116$ (%)	p -value
Median age (years)	55 (range: 18–85)	57 (range: 19–82)	0.279
Gender			
Male	33 (57.9)	79 (68.1)	0.730
Female	24 (42.1)	37 (31.9)	
Smoking			
No	44 (77.2)	90 (77.6)	0.954
Yes	13 (22.8)	26 (22.4)	
Diabetes			
No	54 (94.7)	106 (91.4)	0.431
Yes	3 (5.3)	10 (8.6)	
Hypercholesterolaemia			
No	51 (89.5)	102 (87.9)	0.766
Yes	6 (10.5)	14 (12.1)	
Hypertension			
No	41 (71.9)	93 (80.2)	0.223
Yes	16 (28.1)	23 (19.8)	
History of ischemic heart disease			
No	55 (96.5)	115 (99.1)	0.210
Yes	2 (3.5)	1 (0.9)	
History of cerebrovascular disease			
No	54 (94.7)	109 (94.0)	0.838
Yes	3 (5.3)	7 (6.0)	
Clinical stage ^a			
I	3 (5.3)	5 (4.3)	0.787
II	13 (22.8)	29 (25.0)	
III	25 (43.8)	57 (49.1)	
IV	16 (28.1)	25 (21.6)	

^aAccording to 2010 Union for International Cancer Control (UICC)/American Joint Committee on Cancer (AJCC) stage system.

Figure 1. Contrast-enhanced MR angiography scanning (maximum intensity projection image) showing significant middle cerebral artery (MCA) stenosis (arrow). (a) The patient received radiotherapy 7 years ago. The image shows significant stenosis of the M1 segment in the left MCA. (b) The patient received radiotherapy 6 years ago. The image shows significant stenosis of the M1 segment in the left MCA.

especially for those patients with skull base invasion and/or cavernous sinus involvement. This greatly increases the risk of radiation injury to the MCA, which may be a significant cause of stroke and transient ischaemic attack in these patients after radiotherapy. Ye et al¹³ used duplex ultrasonography to estimate the flow velocities of bilateral MCAs and found that the flow velocities of MCAs in patients with NPC after radiotherapy were significantly higher than those in healthy individuals, especially in those with temporal lobe necrosis. The results provide indirect evidence of radiation damage to the MCA. However, there are few studies assessing MCA stenosis in patients with NPC after radiotherapy using modern imaging diagnostic methods, including digital subtraction angiography, CT angiography and MRA. To our knowledge, this is the first study to evaluate MCA stenosis in patients with NPC after radiotherapy by using MRA. Our results show that the incidence of both MCA stenosis and significant (>50%) MCA stenosis was significantly higher in these patients after radiotherapy than in newly diagnosed patients who did not receive radiotherapy. Three possible mechanisms may be related to radiation injury to the medium and large arteries. The first is ischaemic necrosis caused by occlusion of the vasa vasorum, thereby resulting in loss of elastic tissue and muscle fibres. This is then followed by replacement with fibrosis. The second is adventitial fibrosis resulting in extrinsic compression. The third involves accelerated atherosclerosis.³ These processes are thought to result in morphological features similar to those seen in spontaneous, non-radiation atherosclerosis.¹⁴ Furthermore, Cheng et al¹⁵ found that radiation-induced artery stenosis progressed more rapidly than that of non-irradiated atherosclerotic arteries.

The present study attempted to analyze the risk factors for significant MCA stenosis in patients with NPC after radiotherapy. In the present study, univariate and multivariate analyses revealed that the incidence of significant MCA stenosis in patients with T₃₋₄ stage was higher than that of patients with T₁₋₂ stage. The standard of irradiation volume for patients with T₃₋₄ is to include the entire sphenoid sinus and the cavernous sinus in the radiation field, while the typical fields for patients with T₁₋₂ exclude the superior half of the sphenoid and cavernous sinus.¹⁶ We therefore hypothesize that radiation exposure may play a role in why patients with T₃₋₄ had a higher rate of MCA stenosis. However, we did not define MCA as the organ at risk in the treatment planning before and cannot evaluate the irradiation volume and doses of MCA. In addition, previous published studies have focused on investigating the risk factors of significant radiation-induced extracranial carotid artery stenosis. The time interval from radiotherapy, radiation-affected vessels and irradiation doses are thought to be important risk factors, in addition to increasing age, diabetes mellitus, hypertension, hypercholesterolaemia, obesity and smoking.^{3,17,18} Brown et al¹⁹ revealed that the incidence of significant carotid stenosis increased as the time after radiotherapy increased in head and neck cancer. We found that the time interval from radiotherapy and hypercholesterolaemia were the risk factors of significant MCA stenosis development in univariate analysis only ($p = 0.114$ and $p = 0.072$, respectively). We therefore think that perhaps better control of cholesterol levels may decrease the risk of MCA stenosis in patients with T₃₋₄ NPC.

Table 2. A comparison of the number of patients and vessels involved between the control and irradiation groups in terms of the incidence of middle cerebral artery stenosis

Parameter	Patients				Vessels			
	Control group $n = 57$ (%)	Irradiation group $n = 116$ (%)	χ^2	p -value	Control group $n = 114$ (%)	Irradiation group $n = 232$ (%)	χ^2	p -value
Stenosis	29 (50.9)	103 (88.8)	30.385	0.000	38 (33.3)	180 (77.6)	64.222	0.000
Significant stenosis	0 (0)	10 (8.6)	5.215	0.022	0 (0)	12 (5.2)	6.108	0.013

Table 3. Univariate and multivariate analysis of the risk factors for significant middle cerebral artery stenosis by logistic regression model in patients with nasopharyngeal carcinoma after radiotherapy ($n = 116$)

Variables	Univariate analysis		Multivariate analysis	
	HR (95% CI*)	<i>p</i> -value	HR (95% CI*)	<i>p</i> -value
Sex (male/female)	1.475 (0.390, 5.578)	0.567		
Age at receiving CE-MRA scanning (≤ 57 years/ > 57 years)	2.423 (0.594, 9.876)	0.217		
Time interval from radiotherapy (≤ 55 months/ > 55 months)	4.833 (1.12, 23.844)	0.049	3.929 (0.721, 21.406)	0.114
Smoking (no/yes)	1.547 (0.370, 6.457)	0.550		
Diabetes (no/yes)	1.198 (0.136, 10.551)	0.871		
Hypercholesterolaemia (no/yes)	6.400 (1.542, 26.556)	0.011	4.247 (0.879, 20.535)	0.072
Hypertension (no/yes)	3.053 (0.784, 11.882)	0.108		
History of ischemic heart disease (no/yes)	0.000 (0.000, –)	1.000		
History of cerebrovascular disease (no/yes)	1.852 (0.200, 17.122)	0.587		
T stage (T_{1-2}/T_{3-4})	9.125 (1.835, 45.388)	0.007	8.893 (1.683, 47.005)	0.010
Radiotherapy technique (2D-CRT/IMRT)	0.383 (0.094, 1.560)	0.180		
Chemotherapy (no/yes)	0.513 (0.134, 1.955)	0.328		

2D-CRT, two-dimensional conventional radiotherapy; CE-MRA, contrast-enhanced MR angiography; CI*, confidence interval; HR, hazard ratio; IMRT, intensity-modulated radiotherapy.

CONCLUSION

In conclusion, our results showed that radiation can cause MCA stenosis in patients with NPC after radiotherapy, especially for those with T_{3-4} stage, and further study is needed.

FUNDING

This study was supported by grants from Jiangsu Natural Science Funding (Grant number BK20141185) and Jiangsu Province's Key Medical Person (Grant number RC2011144).

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