Received:
1 March 2015

Revised:
1 April 2015

Accepted:
14 April 2015

doi: 10.1259/bjr.20150175

Cite this article as:

Zhou L, Xing P, Chen Y, Xu X, Shen J, Lu X. Carotid and vertebral artery stenosis evaluated by contrast-enhanced MR angiography in nasopharyngeal carcinoma patients after radiotherapy: a prospective cohort study. *Br J Radiol* 2015;88:20150175.

FULL PAPER

Carotid and vertebral artery stenosis evaluated by contrast-enhanced MR angiography in nasopharyngeal carcinoma patients after radiotherapy: a prospective cohort study

¹L ZHOU, MD, ²P XING, MD, ²Y CHEN, MD, ¹X XU, MS, ¹J SHEN, MD and ²X LU, MD, PhD

¹Department of Radiology, The Second Affiliated Hospital of Soochow University, Suzhou, China

²Department of Oncology & Radiotherapy, The Second Affiliated Hospital of Soochow University, Suzhou, China

Address correspondence to: Dr Xueguan Lu

E-mail: luxueguan@163.com

Objective: To investigate the incidence of carotid artery (CA) and vertebral artery (VA) stenosis by contrast-enhanced MR angiography (CE-MRA) in patients with nasopharyngeal carcinoma (NPC) after radiotherapy.

Methods: 72 patients with NPC after radiotherapy more than 3 years ago were recruited as irradiation group to investigate the incidence and degree of CA and VA stenosis by CE-MRA. The results were compared with those of the control group, which comprised 50 newly diagnosed patients with NPC who had not received radiotherapy.

Results: There was a higher incidence of CA and VA stenosis in the irradiation group than in the control group in terms of patient number as well as vessel involvement. The incidence of significant (>50%) CA and VA stenosis, except for the basilar artery, was also higher in the irradiation group than in the control group. The most commonly detected stenosis in the irradiation group was

found in the internal CA (ICA) and VA, followed by the external CA and common CA (CCA). CCA and/or ICA (CCA/ICA) stenosis was present in 67 (93.1%) of 72 patients, with 27 (37.5%) patients having significant CCA/ICA stenosis. The statistical analysis demonstrated that age at receiving CE-MRA scanning and time interval from radiotherapy were the independent predictors of significant CCA/ICA stenosis.

Conclusion: The CE-MRA scanning results showed that the incidence of stenosis seems to exist in a wider range of CAs and VAs in the patients with NPC after radiotherapy than in the patients who had not received radiotherapy, and the incidence of significant CCA/ICA stenosis is higher in patients with older age and longer interval from radiotherapy.

Advances in knowledge: Radiation-induced CA and VA stenosis exists widely in patients with NPC after radiotherapy, and its prevalence is more common in patients with older age and longer interval from radiotherapy.

Nasopharyngeal carcinoma (NPC) is one of the most common malignancies in China, and radiotherapy remains the standard treatment for these patients. Ongoing improvements in radiotherapeutic techniques and chemoradiotherapy have resulted in excellent locoregional control and survival rates in these patients, even in those with locally advanced disease.¹ Therefore, a significant proportion of patients are long-term survivors, and late complications of radiotherapy, such as temporal lobe necrosis, endocrine dysfunction, xerostomia, fibrosis of soft tissue and ear complications, are of utmost concern for patients and radiation oncologists.^{2,3} In addition, carotid and vertebral artery (VA) stenosis is also a well-documented late complication of radiotherapy in patients with NPC because severe carotid stenosis is associated with a high risk of stroke.^{3–5}

Diagnostic methods that are used to identify carotid artery (CA) and VA stenosis include digital subtraction angiography (DSA), ultrasonography, CT angiography (CTA) and MR angiography (MRA). DSA is the gold standard for the diagnosis and quantification of carotid stenosis. However, DSA is an invasive method with several limitations, including risk of neurological complications and the potential for variability in the quantification of stenosis. Hence, the diagnostic role of DSA has largely been replaced by non-invasive techniques such as ultrasonography, CTA and MRA.^{6,7} Colour Doppler ultrasonography (CDUS), as a rapid, readily available and low-cost technique, has been widely used in the clinic but may be restricted by its instability, operator dependence and limited coverage. Moreover, CDUS cannot provide three-dimensional (3D) and complete visualization of the

anatomical structures.⁸ CTA has the advantages of high spatial resolution, fast imaging and ease of calcified plaque identification. However, the patient needs to receive ionizing radiation.⁷ MRA, including non-enhanced MRA and contrast-enhanced MRA (CE-MRA), is considered to be a safe, convenient and non-invasive tool for detecting vessel stenosis.^{7–9} However, non-enhanced MRA is limited by local reduction of signal intensity related to slow and turbulent flow and also prolongs the imaging time.¹⁰ CE-MRA helps to overcome these limitations.^{7,11} Several studies revealed that CE-MRA was similarly accurate to CTA for evaluating carotid stenosis but was more accurate than CDUS.^{7–9} In most of the previous studies, radiation-induced CA and VA stenosis has been evaluated by ultrasonography and DSA in head and neck cancers,^{2–4} but few studies have assessed stenosis by CE-MRA. Therefore, we undertook the present prospective study in patients with NPC after receiving radiotherapy more than 3 years ago using newly diagnosed patients with NPC as control and investigated the incidence of CA and VA stenosis by CE-MRA.

METHODS AND MATERIALS

Patients

The ethics committee of The Second Affiliated Hospital of Soochow University approved the present study. Because CE-MRA has been routinely used to evaluate vascular diseases in the hospital, only verbal informed consent was required from patients before CE-MRA, in addition to routine follow-up MRI scanning at the same time. During the consecutive 18-month period between January 2013 and June 2014, patients with NPC after receiving radiotherapy more than 3 years ago were recruited from a follow-up clinic at the Department of Radiation Oncology. The irradiation group recruited 72 patients, including 44 males and 28 females, with a median age of 54 years (range, 19–81 years). The control group comprised 50 patients, including 29 males and 21 females with a median age of 54 years (range, 20–85 years), with newly diagnosed NPC who had not received radiotherapy.

57 of 72 patients in the irradiation group received two-dimensional conventional radiotherapy (2D-CRT), and 15 patients received intensity-modulated radiotherapy (IMRT). 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 fractionation (1.8–2.2 Gy daily fractions). The median total dose to the primary tumour was 71.0 Gy (range, 66.0–76.0 Gy). The median accumulated doses were 66.0 Gy (range, 60.0–75.0 Gy) to the involved areas of the neck and 51.4 Gy (95% range, 45.0–57.8 Gy) to the uninvolved areas of the neck. Systemic concurrent, neoadjuvant and/or adjuvant chemotherapy was administered to 44 patients.

Contrast-enhanced MR angiography scanning

All examinations were performed on a 1.5-T MRI scanner (Achieva®; Philips Healthcare, Best, Netherlands) by using a 16-channel SENSE head and neck phased-array coil. For the CE-MRA series, a three-dimensional T_1 fast field echo (3D-FFE) sequence was acquired before (*i.e.* mask) and after the intravenous injection of contrast agent in the coronal plane

with the following parameters: repetition time/echo time/flip angle, 4.70 ms/1.72 ms/35°; matrix, 492×492; field of view, 320×320 mm²; slab thickness, 80 mm; section thickness, 1.30 mm with 0.65-mm overlap; and 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 an elliptic centric view ordering, and the scanning time was 1 min 4 s per acquisition. 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, 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) of body weight. The Bolus Trak technique was used to track the bolus and immediately start the post-contrast scan at bolus arrival in the aortic arch.

CE-MRA image data were sent to a dedicated workstation (Extended MR WorkSpace 2.6.3.2; Philips Medical System, Best, Netherlands), and the vessel analysis software (vessel explorer, Philips Medical System) was used to assess CA and VA stenosis. Two neuroradiologists (LZ and JS) performed the digital image processing to obtain both the maximum intensity projection (MIP) and multiplanar reformation images for the identification of the site of stenosis of every carotid and vertebral basilar artery (BA). In addition, they defined the key anatomic points of interest, namely the point of maximal stenosis and the reference point according to the North American Symptomatic Carotid Endarterectomy Trial (NASCET). The software automatically detects the vessel centre line and computes the cross-sectional area and minimum diameter at each point. The degree of CA and VA stenosis was evaluated by measuring the percentage reduction in the area of the true lumen, which was calculated according to the NASCET using the following equation:¹²

$$\text{stenosis degree in percentage} = [1 - \frac{\text{the area of the minimal residual lumen (mm}^2\text{)}}{\text{the area of the reference lumen (mm}^2\text{)}}].$$

According to the description of Steele et al¹³ and Lam et al,⁴ significant stenosis was defined as stenosis of >50% or occlusion.

Data analysis

Statistical analysis was performed using a commercially available software package (SPSS® v. 10 for Windows; SPSS, Chicago, IL). Categorical variables were expressed as number (percentage), and χ^2 test was used to identify the difference between two groups and the risk factors associated with significant common CA and/or internal CA (CCA/ICA) stenosis, respectively. Significant variables were then entered into a multivariate logistic regression model to identify the independent risk factors. For all tests, a two-sided $p < 0.05$ was considered significant.

RESULTS

Patients

All patients in the irradiation group had radiotherapy completed for 36–191 months (median, 68 months). There was no

statistically significant difference in the median age and the male-to-female ratio between the irradiation group and control group. Also, between the two groups significant differences did not exist between the number of patients with smoking, diabetes, hypercholesterolaemia, hypertension, history of ischaemic heart disease and cerebrovascular disease. The patient characteristics are summarized in Table 1. There were three and six patients with symptomatic cerebrovascular disease in the control group and the irradiation group, respectively.

Contrast-enhanced MR angiography findings

There was higher incidence of CA and VA stenosis in the irradiation group than in the control group in terms of patient number as well as vessel involvement. The incidence of significant CA and VA stenosis, except for the BA, was also higher in

the irradiation group than in the control group. No incidence of significant BA stenosis was found in both the groups (Figure 1, Tables 2 and 3).

The most commonly detected stenosis in the irradiation group was found in ICA and VA, followed by external CA (ECA) and CCA. CCA/ICA stenosis was present in 67 (93.1%) of 72 patients, with 27 (37.5%) patients having significant CCA/ICA stenosis. 2 of 27 patients with significant CCA/ICA stenosis received stenting treatment.

Univariate analysis by χ^2 test showed that significant CCA/ICA stenosis was correlated with age at receiving CE-MRA scanning ($p = 0.001$) and time interval from radiotherapy ($p = 0.028$). Smoking, diabetes, hypercholesterolaemia, hypertension, history

Table 1. Patient characteristics

Parameters	Control group <i>n</i> = 50 (%)	Irradiation group <i>n</i> = 72 (%)	<i>p</i> -value
Median age (years)	54 (range, 20–85)	54 (range, 19–81)	0.933
Gender			
Male	29 (58.0)	44 (61.1)	0.730
Female	21 (42.0)	28 (38.9)	
Smoking			
No	39 (78.0)	59 (81.9)	0.590
Yes	11 (22.0)	13 (18.1)	
Diabetes			
No	47 (94.0)	68 (94.4)	0.917
Yes	3 (6.0)	4 (5.6)	
Hypercholesterolaemia			
No	44 (88.0)	58 (80.6)	0.275
Yes	6 (12.0)	14 (19.4)	
Hypertension			
No	36 (72.0)	60 (83.3)	0.133
Yes	14 (28.0)	12 (16.7)	
Symptomatic ischaemic heart disease			
No	48 (96.0)	71 (98.6)	0.360
Yes	2 (4.0)	1 (1.4)	
Symptomatic cerebrovascular disease			
No	47 (94.0)	66 (91.7)	0.628
Yes	3 (6.0)	6 (8.3)	
Clinical stage ^a			
I	3 (6.0)	3 (4.2)	0.941
II	13 (26.0)	19 (26.4)	
III	23 (46.0)	36 (50.0)	
IV	11 (22.0)	14 (19.4)	

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

of ischaemic heart disease and cerebrovascular disease, different radiotherapeutic techniques and chemotherapy were not significant variables (Table 4). On multivariate logistic regression analysis, age at receiving CE-MRA scanning and time interval from radiotherapy were the independent predictors of significant CCA/ICA stenosis (Table 5).

DISCUSSION

CA and VA stenosis is a common complication of external irradiation in head and neck cancers.^{4,13–18} Several studies found increased rates of CA stenosis more than 5 years after radiotherapy,^{15,19} but many have noted significant rates of CA stenosis as early as 1–2 years after radiotherapy.^{20,21} Therefore, the eligibility criteria were different in different studies. In the present study, we recruited patients with NPC more than 3 years after radiotherapy to evaluate radiation-induced carotid stenosis according to the study by Lam et al.² Radiation-induced vessel stenosis is believed to be caused by

a combination of direct vessel wall damage leading to intimal proliferation, necrosis of the media, periadventitial fibrosis and accelerated atherosclerosis, and indirect effects resulting from radiation-induced obliteration of the adventitial vasa vasorum.^{3,15} Cheng et al²² found that carotid stenosis associated with external irradiation progressed more rapidly than that in non-irradiated atherosclerotic arteries. The reported annual progression rate of carotid stenosis was 15.4% and 4.8% in the irradiated and non-irradiated groups, respectively. These results suggest that the development of radiation-induced stenotic lesions cannot be attributed to pre-mature atherosclerosis alone but rather to a more aggressive disease with a different biological behaviour. Lam et al⁴ studied the incidence of carotid stenosis by using CDUS in 71 patients with NPC after radiotherapy. They found that CCA/ICA in the post-radiation group was more commonly involved than in the non-irradiated group [77.5% (55/71) vs 21.6% (11/51); $p < 0.01$], followed by ECA [45.1% (32/71) vs 2.0% (1/51); $p < 0.01$] and

Figure 1. Contrast-enhanced MR angiography scanning showing significant stenosis in different carotid arteries (CAs) and vertebral arteries (VAs) (arrows): (a) left common CA stenosis; (b) left internal CA stenosis; (c) left external CA stenosis; and (d) left VA stenosis (thick arrow) and right VA occlusion (thin arrows) and right ECA stenosis (curved arrow).

Table 2. Comparison of number of patients between two groups with the incidence of carotid artery (CA) and vertebral artery (VA) stenosis

Vessel	Stenosis				Significant stenosis			
	Control group <i>n</i> = 50 (%)	Irradiation group <i>n</i> = 72 (%)	χ^2	<i>p</i> -value	Control group <i>n</i> = 50 (%)	Irradiation group <i>n</i> = 72 (%)	χ^2	<i>p</i> -value
CCA	4 (8.0)	49 (68.1)	43.316	0.000	0 (0)	9 (12.5)	6.748	0.009
ICA	21 (42.0)	66 (91.7)	35.580	0.000	2 (4.0)	22 (30.6)	13.168	0.000
CCA/ICA	22 (44.0)	67 (93.1)	35.986	0.000	2 (4.0)	27 (37.5)	18.276	0.000
External CA	2 (4.0)	53 (73.6)	57.754	0.000	0 (0)	12 (16.7)	9.242	0.002
VA	19 (38.0)	59 (81.9)	24.713	0.000	2 (4.0)	25 (34.7)	16.161	0.000
Basilar artery	1 (2.0)	12 (16.7)	9.242	0.002	0 (0.0)	0 (0)	–	–

CCA, common CA; ICA, internal CA.

VA [7.0% (5/71) *vs* 0% (0/51); $p < 0.069$]. The significant stenosis was only found in the post-radiation group [29.6% (21/71) in CCA/ICA, 15.5% (11/71) in ECA and 5.6% (4/71) in VA]. In the present study, we applied CE-MRA to investigate CA and VA stenosis. The results showed that there was no significant difference in the incidence of risk factors between the irradiation group and control group. However, the incidence of CA and VA stenosis was more common in the irradiation group than in the control group. Our results further confirmed that radiation might be the main reason for the high incidence of CA and VA stenosis in patients with NPC after radiotherapy.

In addition, our results also showed that the incidence of CA and VA stenosis in our study (Tables 2 and 3) was higher than in previous studies.^{2,4} The differences in these results may be caused by different measurement methods. The percentage reduction in the diameter of the true lumen, as detected by ultrasonography, was used to define the degree of vessel stenosis in previous studies. By contrast, we evaluated the degree of vessel stenosis by measuring the percent reduction

in the area of the true lumen. Several studies confirmed that area measurement correlated well with the results of DSA for assessment of vessel stenosis, and it was more accurate than the diameter assessment, especially for arteries with an irregular lumen.^{23,24} In addition, ultrasonography cannot provide 3D images or detect intracranial carotid stenosis. However, MIP images of CE-MRA can provide multiple projections of the CAs and can display a panoramic view of the CAs.⁸

The present study also attempted to identify significant risk factors for carotid stenosis in patients with NPC after radiotherapy. We found that the patient age was an independent predictor of significant CCA/ICA stenosis, which was in agreement with the findings of Li et al,³ Cheng et al¹⁵ and King et al.²⁵ Moreover, time interval from radiotherapy was also an independent predictor of significant CCA/ICA stenosis. Cheng et al²⁶ found that patients with NPC who had undergone radiotherapy more than 5 years ago had a higher chance of having severe carotid stenosis than those less than 5 years ago (26% *vs* 6%; $p = 0.001$). Similarly, Brown et al¹⁶ also revealed that the incidence of significant carotid stenosis

Table 3. Comparison of the number of vessels between two groups with the incidence of carotid artery (CA) and vertebral artery (VA) stenosis

Vessel	Stenosis				Significant stenosis			
	Control group <i>n</i> = 100 (%)	Irradiation group <i>n</i> = 144 (%)	χ^2	<i>p</i> -value	Control group <i>n</i> = 100 (%)	Irradiation group <i>n</i> = 144 (%)	χ^2	<i>p</i> -value
Common CA	7 (7.0)	71 (49.3)	48.567	0.000	0 (0)	12 (8.3)	8.764	0.003
Internal CA	28 (28.0)	114 (79.2)	63.509	0.000	2 (2.0)	33 (22.9)	21.015	0.000
External CA	2 (2.0)	82 (56.9)	78.922	0.000	0 (0)	16 (11.1)	11.891	0.001
VA	25 (25.0)	98 (68.1)	43.764	0.000	2 (2.0)	31 (21.5)	19.243	0.000

increased as the time after radiotherapy increased in head and neck cancer. Other risk factors such as smoking, diabetes, hypercholesterolaemia, hypertension and history of ischaemic heart disease were not related to the prevalence for carotid stenosis in the present study. The results were in agreement with the findings reported by Steele *et al*¹³ and So *et al*.²⁷ In addition, different types of radiotherapeutic techniques

(2D-CRT *vs* IMRT) also had no effect on the incidence of significant CCA/ICA stenosis. The possible reason for this was that the irradiated field of both the two techniques included all of the CCA/ICA.

There are several treatment choices to deal with significant carotid stenosis, including endarterectomy, and angioplasty and

Table 4. Risk factors for significant common carotid artery (CCA)/internal carotid artery (ICA) stenosis in patients with nasopharyngeal carcinoma after radiotherapy evaluated by χ^2 ($n = 72$)

Variable	Significant CCA/ICA stenosis		
	n (%)	χ^2	p -value
Gender			
Male	17/44 (38.6)	0.062	0.803
Female	10/28 (35.7)		
Age at receiving contrast-enhanced MR angiography scanning (years)			
≤ 54	6/34 (17.6)	10.833	0.001
> 54	21/38 (55.3)		
Time interval from radiotherapy (months)			
≤ 68	9/36 (25.0)	4.800	0.028
> 68	18/36 (50.0)		
Smoking			
No	22/59 (37.3)	0.006	0.937
Yes	5/13 (38.5)		
Diabetes			
No	25/68 (36.8)	0.282	0.595
Yes	2/4 (50.0)		
Hypercholesterolaemia			
No	22/58 (37.9)	0.024	0.878
Yes	5/14 (35.7)		
Hypertension			
No	22/60 (45.5)	0.107	0.744
Yes	5/12 (54.5)		
History of ischaemic heart disease			
No	26/71 (36.6)	1.690	0.194
Yes	1/1 (100.0)		
History of cerebrovascular disease			
No	24/66 (36.4)	0.436	0.509
Yes	3/6 (50.0)		
Radiotherapy technique			
Two-dimensional conventional radiotherapy	24/57 (41.1)	2.476	0.116
Intensity-modulated radiotherapy	3/15 (20.0)		
Chemotherapy			
No	7/22 (31.8)	0.295	0.587
Yes	17/44 (38.6)		

Table 5. Multivariate logistic regression analysis of significant common carotid artery/internal carotid artery stenosis in patients with nasopharyngeal carcinoma after radiotherapy ($n = 72$)

Variable	Beta	95% confidence interval	p-value
Age at receiving contrast-enhanced MR angiography scanning (years)	1.737	(1.851, 17.422)	0.002
Time interval from radiotherapy (months)	1.076	(0.998, 8.621)	0.050

stenting. Endarterectomy may be difficult to use to treat the radiation-induced carotid stenosis because of arterial wall fibrosis, tissue plane scarring, prosthetic infection, anastomotic dehiscence, surgically inaccessible proximal lesions and increased risk of wound complications.²⁸ Moreover, radiation-induced carotid stenotic lesions often extensively involve bilateral CAs, rendering endarterectomy infeasible. Carotid angioplasty and stenting has become a good alternative for these patients. Yu et al²⁹ evaluated the procedural safety, clinical and angiographic outcome of carotid angioplasty and stenting for significant (>70%) radiation-induced carotid stenosis using atherosclerotic stenosis as the control in a 6-year prospective non-randomized study. The results showed that the safety, effectiveness and technical difficulty of carotid angioplasty and stenting for radiation-induced carotid stenosis are comparable with that of atherosclerotic stenosis. However, the patients with radiation-induced carotid stenosis have higher incidence of in-stent restenosis. In the present study, 2 of 27 patients

with significant CCA/ICA stenosis had also received the stenting treatment safely.

CONCLUSIONS

In conclusion, CE-MRA scanning results showed that the incidence of stenosis seems to exist in a wide range of CAs and VAs in the patients with NPC after radiotherapy compared with the patients who had not received radiotherapy, and the incidence of significant CCA/ICA stenosis is higher in patients with older age and longer interval from radiotherapy. The aggressive screening for CA and VA stenosis as a part of routine post-irradiation care should be warranted in these patients.

FUNDING

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

REFERENCES

- Wang R, Wu F, Lu H, Wei B, Feng G, Li G, et al. Definitive intensity-modulated radiation therapy for nasopharyngeal carcinoma: long-term outcome of a multicenter prospective study. *J Cancer Res Clin Oncol* 2013; **139**: 139–45. doi: [10.1007/s00432-012-1313-0](https://doi.org/10.1007/s00432-012-1313-0)
- Lam WW, Yuen HY, Wong KS, Leung SF, Liu KH, Metreweli C. Clinically underdetected asymptomatic and symptomatic carotid stenosis as a late complication of radiotherapy in Chinese nasopharyngeal carcinoma patients. *Head Neck* 2001; **23**: 780–4.
- Li CS, Schminke U, Tan TY. Extracranial carotid artery disease in nasopharyngeal carcinoma patients with post-irradiation ischemic stroke. *Clin Neurol Neurosurg* 2010; **112**: 682–6. doi: [10.1016/j.clineuro.2010.05.007](https://doi.org/10.1016/j.clineuro.2010.05.007)
- Lam WW, Leung SF, So NM, Wong KS, Liu KH, Ku PK, et al. Incidence of carotid stenosis in nasopharyngeal carcinoma patients after radiotherapy. *Cancer* 2001; **92**: 2357–63.
- Dorresteijn LD, Kappelle AC, Boogerd W, Klokman WJ, Balm AJ, Keus RB, et al. Increased risk of ischemic stroke after radiotherapy on the neck in patients younger than 60 years. *J Clin Oncol* 2002; **20**: 282–8.
- Holmstedt CA, Turan TN, Chimowitz MI. Atherosclerotic intracranial arterial stenosis: risk factors, diagnosis, and treatment. *Lancet Neurol* 2013; **12**: 1106–14. doi: [10.1016/S1474-4422\(13\)70195-9](https://doi.org/10.1016/S1474-4422(13)70195-9)
- Lv P, Lin J, Guo D, Liu H, Tang X, Fu C, et al. Detection of carotid artery stenosis: a comparison between 2 unenhanced MRAs and dual-source CTA. *AJNR Am J Neuroradiol* 2014; **35**: 2360–5. doi: [10.3174/ajnr.A4073](https://doi.org/10.3174/ajnr.A4073)
- Anzidei M, Napoli A, Zaccagna F, Di Paolo P, Saba L, Cavallo Marincola B, et al. Diagnostic accuracy of colour Doppler ultrasonography, CT angiography and blood-pool-enhanced MR angiography in assessing carotid stenosis: a comparative study with DSA in 170 patients. [In English, Italian.] *Radiol Med* 2012; **117**: 54–71. doi: [10.1007/s11547-011-0651-3](https://doi.org/10.1007/s11547-011-0651-3)
- Randoux B, Marro B, Koskas F, Duyme M, Sahel M, Zouaoui A, et al. Carotid artery stenosis: prospective comparison of CT, three-dimensional gadolinium-enhanced MR, and conventional angiography. *Radiology* 2001; **220**: 179–85.
- Miyazaki M, Lee VS. Nonenhanced MR angiography. *Radiology* 2008; **248**: 20–43. doi: [10.1148/radiol.2481071497](https://doi.org/10.1148/radiol.2481071497)
- Weber J, Veith P, Jung B, Ihorst G, Moske-Eick O, Meckel S, et al. MR angiography at 3 Tesla to assess proximal internal carotid artery stenoses: contrast-enhanced or 3D time-of-flight MR angiography? *Clin Neuro-radiol* 2015; **25**: 41–8. doi: [10.1007/s00062-013-0279-x](https://doi.org/10.1007/s00062-013-0279-x)
- North American Symptomatic Carotid Endarterectomy Trial Collaborators. Beneficial effect of carotid endarterectomy in symptomatic patients with high-grade carotid stenosis. *N Engl J Med* 1991; **325**: 445–53. doi: [10.1056/NEJM199108153250701](https://doi.org/10.1056/NEJM199108153250701)
- Steele SR, Martin MJ, Mullenix PS, Crawford JV, Cuadrado DS, Andersen CA. Focused high-risk population screening for carotid arterial stenosis after radiation therapy for head and neck cancer. *Am J Surg* 2004; **187**: 594–8.
- Greco A, Gallo A, De Virgilio A, Marinelli C, Macri GF, Fusconi M, et al. Carotid stenosis after adjuvant cervical radiotherapy in patients with head and neck cancers: a prospective controlled study. *Clin Otolaryngol* 2012; **37**: 376–81. doi: [10.1111/coa.12007](https://doi.org/10.1111/coa.12007)

15. Cheng SW, Wu LL, Ting AC, Lau H, Lam LK, Wei WI. Irradiation-induced extracranial carotid stenosis in patients with head and neck malignancies. *Am J Surg* 1999; **178**: 323–8.
16. Brown PD, Foote RL, McLaughlin MP, Halyard MY, Ballman KV, Collie AC, et al. A historical prospective cohort study of carotid artery stenosis after radiotherapy for head and neck malignancies. *Int J Radiat Oncol Biol Phys* 2005; **63**: 1361–7.
17. Chang YJ, Chang TC, Lee TH, Ryu SJ. Predictors of carotid artery stenosis after radiotherapy for head and neck cancers. *J Vasc Surg* 2009; **50**: 280–5. doi: [10.1016/j.jvs.2009.01.033](https://doi.org/10.1016/j.jvs.2009.01.033)
18. Martin JD, Buckley AR, Graeb D, Walman B, Salvian A, Hay JH. Carotid artery stenosis in asymptomatic patients who have received unilateral head-and-neck irradiation. *Int J Radiat Oncol Biol Phys* 2005; **63**: 1197–205.
19. Wilbers J, Kappelle AC, Kessels RP, Steens SC, Meijer FJ, Kaanders JH, et al. Long term cerebral and vascular complications after irradiation of the neck in head and neck cancer patients: a prospective cohort study: study rationale and protocol. *BMC Neurol* 2014; **14**: 132. doi: [10.1186/1471-2377-14-132](https://doi.org/10.1186/1471-2377-14-132)
20. Carmody BJ, Arora S, Avena R, Curry KM, Simpkins J, Cosby K, et al. Accelerated carotid artery disease after high-dose head and neck radiotherapy: is there a role for routine carotid duplex surveillance? *J Vasc Surg* 1999; **30**: 1045–51.
21. Cugini G, Sciacero P, Geda C, Ferrari G. Injury of the large vessels of the neck caused by radiation of neoplasms of the otorhinolaryngologic region: a study using Doppler echography. [In Italian.] *Radiol Med* 1990; **80**: 56–62.
22. Cheng SW, Ting AC, Ho P, Wu LL. Accelerated progression of carotid stenosis in patients with previous external neck irradiation. *J Vasc Surg* 2004; **39**: 409–15.
23. Bucek RA, Puchner S, Haumer M, Reiter M, Minar E, Lammer J. CTA quantification of internal carotid artery stenosis: application of luminal area vs. luminal diameter measurements and assessment of inter-observer variability. *J Neuroimaging* 2007; **17**: 219–26.
24. Zhang Z, Berg MH, Ikonen AE, Vanninen RL, Manninen HI. Carotid artery stenosis: reproducibility of automated 3D CT angiography analysis method. *Eur Radiol* 2004; **14**: 665–72.
25. King LJ, Hanain SN, Webb JA, Kingston JE, Shafford EA, Lister TA, et al. Asymptomatic carotid arterial disease in young patients following neck radiation therapy for Hodgkin lymphoma. *Radiology* 1999; **213**: 167–72.
26. Cheng SW, Ting AC, Lam LK, Wei WI. Carotid stenosis after radiotherapy for nasopharyngeal carcinoma. *Arch Otolaryngol Head Neck Surg* 2000; **126**: 517–21.
27. So NM, Lam WW, Chook P, Woo KS, Liu KH, Leung SF, et al. Carotid intima-media thickness in patients with head and neck irradiation for the treatment of nasopharyngeal carcinoma. *Clin Radiol* 2002; **57**: 600–3.
28. Rockman CB, Riles TS, Fisher FS, Adelman MA, Lamparello PJ. The surgical management of carotid artery stenosis in patients with previous neck irradiation. *Am J Surg* 1996; **172**: 191–5.
29. Yu SC, Zou WX, Soo YO, Wang L, Hui JW, Chan AY, et al. Evaluation of carotid angioplasty and stenting for radiation-induced carotid stenosis. *Stroke* 2014; **45**: 1402–7. doi: [10.1161/STROKEAHA.113.003995](https://doi.org/10.1161/STROKEAHA.113.003995)