Neurology Asia 2013; 18(2) : 143 – 151

Extracranial carotid stenosis after radiotherapy in nasopharyngeal carcinoma, a Malaysian study

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Abstract

Background and objectives: Radiation treatment in nasopharyngeal carcinoma (NPC) is known to be associated with increased prevalence of carotid stenosis. The objectives of the study was to determine the prevalence of radiation-induced extracranial carotid stenosis, plaque, carotid intima thickness (CIMT) in NPC patients; to explore whether the stenosis is due to direct effect of radiation rather than general tendency to atherosclerosis. *Methods***:** This was a cross-sectional study conducted in the University Malaya Medical Centre from July 2011 to February 2012. The study subjects consisted of 47 NPC patients who were treated with radiation, and 47 healthy control. The patients and control had carotid duplex ultrasound and transcranial Doppler (TCD). *Results:* The mean age of the patients was 55.1 years, the time lapse from radiation was 76.7 ± 95.3 months. Internal carotid artery (ICA) and common carotid artery (CCA) stenosis of ≥50% was seen in 17.0% of patients vs 2.1 % of controls (p = 0.031), with 61.7% of patients and 19.1% of controls having plaque in ICA and CCA (p=0.004). CIMT was increased in 70.2% of patients and 44.7% of controls (p =0.022). Both the patient group and control had similar rate of intracranial stenosis of 12.8% in TCD.
Conclusion: Extracranial internal carotid artery is the most common site of stenosis following radiotherapy in NPC. This suggests that local trauma from irradiation is the most important factor in predisposition to atherosclerosis following radiation therapy.

INTRODUCTION

Stroke causes significant mortality and morbidity. About 10% of stroke is due to carotid artery disease.[1] Head and neck radiotherapy causes carotid artery stenosis.[2] Nasopharyngeal carcinoma (NPC) is a common cancer of the head and neck.[3] It is the second most common cancer among men in Malaysia (8.8% of total male cancers).[4] The outcome of NPC treatment has greatly improved with advances in imaging, radiotherapy techniques and concurrent chemoradiation.[5] However, high dose radiation to the neck exposes the arteries to radiation injury.[6] The radiation vasculopathy affecting medium and large arteries is not uncommon, resulting in haemodynamically significant stenosis.[3,7] Damage to intima media causes premature atherosclerosis and this process is accelerated in patients with risk factors for atherosclerosis.[8]

NPC patients post radiotherapy with carotid stenosis are at risk for stroke.[9] As NPC patients have good prognosis with a high survival rates, and they are relatively young, it is important for these patients to be screened for radiation induced carotid stenosis.[5] A recent study showed that young NPC patients had higher risk of stroke compared to general population.[10]

Intracranial atherosclerosis is relatively common in Asia, particularly in the presence of vascular risk factors of diabetes mellitus (DM), hypertension and hyperlipidaemia. In NPC, irradiation injury to the large arteries is thought to be caused by the direct effect of radiation, with risk of atherosclerosis being limited to the local area within the radiation field.[6,8] The objective of this study was to evaluate the prevalence of radiation induced carotid stenosis, plaque and CIMT. We also aimed to assess whether the carotid stenosis was only due to direct radiation effect on the extracranial carotid artery, or contributed by an increased generalized atherosclerosis secondary to underlying chronic illness from the carcinoma. Transcranial Doppler (TCD) was useful to evaluate the intracranial vessels, not within the radiation field. We hypothesized that there may also be increased intracranial stenosis due to chronic inflammation in NPC.

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METHODS

This was a cross-sectional study conducted from July 2011 to February 2012 in the University Malaya Medical Centre, a tertiary teaching hospital in Kuala Lumpur, Malaysia. The study was approved by the Ethics Committee of the Centre. The study subjects consisted of NPC patients with previous radiotherapy. The controls consisted of healthy relatives of patients visiting the Medical Centre. The control subjects were age, gender and ethnic group matched. They had similar vascular risk factors as the patients, i.e., DM, hypertension (HT), smoking, hyperlipidaemia, ischaemic heart disease, and family history of transient ischaemic attack or stroke. The exclusion criteria for NPC patients were those who had carotid artery intervention or surgery prior to diagnosis of NPC, not treated with radiotherapy, history of transient ischemic attack (TIA) or stroke prior radiotherapy. Control subjects with previous history of TIA or stroke were excluded. Informed consent was obtained from the study participants.

For the patients, the data acquired included risk factors for atherosclerosis such as past history of DM, HT, ischemic heart disease (IHD), hyperlipidaemia, smoking and family history of cerebrovascular disease (stroke/TIA); details of the NPC, previous radiotherapy (nature, dose and date), chemotherapy and any surgical intervention. The patients were asked whether they had stroke or TIA after exposure to radiotherapy. The blood test done included fasting blood glucose and fasting lipid profile. Fasting blood glucose >6.1 mmol/L, fasting total cholesterol ≥ 5.2 mmol/L and low density lipoprotein (LDL) ≥ 2.59 were taken as abnormal. The control subjects had the same history, clinical examination and blood tests taken. All the study participants had carotid duplex ultrasound to assess the extracranial internal carotid artery, common carotid artery and vertebral artery, and TCD to assess the intracranial vessels.

Radiotherapy

All the NPC patients had either two-dimensional conventional or three–dimensional conformal external beam radiotherapy (EBRT). Shielding was applied to the brain, oral cavity, and the orbit to avoid the radiation dose. The radiation was given in fractionated doses of two Gy daily for 33-35 days.The nasopharynx (primary site) was irradiated with 70 Gy whereas the neck was given 66 Gy, if there were no cervical lymph nodes involvement. Additional doses were given to the neck area if cervical lymph nodes were present.

Carotid duplex ultrasound

The ultrasound was performed in the Radiology Department of the Medical Centre by a single experienced Ultrasonographer (Technologist). The ultrasound was done using Phillips IU22 scanner (Seattle, USA) with a 4 MHz probe. The examination was performed according to standard protocol.[11] The common carotid artery (CCA), external Carotid artery (ECA), internal carotid artery (ICA) and the vertebral artery (VA) on both sides were insonated.

An atherosclerotic plaque was defined as a focal structural encroachment into the arterial lumen of at least 0.5 mm.[12] The presence of plaque, the degree of stenosis and the locations of stenosis were documented. The diagnostic criteria for stenosis were according to the Society of Radiologists in Ultrasound Consensus Criteria for Carotid Stenosis.[13] Carotid intima media thickness (CIMT) was measured according to the Consensus Statement from the American Society of Echocardiography Carotid Intima-Media Thickness Task Force.[12] CIMT measurements were taken at three different angles from the distal one cm of the far wall of both Common Carotid arteries and a mean value was taken for both right and left CCA. We defined mean CIMT as increased if ≥ 0.8 mm similar to other studies.[14,15] CIMT was analysed in two different methods. Firstly, the CIMT was taken as increased (≥ 0.8 mm) and not increased (<0.8 mm). In addition, the mean CIMT (mean of right and left CIMT) was taken.

Transcranial Doppler (TCD)

TCD was performed in the Neurology Laboratory of the Medical Centre. All the TCD were done by a single certified laboratory technician and the results were interpreted by a single Neurologist (SMLT). All the tests were performed by TCD machine Nicolet Companion III equipment with a 2 MHz transducer.

Statistical analysis

All descriptive statistics were done using Statistical Package for Social Sciences, SPSS (Version 16.0, SPSS Inc., Chicago, USA). Descriptive analysis was performed on basic demography. Chi square test (or Fisher's exact test) was used to evaluate for association between radiotherapy and extracranial carotid stenosis, plaque, increased CIMT and intracranial stenosis. Mann Whitney U test was used to look for association between radiotherapy and mean CIMT as well as for association between time elapsed from radiotherapy with carotid stenosis, plaque and CIMT.

Multilogistic regression was used to assess the effect of radiation and vascular risk factors on carotid stenosis, plaque and CIMT. The correlation between mean CIMT and time elapsed from radiation, was analysed using Spearman's correlation. P < 0.05 was taken as statistically significant.

RESULTS

One hundred forty nine patients with NPC were screened at the NPC clinic of the Medical Centre, 148 patients fulfilled the inclusion criteria. Forty seven NPC patients consented to the study and were recruited. There were 47 subjects recruited as control. Most of the patients were Chinese (83%), the others were Malays (17%). The demography and vascular risk factors of the NPC patients and control are shown in Table 1. Twelve (25.5%) patients had radiation only, 35 (74.5%) had combined chemotherapy and radiotherapy (CCRT). The exact dose of radiotherapy was not available for 16 patients. The mean total radiation dose was 159.2 ± 31.9 Gy; paranasal sinus 71.4 ± 12.1 Gy, total neck area 87.8 ± 30.2 Gy, anterior neck 66.0 ± 17.8 Gy, right neck 11.5 ± 12.4 Gy, left neck 10.3 ± 11.9. Gy. The mean time elapsed from radiation was 76.7 ± 95.3 months.

Carotid duplex ultrasound

Significantly more NPC patients had carotid stenosis ≥50% in the ICA and CCA than control (8 (17.0%) vs 1 (2.1%), p=0.03). Significantly more NPC patients had plaque in the ICA and CCA than control (29 (61.7%) vs 14 (29.8%), p=0.004). There was significant increase in IMT thickening in the ICA and CCA among the NPC patients as compared to control (33 (70.2%) vs 21 (44.7%), p=0.02). (Table 2)

The results of the carotid duplex ultrasound according to the individual neck arteries and degree of arterial stenosis in the NPC patients and control is summarized in Table 3. Overall stenosis was most common in the ICA (10), followed by CCA (3), ECA (2) and VA (1). There were 13 CCA and ICA arteries in 8 patients (17%) with ≥ 50% stenosis: 9 arteries with 50-69% stenosis (7 patients, 14.9%), 2 arteries with ≥70% stenosis (2 patients, 4.3%) and 2 arteries with total occlusion (1 patient). As for ICA stenosis, there were 7

Table 1: Basic demography and vascular risk factors of the nasopharyngeal carcinoma patients and control

		Patients (n=47)	Control (n=47)	p-value
Age in year	Mean ± SD	55.1 ± 12.4	55.0 ± 12.9	0.92
Gender (n, %)	male female	31 (66) 16 (34)	12 (22) 16 (34)	1.00
Ethnic group (n, %)	Malay Chinese	8 (17) 39 (83)	8 (17) 39 (83)	1.00
Smoking (n, %)	yes	9 (19)	9 (19)	0.33
Diabetes mellitus (n, %)	yes	5 (11)	42 (89) 5 (11)	1.00
Hypertension (n, %)	yes	9 (19)	9 (19)	1.00
Hyperlipidaemia (n, %)	yes	3 (6)	4 (9)	1.00
Ischemic heart disease (n, %)	yes	1 (2)	1 (2)	1.00
Fasting blood cholesterol (n, %)	≥5.2	25 (53)	20 (43)	0.41
LDL ≥2.59 (n, %)	≥2.59	33 (70)	28 (60)	0.38
Fasting blood sugar	>6.1	2 (4)	4 (9)	0.67

LDL, low density lipoprotein

Table 2: Overall summary of the results of carotid duplex ultrasound study on the neck arteries showing stenosis, intima media thickening and plaque formation of the nasopharyngeal carcinoma patients and control

	Patients, N=47 n (%)	Control, N =47 n (%)	p-value
Carotid stenosis (ICA and CCA)			
Absent	39 (83.0)	46 (97.9)	0.03
Present	8 (17.0)	1 (2.1)	
Intima media thickening (CCA)			
Not increased	14 (29.8)	26 (55.3)	0.02
Increased	33 (70.2)	21 (44.7)	
Plaque (ICA and CCA)			
Absent	18 (38.3)	33 (70.2)	0.004
Present	29 (61.7)	14 (29.8)	
ECA stenosis			
Absent	45 (95.7)	47 (100.0)	0.49
Present	2 (4.3)	0 (0.0)	
Plaque in ECA			
Absent	43 (91.5)	45 (95.7)	0.67
Present	4 (8.5)	2 (4.3)	
Vertebral artery stenosis			
Absent	46 (97.8)	47 (100.0)	1.00
Present	1 (2.1)	0 (0.0)	

ICA, internal carotid artery; CCA, common carotid artery; ECA, external carotid artery

arteries with 50-69% stenosis (7 patients), 2 arteries with ≥70% stenosis (2 patients) and 1 artery with total occlusion (1 patient). As for CCA stenosis, there were 2 arteries with 50-69% stenosis (2 patients), none with ≥70% stenosis and 1 with total occlusion (1 patient). This was in comparison to only one artery with total occlusion in 1 patient in control.

Table 4 lists the results of the plaque demonstrated by carotid duplex ultrasound. Significantly more (29, 61.7%) patients as compared to control (9, 19.1%, p=0.004) had plaque in ICA and CCA. There were more plaques present at CCA compared to ICA among the patients. There were plaques present at 44 CCA in 27 patients and 14 ICA in 12 patients. There were plaques present at 14 CCA in 9 subjects and 4 ICA in 3 subjects among the control.

CIMT was significantly thickened (mean 0.85 ± 0.3) in the NPC patients as compared to control (mean 0.68 ± 0.13, p=0.001).

On multilogistic regression analysis, radiotherapy was the only statistically significant factor associated with carotid stenosis; age and radiotherapy was significantly associated with plaque formation; radiotherapy, age and gender were significantly associated with CIMT on multilogistic regression analysis (Table 5).

Table 3: **Degree of stenosis in the individual neck arteries by the carotid duplex ultrasound in the nasopharyngeal carcinoma patients and control**

	Nasopharyngeal carcinoma patients			
	Normal	**50-69% stenosis**	**≥ 70% stenosis**	**Total occlusion**
Right CCA	47 (100%)	-	-	-
Right ICA	42 (89.3%)	4 (8.5%)	1 (2.1%)	-
Left CCA	44 (93.6%)	2 (4.3%)	-	1 (2.1%)
Left ICA	42 (89.3%)	3 (6.4%)	1 (2.1%)	1 (2.1%)
Right ECA	45 (95.7%)	1 (2.1%)	-	1 (2.1%)
Left ECA	46 (97.9%)	-	1 (2.1%)	-
Right VA	46 (97.9%)	-	1 (2.1%)	-
Left VA	47 (100 %)	-	-	-
	Control			
Right ICA	46 (97.9 %)	-	-	1 (2.1 %)

CCA, common carotid artery; ICA, internal carotid artery; ECA, external carotid artery; VA, vertebral artery
The left ICA, right CCA, right ICA, both ECA, both VA of the controls were all normal.

Based on Mann Whitney U test, there was statistically significant association between plaque with time elapsed from radiation and radiation dose to the neck (Table 6).

Transcranial Doppler (TCD)

Intracranial stenosis was present in 6 NPC patients and 6 control. The locations of the intracranial stenosis in TCD were left MCA (2 patients, 2 control), left ICA siphon (no patient, 1 control), left VA (2 patients, 4 control), basilar artey (3 patients, no control), right MCA (2 patients, 1 control), right ACA (no patient, 1 control), right ICA siphon (2 patients, 1 control), and right vertebral artery (2 patients, 1 control).

Clinical outcome in stroke

Only one NPC patient had stroke which involved the cerebellum, none had TIA.

DISCUSSION

We have shown by carotid duplex ultrasound that NPC patients with radiation has significantly increased risk of stenosis in the ICA and CCA, about eight times more than control in developing stenosis $\geq$ 50%. The stenosis was particularly prevalent in the ICA (10 arteries), followed by CCA (3 arteries) and ECA (2 arteries). There were also significantly more plaques in the CCA and ICA, with thickened CIMT. Radiotherapy was

Table 4: Carotid duplex ultrasound showing location of plaque in nasopharyngeal carcinoma patients and control

	Patient	**Control**
Right CCA	20 (42.6%)	5 (10.6%)
Right ICA	6 (12.8%)	1 (2.1%)
Left CCA	24 (51.1%)	7 (14.9%)
Left ICA	7 (14.9%)	2 (4.3%)
Right ECA	2 (4.3%)	1 (2.1 %)
Left ECA	0	2 (4.3%)
Right VA	0	0 (0 %)
Left VA	0	0 (0 %)

CCA, common carotid artery; ICA, internal carotid artery; ECA, external carotid artery; VA, vertebral artery

Table 5: Multilogistic regression for carotid stenosis, plaque and carotid intima thickness (CIMT) with respect to radiotherapy and other risk factors

Risk factors for carotid stenosis	β	p-value	95% confidence interval
Age	1.06	0.097	0.98 – 1.15
Sex	1.30	0.80	0.16 – 10.39
Smoking	0.08	0.06	0.006 – 1.10
Diabetes	0.77	0.85	0.05 – 10.80
Hypertension	10.30	0.12	0.51 – 204.68
Heart Disease	0.12	0.43	0.001 - 21.94
Hyperlipidemia	1.36	0.84	0.06 – 31.21
Radiotherapy	0.03	0.02	0.002 – 0.570
Risk factors for Plaque	**β**	**p-value**	**95% confidence interval**
Age	1.06	0.01	1.01 – 1.11
Sex	0.49	0.19	0.16 – 1.43
Smoking	1.23	0.75	0.34– 4.39
Diabetes	3.16	0.19	0.56 – 17.83
Hypertension	1.82	0.42	0.42 – 7.78
Heart Disease	0.00	0.99	0.00 -
Hyperlipidemia	0.25	0.24	0.02 – 2.52
Radiotherapy	0.198	0.001	0.73 – 0.534
Risk factors for CIMT	**β**	**p-value**	**95% confidence interval**
Age	1.07	0.004	1.02 -1.12
Sex	0.29	0.03	0.09 – 0.87
Smoking	1.65	0.47	0.43 – 6.30
Diabetes	2.15	0.39	0.37 – 12.47
Hypertension	0.41	0.29	0.08 – 2.12
Heart Disease	0.00	0.99	0.00 -
Hyperlipidemia	0.59	0.69	0.04 – 8.18
Radiotherapy	0.27	0.01	0.98 – 0.74

the only significant factor associated with carotid stenosis. The plague formation was significantly associated with time elapsed from radiation and radiation dose to neck. On the other hand, there was no increased prevalence of intracranial stenosis based on TCD, and VA stenosis based on carotid duplex ultrasound.

Table 7 is a summary of previous studies on carotid artery disease in NPC and head and neck cancer patients treated with radiation. Whereas ICA was the main site of stenosis in our patients, with less common involvement of CCA and ECA; previous studies show frequent involvement of CCA[17-20,22-25], ICA[17-20,22], as well as ECA.[7,22] This is probably related to the differences in the radiation field and dosage.

Our study is one of the few which assess comprehensively CIMT, plaque as well as carotid stenosis in NPC patients. Martin *et al*. is another study that has also looked into CIMT, plaque and carotid stenosis in their study population.[24] In our study, age and radiation dose were predictors of plaque. This is similar to previous study by Chang *et al*.[25] Time elapsed from radiation was also significantly associated with plaque formation in our study. Earlier studies have shown an interval of more than 5 years from irradiation an independent significant predictor of ≥70% carotid stenosis.[17-19] The mean CIMT in our study was raised at 0.85mm ± 0.30. This was lower than the Dutch and Hong Kong studies.[26,27]

Only one of our patients had stroke. The incidence of stroke in NPC patients, including those with significant carotid stenosis is variable; low in some studies[23,28,29] and high in others.[18,19,28,30]

Our study was the first that used TCD systematically to assess the intracranial vessels in NPC patients. Li *et al*. also used TCD in some of their patients.[23] In systemic diseases such as

Table 6: Association of carotid stenosis, plaque and carotid intima thickness (CIMT) with time elapsed from radiation

	Carotid Stenosis absent	Carotid Stenosis present	p-value
Time elapsed from radiotherapy			
Mean in month	22.88	29.44	0.21
Radiation dose to neck			
Mean in Gy	23.97	24.12	0.98
	CIMT normal	**CIMT abnormal**	
Time elapsed from radiotherapy			
Mean in month	20.93	25.30	0.31
Radiation dose to neck			
Mean in Gy	27.96	22.32	0.18
	Plaque absent	**Plaque present**	
Time elapsed from radiotherapy			
Mean in month	16.42	28.71	0.003
Radiation dose to neck			
Mean in Gy	30.39	20.03	0.009

immune mediated conditions and infection as well as diabetes, hypertension, hyperlipidaemia, inflammation is able to trigger the process that leads to premature atherosclerosis.[31] There is limited studies reported in the literature about inflammation in cancer. After radiotherapy, CRP and ferritin levels as inflammatory markers has been reported to be significantly higher in stage three lung cancer. [29]

Intracranial atherosclerosis is frequently found in the setting of the widespread atherosclerosis.[32] In our study, there was no significant increase in intracranial stenosis in the patients, demonstrating that there was no widespread atherosclerosis from the direct or indirect effect of cancer. The intracranial vessels are not directly within the radiation port and therefore they are not exposed to radiotherapy directly as compared to the extracranial carotid arteries. The arterial stenosis appears to be localized to within the radiation field in the neck. Localized hemodynamic factor may also be important in the predisposition of ICA to develop stenosis.

It has been reported that NPC most commonly metastasize to the upper cervical chain and jugulo-digastric lymph nodes (70%), followed by the jugulo-omohyoid nodes (45%) in the neck.[33] Jugulo-omohyoid nodes is close to the origin of the ICA, which is common site of stenosis post-radiation. The risk of carotid artery injury should thus be balanced against the benefit of treatment to the metastasis when determining the field and dose of the radiation in the NPC patient.

In conclusion, we have shown a high prevalence of carotid artery stenosis, plaque, and increased CIMT in NPC patients post radiotherapy. On the other hand, there was no increased intracranial stenosis away from the radiation field. This confirms that the predisposition to carotid stenosis is due to the direct effect of irradiation, localized to the area within the radiation field and not due to generalized atherosclerosis.

ACKNOWLEDEMENTS

Sources of funding: Postgraduate Research grant P0087/2012A, University of Malaya. We would like to thank technologists, Azly bin Yahya and Nevehta Kunaratanam for their assistance in performing Carotid Duplex Ultrasound and TCD. We would also like to thank hospital radiotherapist, Jeannie Wong Hsiu Ding for her help.

Table 7: A summary of previous studies of carotid artery disease in NPC patients with radiotherapy

Author, year of publication, location	Details of study	Results
Steele *et al.* [16], 1994, *Fort Lewis, USA*	40 NPC patients with radiation	15 patients (40%) with significant carotid artery stenosis. 6 patients (15%) with unilateral complete carotid occlusion 6 patients (15%) with significant bilateral carotid stenosis
Dubec *et al.* [17], *1998, Vancouver, Canada*	45 NPC patients vs 348 controls	≥50% stenosis: 17 patients (38%) vs 13 controls (4%)
Cheng *et al.*[18], 1999, Hong Kong	240 patients with primary head and neck malignancies	ICA ≥70% stenosis: in 29 patients (10 occlusions) vs 0 in controls CCA ≥70% stenosis: in 13 patients (5 occlusions) vs 0 in controls ECA ≥70% stenosis: in 18 patients (8 occlusions) vs 0 in controls
Cheng *et al.*[19], 2000, *Hong Kong*	96 NPC patients vs 96 healthy controls	ICA ≥70% stenosis: 14 arteries in 12 patients (6 occlusions) vs 0 in controls CCA ≥70% stenosis: 11 arteries in 9 patients (4 occlusions) vs 0 in controls
Lam *et al.*[20], 2001, *Hong Kong*	71 post-radiation NPC patients vs 51 pre-radiation patients	Stenosis more common in irradiated group vs pre-radiation group (56 of 71 vs. 11 of 51). The CCA and ICA most commonly involved (55 of 71 vs. 11 of 51; $P < 0.01$), followed by ECA (32 of 71 vs. 1 of 51; $P < 0.01$) and VA (5 of 71 vs. 0; $P = 0.069$). Significant stenosis (> 50% reduction of luminal diameter) only found in post-radiation group (21 of 71 in CCA/ICA, 11 of 71 in ECA, 4 of 71 in VA).
Lam *et al.*[21], 2001, *Hong Kong*	80 post-radiation NPC patients vs 58 controls	24 patients with more than 50% diameter reduction in extracranial carotid artery.
Lam *et al.* [22], 2002, Hong Kong	71 NPC patients vs 142 controls who had symptoms of cerebrovascular disease or carotid bruit	CCA >50% stenosis: 25 NPC patients vs 2 controls ($p<0.05$) ICA >50% stenosis: 14 NPC patients vs 25 controls ($p=0.72$) ECA >50% stenosis: 12 NPC patients vs 8 controls ($p<0.05$)
Li *et al.*[23] , *2010, Taiwan*	43 NPC patients with stroke or TIA (31 patients with complete ultrasonography data)	ICA ≥70% stenosis: in 8 patients (6 occlusions) vs 0 in controls CCA ≥70% stenosis: in 3 patients (1 occlusion) vs 0 in controls

NPC, nasopharyngeal carcinoma; ICA, internal carotid artery; CCA, common carotid artery; ECA, external carotid artery

DISCLOSURE

Conflict of interest: none

REFERENCES

1. Derdeyn CP. Carotid stenting for asymptomatic carotid stenosis: Trial It. *Stroke* 2007; 38:715-20.
2. Eisenberg RL, Hedgcock MW, Wara WM, Jeffrey RB. Radiation induced disease of the carotid artery. *West J Med* 1978*;* 129(6):500-3.
3. Plummer C, Henderson RD, O'Sullivan JD, Read SJ. Ischemic stroke and transient ischemic attack after head and neck radiotherapy. *Stroke* 2011; 42:2410-8.
4. Lim GCC, Halimah Y. Report of the National Cancer Registry. Cancer incidence in Malaysia. 2003. National Cancer Registry. Kuala Lumpur.
5. Chan ATC, Gre´goire V, Lefebvre JL, Licitra L, Felip E. Nasopharyngeal carcinoma: EHNS–ESMO–ESTRO Clinical Practice Guidelines for diagnosis, treatment and follow-up). *Ann Oncol* 2010; 21(Suppl 5):v187–v189.
6. Weintraub NL, Jones WK, Manka D. Understanding radiation-induced vascular disease. *J Am Coll Cardiol* 2010; 55:1237-9.
7. Grady PA. Pathophysiology of extracranial cerebral arterial stenosis – A critical review. *Stroke* 1984; 15:224-36.
8. Schultz-Hector S, Kallfass E, Sund M. Radiation sequelae in the large arteries. A review of clinical and experimental data. *Strahlenther Onko* 1995; 171 (8):427-36.
9. Norris JW, Zhu CZ, Bronstein NM, Chambers BR. Vascular risks of asymptomatic carotid stenosis. *Stroke* 1991; 22:1485-90.
10. Lee CC, Su YC, Ho HC, *et al*. Increased risk of ischemic stroke in young nasopharyngeal carcinoma patients. *Int J Radiat Oncol Biol Phys* 2012; 82(4):1321.
11. Alexandrov AV, Hacke W. Cerebrovascular ultrasound in stroke prevention and treatment. 2nd Edition. United Kingdom: Blackwell. 2011
12. Stein JH, Korcarz CE, Hurst RT, *et al*. Use of carotid ultrasound to identify subclinical vascular disease and evaluate cardiovascular disease risk. *J Am Soc Echocardiogr* 2008; 22(2):93-111.
13. Grant EG, Benson CB, Moneta GL, *et al*. Carotid artery stenosis: Gray-Scale and Doppler US diagnosis. *Radiology* 2003; 229:340-6.
14. O'Leary DH, Bots ML. Imaging of atherosclerosis: Carotid intima media thickness. *Eur Heart J* 2010; 31(14):1682-9.
15. Nambi V, Chambless L, Folsom AR, *et al*. Carotid intima-media thickness and presence or absence of plaque improves prediction of coronary heart disease risk. *JACC* 2010; 55(15):1600-7.
16. 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(5):594-8.
17. Dubec JJ, Munk PL, Tsang V, *et al*. Carotid artery stenosis in patients who have undergone radiation therapy for head and neck malignancy. *Br J Radiol* 1998; 71:872-5.
18. Cheng SWK, Wu LLH, Ting ACW, Lau H, Lam LK, Wei WI. Irradiation-induced extracranial carotid stenosis in patients with head and neck malignancies. *Am J Surg* 1999; 178(4):323-8.
19. Cheng SWK, Ting ACW, Lam LK, Wei WI. Carotid stenosis after radiotherapy for nasopharyngeal carcinoma. *Arch Otolaryngol Head Neck Surg* 2000; 126(4): 517-21.
20. Lam WW, Leung SF, So NMC, *et al*. Incidence of carotid stenosis in nasopharyngeal carcinoma patients after radiotherapy. *Cancer* 2001; 92(9): 2357-63.
21. Lam WW, Yuen HY, Wong KS, Leung SF, Liu KH, Metreweli C. Clinically under detected asymptomatic and symptomatic carotid stenosis as a late complication of radiotherapy in Chinese nasopharyngeal carcinoma patients. *Head Neck* 2001; 23:780-4.
22. Lam WW, Liu KH, Leung SF, Wong KS, So NM, Yuen HY, Metreweli C. Sonographic characterisation of radiation-induced carotid artery stenosis. *Cerebrovasc Dis* 2002;13:168-73.
23. Li CS, Schminke U, Tan TY. Extracranial carotid artery disease in nasopharyngeal carcinoma patients with post-irradiation ischemic stroke. *Clin Neurol Neurosurg* 2010; 112(8):682-6.
24. 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 Rad Oncol Biol Phys* 2005; 63(4):1197-205.
25. Chang YJ, Chang TC, Lee TH, Tyu SJ. Predictors of carotid artery stenosis after radiotherapy for head and neck cancers. *J Vasc Surg* 2009; 50(2):280-5.
26. So NMC, Lam WWM, Chook P, *et al*. Carotid intima-media thickness in patients with head and neck irradiation for the treatment of nasopharyngeal carcinoma. *Clin Radiol* 2002; 57(7):600-3.
27. Dorresteiin LDA, Kappelle AC, Scholz NMJ, *et al*. Increased carotid wall thickening after radiotherapy on the neck. *European Journal of Cancer* 2005; 41(7):1026-30.
28. Haynes JC, Machtay M, Weber RS, Weinstein GS, Chalian AA, Rosenthal DI. Relative risk of stroke in head and neck carcinoma patients treated with external cervical irradiation. *Laryngoscope* 2002; 112:1883-7.
29. Maria TG, Vasileios KE, Panagiotis PS, Kostas SN. Changes of acute-phase protein levels in the serum of lung cancer patients following radiotherapy. *Int J Clin Exp* 2013; 6(1):50-6.
30. Dorresteijn LDA, Kappelle AC, Boogerd W, *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.
31. Atkins PT, Pilgram TK, Cross III DT, Moran CJ. Natural history of stenosis from intracranial atherosclerosis by serial angiography. *Stroke* 1998; 29:433-8.
32. Libby P, Ridker PM, Maseri A. Inflammation and atherosclerosis. *Circulation* 2002; 105:1135-43.
33. Ho FC, Tham IW, Earnest A, Lee KM, Lu JJ. Patterns of regional lymph node metastasis of nasopharyngeal carcinoma: A meta-analysis of clinical evidence. *BMC Cancer* 2012; 12:98.