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ORIGINAL ARTICLE

Association of Post-irradiation Temporal Lobe Necrosis and Extra-cranial Carotid Stenosis in Nasopharyngeal Carcinoma

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ABSTRACT

Aim: *To ascertain whether temporal lobe necrosis and extracranial carotid stenosis as long-term complications of radiation are associated.*

Patients and Methods: *Ninety two patients underwent colour doppler ultrasound examinations for the assessment of carotid artery and cross sectional imaging of the brain. The presence of extracranial carotid stenosis was correlated with the presence of temporal lobe necrosis.*

Results: *Sixty three patients had carotid artery stenosis (87 common carotid arteries and 65 internal carotid arteries). Twenty patients had temporal lobe necrosis diagnosed by computed tomography or magnetic resonance imaging. The 2 complications were associated (p = 0.072). When extracranial carotid stenosis is used to predict the presence of temporal lobe necrosis, the positive predictive value, negative predictive value, sensitivity, specificity, and accuracy were 27.0%, 89.7%, 85.0%. 36.1%, and 46.7%, respectively.*

Conclusion: *The presence of extracranial carotid stenosis is not a reliable test to predict the presence of temporal lobe necrosis, but the absence of this complication makes the presence of temporal lobe necrosis unlikely.*

Key Words: *Carotid stenosis, Necrosis, Temporal lobe*

INTRODUCTION

Temporal lobe necrosis and extracranial carotid artery stenosis are known complications of radiotherapy. The actual pathophysiology for temporal lobe necrosis is not certain, but it may be related to blood-brain barrier disruption, parenchymal necrosis and small vessel angiopathy.[1] Radiation-induced carotid artery stenosis, on the other hand, involves large arteries. Despite the difference in size, the underlying mechanism of the vascular injury in these 2 conditions could be the same. It was therefore hypothesised that the occurrence of temporal lobe necrosis and extracranial carotid artery stenosis in patients receiving radiotherapy could be associated. This study was performed to testify the hypothesis. The accuracy, specificity, sensitivity, positive predictive value, and negative predictive value of the presence of extracranial carotid stenosis to predict for temporal lobe necrosis were also assessed.

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PATIENTS AND METHODS

160 consecutive patients with nasopharyngeal carcinoma (NPC) at post-radiotherapy follow up were recruited into a study of extracranial carotid artery stenosis diagnosed by colour doppler ultrasound. The study was approved by the Ethics Committee of The Chinese University of Hong Kong and written informed consent was obtained from all patients.

The reports of all imaging studies performed within 2 years prior to and 1 month after the colour doppler ultrasound examination were retrieved and screened for the availability of any imaging of the brain (either computed tomography [CT] or magnetic resonance imaging [MRI]). Ninety two patients had had brain imaging and were included in this retrospective study. There were 65 men and 27 women, ranging in age from 33 to 75 years (mean, 51.8 years). Of these patients, 5 had hypertension, 11 had hyperlipidaemia, and 9 had diabetes mellitus. The patients had completed

curative-intent radiotherapy treatment 2 to 22 years (mean, 8 years) before the study, with radiation portals that covered the nasopharynx and adjacent at-risk regions, and the complete length of the neck on both sides. None of the patients had had repeated radiotherapy for local recurrence before the imaging. The brain imaging had been performed because of clinical suspicion of local tumour recurrence or suspicion of post-irradiation brain injury. The presence or absence of temporal lobe necrosis was noted.

Ultrasound Technique

All colour doppler ultrasound examinations were performed by one sonographer and the results were checked by a radiologist. All examinations were performed using an ATL HDI 5000US scanner (ATL, Bothell, USA) with a linear array ultrasound probe (L12-5/ATL, Bothell, USA). The extracranial common and internal carotid arteries were assessed. Both longitudinal and transverse scans were performed. The presence or absence of stenosis was documented (Figures 1 and 2).

The degree of stenosis was expressed by the percentage of diameter reduction of the individual artery. Any artery with more than 50% diameter reduction was defined as significantly stenosed.

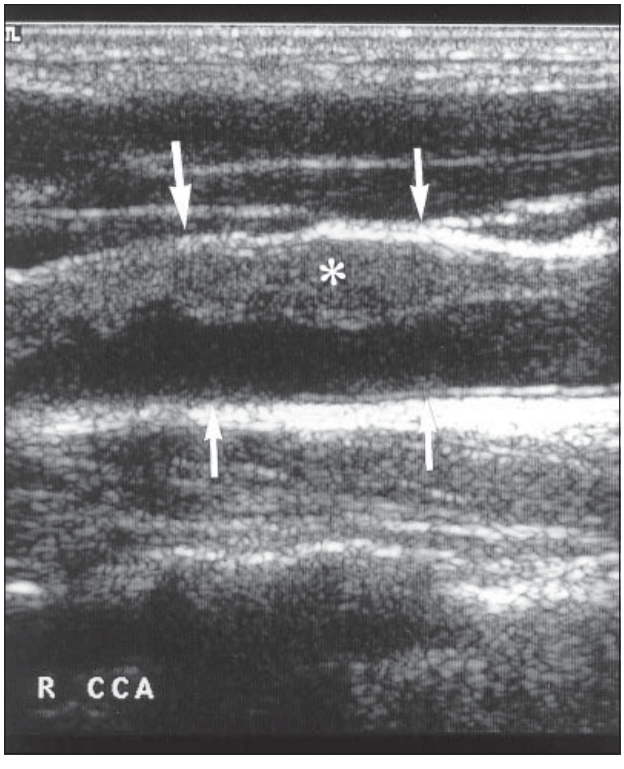

Figure 1. Longitudinal section of the common carotid artery showing irregular plaque (asterisk) causing narrowing of the artery. The wall of the artery is indicated by arrows.

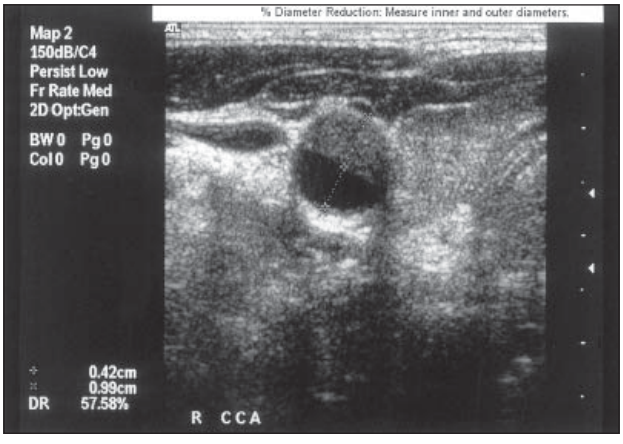

Figure 2. Transverse section of the carotid artery showing the measurement of the degree of stenosis.

Computed Tomography and Magnetic Resonance Imaging Findings

The diagnosis of temporal lobe necrosis was established when CT or MRI showed typical bilateral involvement of the temporal lobes (Figure 3). When there was only unilateral involvement, the diagnosis was established when serial imaging (at least 1 year apart) showed the changes to be either static or decreased in extent with time or after steroid therapy (Figure 4).

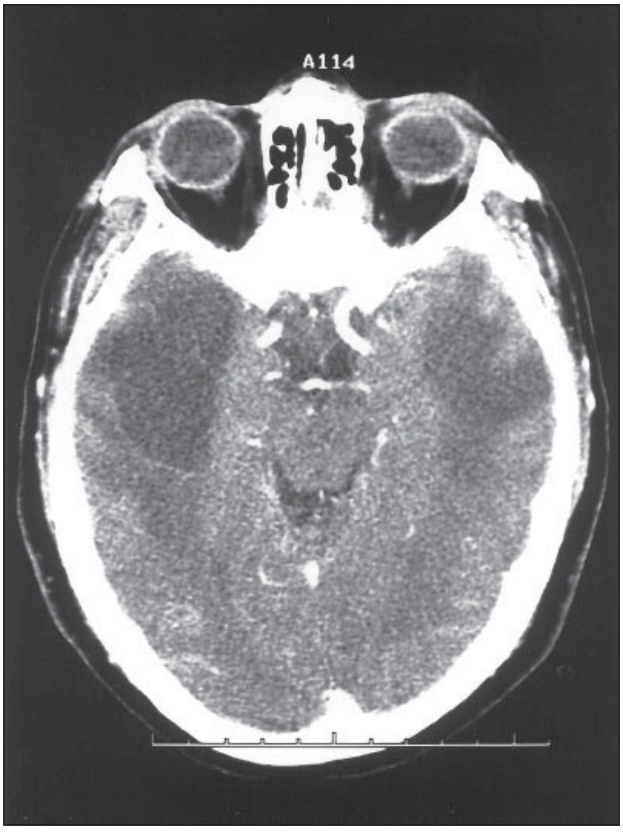

Figure 3. Computed tomography showing hypodense areas in bilateral temporal lobes with no significant mass effect and enhancement, representing typical bilateral temporal lobe necrosis.

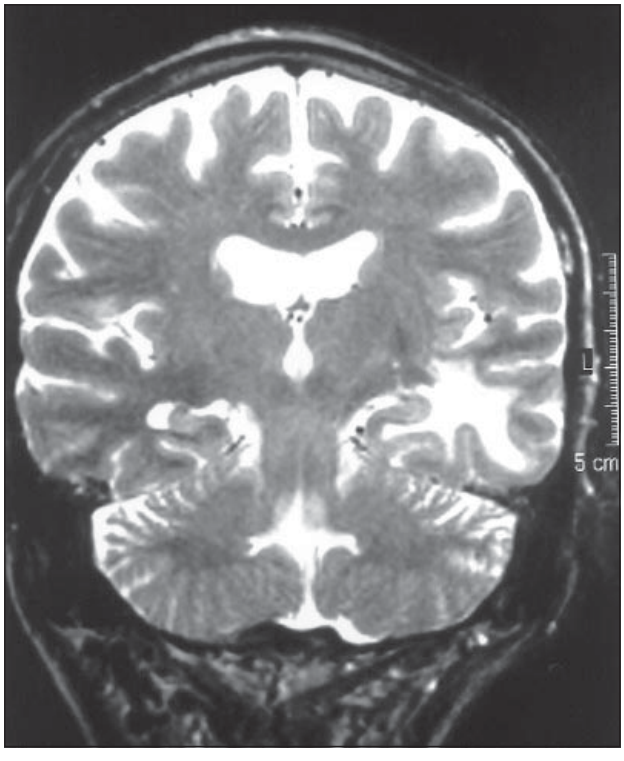

Figure 4. Magnetic resonance imaging showing unilateral temporal lobe necrosis.

Data Analysis

All the data were analysed by the Statistical Package for the Social Sciences. The association of the presence of carotid stenosis and risk factors such as hyperlipidaemia, hypertension, and diabetes mellitus and the association of carotid stenosis and temporal lobe necrosis were evaluated. Pearson Chi square test was used to evaluate the results.

RESULTS

Ultrasound Results

True transverse sections of the individual arteries were obtained for all 160 patients. Of these, 152 common carotid arteries and 104 internal carotid arteries showed some degree of stenosis.

Of the 92 patients who had cross sectional images of the brain, 63 patients had some degree of stenosis — 87 common carotid arteries and 65 internal carotid arteries. Of these patients, 25 had significant carotid artery stenosis (more than 50% diameter reduction) — 28 common carotid arteries and 21 internal carotid arteries.

Computed Tomography and Magnetic Resonance Imaging Results

36 patients had CT examinations and 56 had MRI examinations. Twenty patients (30 sides) were diagnosed to have temporal lobe necrosis. Six patients (8 sides) were diagnosed by computed tomography and 14 patients (22 sides) were diagnosed by magnetic resonance imaging.

Data Analysis

The association between carotid stenosis and risk factors such as hyperlipidaemia, hypertension, and diabetes mellitus and the association of carotid stenosis and temporal lobe necrosis is shown in Table 1. When the presence of any degree of carotid artery stenosis was used to predict the occurrence of temporal lobe necrosis, the positive predictive value was 27.0%, the negative predictive value was 89.7%, sensitivity was 85.0%, the specificity was 36.1%, and accuracy was 46.7%.

DISCUSSION

Medium and large arteries can be affected by radiation.[2,3] Extracranial carotid arteries are always included in the radiation port for nasopharyngeal carcinoma and can therefore be injured by radiotherapy. It is speculated that injury to the vasa vasorum is an important mechanism in radiation-induced angiopathy in large arteries. The vessels recover by adventitial and periadventitial fibrosis with acceleration of atherosclerosis.[4] In an earlier study, a higher incidence of extracranial carotid stenosis was found in patients

Table 1. Distribution of carotid stenosis and risk factors for carotid stenosis and temporal lobe necrosis.

	Carotid stenosis (any degree) -positive	Carotid stenosis -negative	Carotid stenosis (>50% stenosis) -positive	Carotid stenosis (>50% stenosis) -negative
Hyperlipidaemia	6	5		
χ^2	1.98			
Diabetes mellitus	6	3		
χ^2	0.25			
Hypertension	5	0		
χ^2	1.13			
Temporal lobe necrosis-positive	17	3	5	15
Temporal lobe necrosis-negative	46	26	20	52
χ^2	0.072		0.805	

with NPC receiving radiotherapy.[5] Risk factors such as diabetes, smoking, and hypercholesterolaemia are not associated with development of carotid stenosis in patients receiving radiation.

The role of ultrasound for evaluation of carotid artery stenosis has been well established. The amount of plaque and degree of stenosis can be accurately assessed by real time high-resolution images when the vessel walls are clearly demonstrated.[6] In this study, the degree of stenosis in all patients was determined by real time high-resolution images.

Temporal lobe necrosis following radiotherapy in patients with NPC has been described.[7,8] This complication is related to radiation and is not confined only to patients with NPC. Patients who have received radiotherapy for skull base tumours may also experience this delayed complication.[9-11] The pathophysiology of temporal lobe injury is not known. One possible mechanism is irradiation angiopathy affecting the small vessels causing ischaemic and necrotic changes.[1] The occurrence of temporal lobe necrosis is related to both the total radiation dose and the size of the dose fraction.[12] The latent interval is variable and can range from 9 months to 16 years,[13,14] with a median of 33 months.[13] At the Prince of Wales Hospital, these patients do not have routine cross sectional imaging of the brain. The reasons for brain imaging for patients in this study were either clinical suspicion for temporal lobe necrosis or suspicion for recurrence of tumour. This may explain the high incidence of temporal lobe necrosis in this study compared with the overall incidence rate of 1.03% quoted by other authors.[13] MRI is more sensitive than CT for the detection of temporal lobe necrosis. If all patients had access to MRI, the diagnosis of temporal lobe necrosis might be more reliable. However, this is limited by finite resources.

Temporal lobe necrosis may be asymptomatic and can therefore remain clinically undetected.[14] Patients may present with memory loss or hallucinations.[15,16] Interestingly, affected patients have a significantly poorer in overall intelligence quotient and non-verbal memory recall and have more memory-related problems.[17] The clinical presentation can therefore be subtle but routine regular brain imaging for asymptomatic patients is not indicated because of the relatively low incidence.

Radiologically, temporal lobe necrosis has been used as a relatively loose term. The term is applied when there are radiation-related changes, varying from white matter hyperintensities shown on MRI to frank cystic necrotic lesions. Up to 50% of these changes may enhance and some show mass effect and may mimic glioma.[18,19]

The long latency period, lack of clinical symptoms, subtlety of the clinical symptoms when present, and the variable radiological features of temporal lobe necrosis add to the difficulty of making the correct diagnosis. Surgery for histological proof is not justified for those patients with typical clinical features and bilateral temporal lobe involvement. However, unilateral lesions in asymptomatic patients, especially if the lesion shows mass effect and enhancement, can cause diagnostic difficulties. Other authors have suggested the presence of associated endocrine disturbance may be useful to establish the diagnosis.[20]

Extracranial carotid stenosis is a common condition. While its presence is not specific for predication of temporal lobe necrosis, patients who do not have carotid stenosis are less likely to have temporal lobe necrosis, which may be a useful clue when diagnosis is difficult.

There are 2 explanations for the observed association between these 2 complications. The first is that carotid artery stenosis has a causal effect on occurrence of temporal lobe necrosis. However, this is unlikely in view of the distribution of cerebral imaging abnormalities not corresponding to the supply area of the carotid arteries. The imaging changes were always at least partly within the radiation portals at the lowest part of the temporal lobes, with variable degrees of extension beyond. Since the timing of the carotid imaging was after the detection of temporal lobe necrosis for most patients due to the study design, it is difficult to substantiate that the former is a causative factor of the latter.

The alternative explanation of the association is that the 2 organs had both sustained parallel radiation damage, owing to individual tissue-organ susceptibility to radiation. This is compatible with the radiation therapy plan in which the skull base and the whole of the neck were irradiated for all patients.

In conclusion, the absence of carotid stenosis shows a high negative predictive value for temporal lobe necrosis. This clue might be important when patients present with unilateral involvement and atypical radiological features.

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