Cancer Imaging (2003) **3**, 88–91
DOI: 10.1102/1470-7330.2003.0008

Aetiological factors and imaging program for severe radiation-induced extracranial carotid stenosis in nasopharyngeal carcinoma

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Date accepted for publication 14 February 2003

Abstract

Over a period of 3 years, we have collected the carotid ultrasound findings of 189 post-radiotherapy (RT) nasopharyngeal carcinoma patients. The patients had duplex ultrasound examination for assessment of extracranial carotid stenosis. Factors including age, sex, hyperlipidaemia, diabetes mellitus, smoking history, time lapsed after RT, symptoms of cerebrovascular disease were recorded. Association of individual factor with development of severe stenosis was assessed.

Eighty-two (43%) patients developed moderate to severe stenosis of the common carotid and/or internal carotid artery. Age and time lapsed after RT were the only factors found to be associated with development of severe stenosis. When age >57 years and >12 years post-RT were used as rules to identify patients with severe stenosis, the sensitivity was 46.7%, specificity 98.2%, PPV 77.8% and NPV 95.6%.

Radiation-induced carotid stenosis is a common event. If available resources do not allow routine surveillance, age and time lapsed after RT help to identify high-risk patients.

Keywords: *Ultrasound colour Doppler; radiation effect; carotid stenosis.*

Introduction

Carotid stenosis is a late complication of radiotherapy (RT), and has a significant impact on long-term mortality and morbidity. In a previous study, we documented that neurological symptomatology is under-reported during routine oncology follow-up[1]. The detection of this complication therefore relies on routine screening by duplex ultrasound. With limited resources, serial duplex ultrasound for every single patient might be difficult. We attempt to identify the crucial factors for development of this complication, with the aim of highlighting high-risk patients.

Materials and methods

In the period of June 1999–November 2001, 189 nasopharyngeal carcinoma (NPC) patients completing curative-intent RT for at least 1 year were recruited to this study. Most of these patients were followed-up in our oncology clinic. Seven patients were followed-up in our neurology clinic because of their co-existing neurological problems.

The RT ports for treatment of NPC covered the nasopharynx, adjacent tissues at risk, and both sides of the neck. The whole neck was treated by an anterior 6 MV photon beam with a 1–1.5 cm wide midline shield to protect the spinal cord. The median dose to the carotids was 56.4 Gy. Duplex ultrasound was performed for the assessment of the extracranial carotid arteries. Fasting blood glucose and cholesterol were determined. The smoking habits, history of cerebrovascular symptoms and history of hypertension were recorded. The year of completion of RT was noted. The study was approved by the Ethics Committee of the authors' affiliated institution

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and informed written consent was obtained from all subjects.

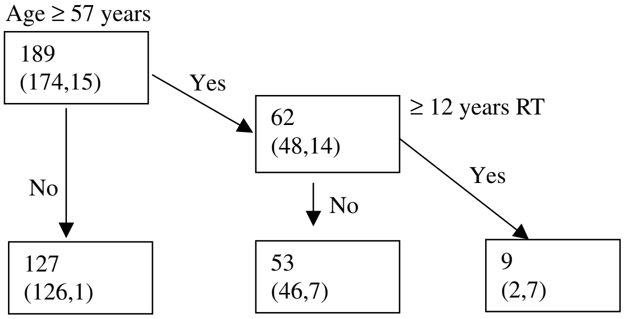

Figure 1 **Classification-tree for development of severe radiation-induced carotid stenosis. The uppermost number shown inside each square indicates the total number of patients at each node. The first number inside the parentheses represents the number of patients with no/mild/moderate outcome, the second shows the number with severe outcome. Age ≥ 57.**

Ultrasound technique

All patients had the duplex ultrasound performed with an ATL HDI 5000US scanner (Bothell, WA, USA) with a linear array ultrasound probe (L12-5). Longitudinal and transverse images of the extracranial carotid arteries were taken. The carotid arteries were classified into internal carotid arteries, carotid bulbs, common carotid arteries and external carotid arteries. At the site of maximum stenosis, a magnified transverse image was taken. The diameters of the residual lumen and the whole artery were taken by electronic calliper. The automated program of the ultrasound machine gave the percentage of stenosis.

When true transverse images were difficult to obtain or when the boundaries of the arteries were ill defined, degree of stenosis was predicted by the ratio of peak systolic velocity of the internal carotid artery to that of the ipsilateral common carotid artery. Severe stenosis (>70% diameter reduction) was diagnosed when the ratio was equal to or more than 1.5.

Analysis

All the arteries were classified into four grades: no stenosis, mild stenosis (with <30% diameter reduction), moderate stenosis (more than 30% but <70% diameter reduction) and severe stenosis (<70% diameter reduction).

A patient with fasting blood sugar >6.1 mmol/l was diagnosed to be diabetic. A patient with fasting cholesterol higher than 6.2 mmol/l was diagnosed to be hyperlipidaemic. For each of the risk factors, Fisher's exact test or t-test was used to explore the relationship with outcome (classified as no/mild/moderate and severe). The statistical analyses were performed with the outcome (classified as no/mild/moderate and severe), using the package SPSS installed on a personal computer.

The classification-tree method was then used to develop a rule for the prediction of severe outcome. The analysis was carried out by S-Plus 2000 (Seattle, WA). The sensitivity, specificity, positive predictive value and negative predictive value of the rules were calculated.

Results

One hundred and eighty-nine NPC patients (53 female, 136 male, with age range 32–76 years with a mean of 51.94 ± 9.72 years old, time lapsed after RT ranged from 1 to 22 years with a mean of 6.87 ± 3.61 years) were recruited to the study.

Out of 378 common carotid arteries, 204 arteries showed no degree of stenosis, 34 arteries showed mild stenosis, 131 arteries showed moderate stenosis and 9 arteries showed severe stenosis.

Out of 378 internal carotid arteries, 314 arteries showed no stenosis, 17 arteries showed mild stenosis, 34 arteries showed moderate stenosis and 13 arteries showed severe stenosis.

Out of 378 carotid bulbs, 320 segments showed no stenosis, 23 segments showed mild stenosis, 35 segments showed moderate stenosis and no segment showed severe stenosis.

Out of 378 external carotid arteries, 306 arteries showed no stenosis, 11 arteries showed mild stenosis, 55 arteries showed moderate stenosis and 6 arteries showed severe stenosis.

Fifteen (7.9%) patients developed more than 70% stenosis of either internal carotid artery or common carotid artery; 67 (35.4%) patients developed moderate stenosis of either internal or common carotid artery.

Sex, hyperlipidaemia, diabetes mellitus, smoking history, history of cerebrovascular disease, history of hypertension were found to have no association with the development of severe carotid stenosis. Only 178 out of 189 patients had blood results available, either because of the patients' refusal for blood to be taken or technical error.

Only the time lapsed after RT and the age of the patient were found to be significant factors (Table 1). With the classification-tree analysis, patients older than 57 years and with RT more than 12 years ago were at high risk of development of severe carotid stenosis (Fig. 1). When these rules were applied, the sensitivity was 46.7%, specificity 98.2%, positive predictive value 77.8% and negative predictive value 95.6%.

Discussion

Radiation-induced carotid stenosis is not an uncommon event among patients with head and neck tumour

Table 1 ***Association of individual risk factor with development of severe radiation-induced carotid stenosis (F refers to Fisher's exact test, t refers to t-test)***

		No/mild/moderate	Severe	P value
Sex	Female	50	3	
	Male	124	12	0.564 (F)
Cholesterol	Normal	124	12	
	High	39	3	1.000 (F)
Glucose	Normal	149	12	
	High	14	3	1.000 (F)
Smoking	No	126	11	
	Yes	48	4	0.939 (F)
Cerebrovascular symptoms	No	171	13	
	Yes	3	2	1.000 (F)
Hypertension	No	167	13	
	Yes	7	2	1.000 (F)
Age	Mean ± SD (years)	51.14 ± 9.52	61.13 ± 7.13	<0.0005 (t)
RT duration	Mean ± SD (years)	6.47 ± 3.15	11.53 ± 5.17	<0.0005 (t)

receiving RT[2–4]. In our institution's treatment protocol and in most centers, the neck is always included in the radiation post even for N0 stage NPC. Different imaging modalities can be used to assess extracranial carotid arteries[5–8]. We have used duplex ultrasound in this study as it is accurate, safe and easily accessible.

According to the European carotid trial and the North American symptomatic carotid endarterectomy trial, patients with more than 70% stenosis benefit from surgical intervention[9,10]. For patients with severe stenosis, i.e. more than 70% stenosis, this will have an important management bearing. We have therefore adopted Cheng's classification of patients and attempted to identify the crucial factors for patients at risk of developing carotid stenosis of more than 70%[3].

In our study, 15 out of 189 patients (7.9%) developed severe (>70%) carotid stenosis. The internal carotid artery was the most common artery segment with severe stenosis. This group of patients might benefit from surgical intervention and should be evaluated fully for the planning of management. Preoperative digital subtraction angiography (DSA) for accurate assessment of extent of involvement would be necessary. A significant number of our patients (67 patients) developed moderate stenosis of either the common carotid artery or internal carotid artery. Further assessment by DSA in this group of patients is probably not justified. Follow-up with duplex ultrasound to monitor the temporal progress of the carotid stenosis might be a more practical approach.

Dubec recommends routine surveillance of radiation-induced carotid artery stenosis by duplex ultrasound in patients with head and neck malignancy treated with RT[11]. We agree that this is the best way to detect carotid stenosis and identify candidates for more invasive evaluation and intervention. Resources are unfortunately always limited, and routine duplex ultrasound for all post-RT patients might not be feasible. A cost-effective way to scan patients at risk is therefore essential.

Presence or absence of neurological symptomatology is not a reliable predictor for severe carotid stenosis[1]. Most post-RT patients under-report their symptomatology during routine oncology follow-up. We have therefore performed the classification-tree analysis in order to establish rules for the identification of high-risk patients. The Chi-squared test or t-test was used to explore the association of each of the risk factors with the outcome. The classification-tree method was used to develop a rule for the prediction of severe carotid stenosis[12]. The rule was represented in the form of a binary tree. In our analysis, only time lapsed after completion of RT and the age of the patient were associated with the development of severe stenosis. Out of these two factors, age of the patient had a higher association with the development of severe stenosis. It was therefore chosen as the first selection criterion; the time lapsed after RT was used as the second selection criterion. When these rules were applied, we had a high specificity (98.2%) and a high negative predictive value (95.6%) in exclusion/identification of patients who might benefit from surgical intervention or stenting.

It was interesting to note that diabetes mellitus, smoking history, hyperlipidaemia, hypertension, neurological symptoms were not found to be associated with development of severe stenosis in these post-radiation patients. These were risk factors associated with the development of carotid stenosis without radiation exposure. We postulated that the impact of age and radiation were so significant that the impact of other risk factors were out-weighted.

As a conclusion, we have found that up to 43.3% patients develop moderate to severe carotid stenosis post-RT. This is a long-term radiation-induced complication that should not be overlooked. When routine screening is not feasible practically and financially, patients more than 57 years old and with radiation completed more than 12 years ago are useful guidelines for the identification of patients at high risk of developing severe carotid stenosis.

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