Carotid Stenosis After Radiotherapy for Nasopharyngeal Carcinoma

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Objective: To determine the prevalence and risk factors for radiation-induced carotid stenosis in patients with malignant neoplasms of the head and neck.

Design: Prospective cross-sectional screening of extracranial carotid stenosis by color-flow duplex ultrasonography with an analysis of demographic and comorbid risk factors.

Setting: Tertiary oncology and vascular referral center.

Patients: The study included 96 consecutive patients (75 men and 21 women; mean age, 53.6 years) who had undergone cervical radiotherapy (RT) for nasopharyngeal carcinoma more than 12 months ago. The mean post-RT interval was 79.9 months. Fourteen patients had cerebrovascular symptoms. A group of 96 healthy individuals were used as controls.

Main Outcome Measures: Internal carotid stenosis and common carotid artery stenosis were classified by duplex ultrasonography into moderate (30%-69%), severe (70%-99%), and totally occlusive.

Results: Internal carotid artery stenosis of 70% or more was detected in 14 arteries in 12 patients (6 occlusions). Common carotid artery stenosis of 70% or more was found in 11 arteries in 9 patients (4 occlusions). Overall, 15 patients (16%) had critical stenosis in their common or internal carotid arteries, and another 20 (21%) had stenosis in the moderate range. Critical carotid stenosis was not present in any of the control subjects. Severe post-RT carotid stenosis was associated with age ($P = .003$), smoking ($P = .004$), heart disease ($P < .001$), no prior oncological surgery ($P < .001$), cerebrovascular symptoms ($P < .001$), and interval from RT ($P < .001$). Smoking, interval from RT, cerebrovascular symptoms, and no head and neck surgery were significant independent predictors for severe carotid stenosis on multivariate logistic regression analysis.

Conclusions: Patients who undergo irradiation of the head and neck for more than 5 years have a higher risk of developing significant carotid stenosis (relative risk, 15), and routine duplex ultrasound screening is recommended.

PATIENTS AND METHODS

This study was designed as a prospective cross-sectional evaluation of patients who were followed up at the Oncology Clinic, Division of Head and Neck Surgery, University of Hong Kong Medical Centre, Queen Mary Hospital, Hong Kong, China, between January 1998 and February 1999. All patients who had NPC and had previously been treated with external irradiation of the head and neck for a minimum of 12 months, with or without oncological surgery, were included. Patients who had undergone prior carotid surgery were excluded.

A total of 96 consecutive patients were recruited. All had received primary or postoperative adjunctive external irradiation of 64 to 72 Gy to the primary site and 45 to 50 Gy to the neck if the lymph nodes were negative and 60 to 66 Gy to the cervical region if the lymph nodes were positive. The patients were interviewed in the clinic, and the nature and timing of their previous RT and/or surgery were recorded. Standard demographic and comorbidity data, including sex, age, smoking history, and presence of hypertension, diabetes mellitus, and coronary artery and peripheral vascular disease, were also collected prospectively. Patients who were active tobacco users or who had abstained for less than 10 years were regarded as smokers. The patients were also asked whether they had experienced previous symptoms of cerebrovascular insufficiency after undergoing RT.

All patients underwent a carotid color-flow duplex scan in a vascular laboratory by a single registered vascular technologist. The common carotid artery (CCA), internal carotid artery (ICA), and external carotid artery (ECA) on both sides of the neck were insonated with a 5-MHz probe using a color-flow duplex scanner (Acuson 128XP10; Acuson Corp, Mountain View, Calif) in the standard fashion. The waveforms and the peak systolic and end diastolic velocities were recorded, and spectral measurements were taken with a Doppler angle of 35° to 65°. The diagnostic criteria for stenosis were based on peak systolic and end diastolic velocities, as well as ICA/CCA ratios, and modified to detect carotid stenosis at the 70% level, according to the recommendations of the North American Symptomatic Carotid Endarterectomy Trial and the European Carotid Surgery Trial. Carotid stenosis was further defined as mild (0%-29%), moderate (30%-69%), severe (70%-99%), and totally occlusive. Stenosis of 70% or greater was regarded as significant. The sensitivity and specificity of the vascular laboratory were 93% and 82%, respectively.

Statistical analysis was performed comparing patients with and without significant (≥70%) ICA or CCA stenosis with respect to demographic and comorbid data (ie, sex, age, smoking, diabetes mellitus, and ischemic heart disease), cerebrovascular symptoms, and time course and interval from RT using the χ2 test for categorical variables and the t test (independent samples, 2-tailed) for continuous variables. Significant variables were also entered into a multivariate forward stepwise logistic regression model to identify independent risk factors associated with severe carotid stenosis.

Duplex scanning data from a group of 96 consecutive healthy individuals (38 men and 58 women; mean ± SD age, 61.8 ± 10.5 years; and age range, 33-85 years) were used as controls.

RESULTS

The study population consisted of 75 men and 21 women (age, 53.6 ± 11.9 years; age range, 25-77 years). Twenty-eight (29%) of the patients were smokers, 6 had diabetes mellitus, and 6 had ischemic heart disease. None had peripheral arterial insufficiency. Fourteen (15%) had symptoms of cerebrovascular insufficiency since they underwent RT. Twelve had 1 or more transient ischemic attacks in the carotid territory, and 2 had a stroke with fixed deficits. A total of 54 patients (56%) had undergone previous oncological surgery, including radical neck dissections (n = 28), nasopharyngectomy via a maxillary swing approach (n = 22), maxillectomy (n = 1), laryngectomy (n = 2), and glossectomy for concomitant head and neck carcinoma (n = 1). Patients who had undergone surgery were comparable in terms of age, sex, and post-RT interval with those who had not undergone surgery. The mean ± SD follow-up interval from RT was 79.9 ± 64.6 months (range, 12-336 months), with a mean ± SD RT course of 6.0 ± 1.3 weeks (range, 2-10 weeks). The results of carotid duplex scanning according to individual arteries are listed in Table 1. Of the 96 patients scanned, 27 (28%) had ICA stenosis of 30% or more on either side of the neck, and the stenosis was critical (≥70%) in 12 patients (13%). Common carotid artery stenosis of 30% or more was found in 21 patients (22%), 9 (9%) of whom had severe stenosis. In all, 35 patients (37%) were found to have either CCA or ICA stenosis of 30% or more, and 15 (16%) of the 35 patients had ICA or CCA stenosis of 70% or more. Six ICAs and 4 CCAs were totally occluded at the time of the examination. In the control group, only 8 patients (8%) were found to have ICA stenosis of 30% to 69%, and none had CCA or ICA stenosis of 70% or more or occlusions.

On univariate analysis, significant post-RT ICA/CCA stenosis was associated with age (P = .003), smoking (P = .004), and ischemic heart disease (P < .001) but not with sex or diabetes mellitus. Patients who did not undergo surgery had a positive relationship with carotid stenosis (P < .001). Severe ICA/CCA stenosis was also significantly related to cerebrovascular symptoms (P < .001) and to the interval from RT (P < .001). The mean ± SD interval from RT for patients with ICA/CCA stenosis of 70% or more was 132.7 ± 50.9 months, compared with 70.1 ± 62.4 months for those with ICA/CCA stenosis of less than 70% (P < .001). Patients with ICA/CCA stenosis of 70% or more were older (mean ± SD age, 61.7 ± 8.1 years), compared with patients with no significant disease (age, 52.0 ± 11.9 years; P = .003). Critical disease in the CCA alone (with or without ICA stenosis) was also more common in patients with symptoms (36%) than in asymptomatic patients (5%, P < .001).

Multivariate logistic regression analysis of these factors revealed that smoking, post-RT interval, cerebro-
vascular symptoms, and no head and neck surgery were the significant independent predictors of severe ICA/CCA stenosis associated with RT (Table 3).

Patients with (n = 28) and without (n = 68) radical neck dissections did not differ in age (mean, 52.5 vs 54.0 years), sex (75% male vs 79% female), and post-RT interval (mean, 68 vs 85 months; \( P = .28 \)). Only 2 (7%) of the 26 patients who had undergone a radical neck dissection had significant ICA/CCA stenosis, compared with 13 (19%) of those who had not undergone a neck dissection, but this difference was not significant (\( P = .14 \)). Radical neck dissection did not add to the risk of post-RT carotid stenosis.

Of the 15 patients who had ICA/CCA stenosis of 70% or more, 1 underwent surgery and required a CCA to ICA interposition graft replacement. Four patients were treated with percutaneous balloon angioplasty and stenting of the carotid arteries. One of the 4 patients suffered a peri-procedural stroke and subsequently died of cerebral hemorrhage. The other 3 experienced no morbidity. Five others were angiographically evaluated and found to have a total occlusion of their carotid arteries, and no further intervention was offered. The rest were either asymptomatic or declined intervention.

**COMMENT**

External RT is a standard treatment for early NPC and is also used for local recurrences and control of neck node metastasis. Vascular complications that may result from cervical RT include temporal bone osteomyelitis with intrapetrosal carotid artery pseudoaneurysm and extracranial carotid stenosis. The long-term sequelae of radiation exposure of the carotid arteries may take years to manifest clinically. The exact mechanism of radiation-induced carotid artery disease is not clear, although a combination of direct injury and vessel wall ischemia due to obliteration of the vasa vasorum may be responsible. Irradiation of the arteries of the neck induces direct vessel wall damage, with an acute phase of endothelial proliferation, followed by medial degeneration and adventitial fibrosis and thickening. The results may be indistinguishable from atherosclerosis.

Despite the widespread use of RT to treat patients with malignant neoplasms of the head and neck, radiation-induced carotid stenosis in these patients was rarely stud-
to atherosclerosis, but our study showed that radical neck dissection has no additional bearing on the development of carotid stenosis. The North American Symptomatic Carotid Endarterectomy Trial and the Asymptomatic Carotid Atherosclerosis Study confirmed the efficacy of carotid endarterectomy in stroke prevention in patients with critical symptomatic and asymptomatic carotid stenosis, but the benefits of surgery in patients who have undergone RT of the neck must be balanced by its inherent risks. In these patients, carotid endarterectomy has been regarded as hazardous. Previous RT may result in periadventitial fibrosis, hindering dissection of the vessels. The endarterectomy plane is frequently obliterated, with concomitant weakening of the arterial wall, rendering the procedure difficult. Also, cervical RT often produces carotid lesions that are more extensive than the traditional bifurcation stenosis, involving the CCA and necessitating more complicated vascular reconstruction or vessel replacement, as well as adding to the perioperative morbidity. Local wound complications are reported to be more frequent. In the past, these concerns have directed the vascular surgeon’s attention to a more conservative approach. With the rapid evolution of carotid angioplasty and stenting in recent years, a minimally invasive procedure to treat patients with post-RT carotid stenosis is now available, although its efficacy and long-term benefit should be proved before it can be accepted as standard treatment. The development of a new modality of treatment demands additional information about the incidence and distribution of disease.

The present study demonstrated that the prevalence of carotid stenosis in patients who have undergone RT is not low. In 18 patients (16%), critical stenosis of either the CCA or the ICA was present, and 35 (37%) had moderate stenosis that may worsen with time. Many of these patients also have multiple vessel diseases. Four CCAs and 6 ICAs were occluded at the time of diagnosis, precluding effective surgical treatment. No significant disease was identified in the control group. The fact that age is a significant risk factor (patients aged ≥60 years had a 9.5 times higher risk of developing carotid stenosis) suggests that a mechanism of accelerated atherosclerosis may augment the initial radiation injury. Close follow-up of these patients with serial duplex ultrasonography is indicated.

Although the natural history of the lesions could not be established with a cross-sectional study, we have demonstrated a close association of ICA or CCA stenosis with the presence of cerebrovascular symptoms. Two thirds (10/15) of the patients with ICA/CCA stenosis of 70%....
or more had a stroke or transient ischemic attack after they underwent RT, with a relative risk of 38.5. In a large retrospective review of a group of heterogeneous patients, Elerding et al\textsuperscript{13} reported an incidence of stroke of 6.3\% after a mean follow-up of 9 years in patients who received RT for head and neck cancers. These carotid lesions therefore cannot be regarded as benign and should be treated in the same manner as standard carotid stenoses. One of the most important factors associated with significant carotid disease is the time interval after RT. Patients who had undergone RT more than 5 years earlier had a 1.5 times higher chance of having stenosis of 70\% or more in their carotid arteries than those with less than 5 years, with an overall prevalence of 26\%. Routine screening by duplex ultrasonography should therefore be offered to patients who have undergone RT for NPC and who have survived longer than 5 years.

The CCA is also exposed to the field of cervical irradiation; therefore, injury to this artery is a matter of concern. Critical stenosis or a long plaque in the CCA may hinder the proper placement of the proximal clamp in a traditional carotid endarterectomy, may add to the hazard of intraoperative embolization if a shunt is used, and may require replacement of the carotid bifurcation with an interposition graft. In this study, critical CCA stenosis was demonstrated in 9 (9\%) of 96 patients. Five of the 9 patients with significant CCA disease also had critical ICA stenosis. Stenosis of the CCA alone was also associated with cerebrovascular symptoms, indicating that its presence would imply more significant disease with implications of a higher risk of stroke and that treatment with carotid angioplasty might be considered.

The prevalence of carotid stenosis in a group of patients with NPC who had undergone irradiation of the head and neck was not low. Critical stenosis seemed to be associated with symptoms of cerebrovascular insufficiency, a history of smoking, and the duration from RT. Routine duplex screening should be required in these high-risk patients, particularly in those older than 60 years who have received RT more than 5 years previously, and regular diagnostic ultrasound follow-up is advisable until a final treatment strategy can be developed based on long-term observation studies.

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REFERENCES