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Incidence and risk factors of significant carotid artery stenosis in asymptomatic survivors of head and neck cancer after radiotherapy

Jennifer A. Dorth, MD^{1,*}, Pretesh R. Patel, MD¹, Gloria Broadwater, MS², and David M. Brizel, MD^{1,3}

¹Department of Radiation Oncology, Duke Cancer Institute, Durham, North Carolina

²Cancer Center Biostatistics, Duke Cancer Institute, Durham, North Carolina

³Department of Surgery, Duke Cancer Institute, Durham, North Carolina

Abstract

Background—The incidence and risk factors of carotid artery stenosis in asymptomatic patients after head and neck radiation therapy (RT) are unknown.

Methods—This retrospective study reviewed asymptomatic patients treated with RT for head and neck cancer from 2000 to 2009 who underwent screening carotid ultrasound.

Results—Two hundred twenty-four patients were included, the majority of whom had stage III to IV disease and received cisplatin-based chemotherapy. Median time from RT completion to last carotid ultrasound was 3 years. Actuarial rate of carotid artery stenosis at 4 years was 14% (95% confidence interval [CI], 4% to 22%). Multivariate analysis revealed that carotid artery stenosis was associated with Framingham risk factors (hazard ratio [HR], 1.6 per factor; 95% CI, 1.2–2.2; $p = .003$). Among 135 patients treated with intensity-modulated radiation therapy (IMRT), the HR for carotid artery stenosis was 1.4 for every 10 Gy increase in mean RT dose to the carotid bulb plus 2 cm (95% CI, 0.8–2.4; $p = .35$).

Conclusion—Prevention and screening programs should be considered for head and neck cancer survivors given the high risk of carotid artery stenosis.

Keywords

radiation; head and neck cancer; carotid artery stenosis; carotid ultrasound; cerebrovascular disease

INTRODUCTION

Radiation therapy (RT) for head and neck cancer is a known risk factor for the development of cerebrovascular events (CVEs), with relative risks ranging from 2 to 6.^{1,2} In a Surveillance, Epidemiology, and End Results-Medicare analysis of patients with head and neck cancer, those who received RT alone had a hazard ratio (HR) for CVE of 1.5, compared with patients who received surgery alone or surgery and RT.² Overall, the 10-year cumulative incidence of CVE after RT ranges from 12% in patients aged <60¹ to 34% in patients older than 75.²

Two studies demonstrated an increased risk of carotid artery stenosis in patients with head and neck cancer previously treated with RT compared to newly diagnosed, untreated patients with head and neck cancer.^{3,4} In these studies, symptomatic patients and those with a history of CVE or carotid artery stenosis were included. One cross-sectional study found the 2-year incidence of significant carotid artery stenosis (≥ 50%) was 20% in the irradiated group compared to 0% in the control population ($p < .001$).⁴ Another study found the 9-year incidence of carotid artery stenosis (≥ 50%) in 71 patients treated with RT for nasopharyngeal carcinoma was 30%, compared with no cases among 51 patients in the control group ($p < .001$).³ Similarly, 2 investigations of patients receiving unilateral neck RT for head and neck cancer but undergoing bilateral carotid imaging demonstrated a greater risk of subsequent carotid artery stenosis in the irradiated artery.⁵

The incidence and risk factors for developing carotid artery stenosis in asymptomatic survivors of head and neck cancer is not well characterized. It is not routine practice to screen patients with head and neck cancer for carotid artery stenosis. The first patients were screened at Duke Cancer Institute (DCI) in 2000 and, since then, a policy to screen asymptomatic survivors of head and neck cancer has gradually evolved. This report details the initial findings of that experience.

PATIENTS AND METHODS

This institutional review board–approved study evaluated all patients with head and neck cancer who underwent postradiotherapy carotid ultrasound from 2000 to 2009 at DCI. All patients were asymptomatic and had no history of stroke, transient ischemic attack, or carotid artery stenosis. Patients with metastatic disease at diagnosis were excluded, as were patients who developed disease recurrence or second primary cancer before undergoing carotid ultrasound. Patients whose treatment did not include the cervical lymph nodes within the treatment volume (ie, early stage glottis larynx and parotid cancer) were not included.

Baseline Framingham stroke risk factors including sex, age, smoking history, hypertension, hyperlipidemia, diabetes mellitus, cardio/peripheral vascular disease, and atrial fibrillation were collected. Patients were scored as having these risk factors based on their presence before the diagnosis of head and neck cancer. Depending on stage and presentation, some patients received concurrent chemotherapy and/or underwent surgery in addition to RT. Radiation was delivered using conventional or intensity-modulated techniques with a range of fractionation schedules.

Starting in 2005, most patients with head and neck cancer underwent posttreatment carotid artery stenosis screening. Generally, patients underwent screening ultrasound within the first 1 to 2 years of completing RT and every 2 to 3 years thereafter. Patients with significant carotid artery stenosis, which was defined as 50% diameter reduction, were referred to see a vascular surgeon for further evaluation and management. Interventions included use of antihypertensive agents, cholesterol-lowering medications, smoking cessation, antiplatelet drugs, carotid endarterectomy (CEA), and/or carotid artery stenting as clinically indicated.

Ultrasound technique

Duplex ultrasound images were obtained and stenosis was estimated using flow velocities and Doppler spectrum analysis. Hemodynamically significant carotid artery stenosis was defined as 50% reduction in luminal diameter of the common or internal carotid arteries.

Statistical analysis

Actuarial freedom from carotid artery stenosis was estimated using the Kaplan–Meier product limit method. Incidence of carotid artery stenosis was calculated as the time from completion of radiation until development of carotid artery stenosis detected on radiologic imaging. Patients were censored at the date of death, disease progression, or last radiologic assessment of the carotid arteries.

A multivariate Cox proportional hazards model was used to quantify the risk of carotid artery stenosis, where an event was defined as a patient who developed stenosis on either/both sides of the neck. Variables were included in the analysis without selection: number of Framingham risk factors, age at head and neck cancer diagnosis, and administration of chemotherapy because they predict greater risk of carotid artery stenosis in the general population.^{6,7} All *p* values are given for 2-tailed tests, and all analyses were performed using SAS v 9.2 (Cary, NC).

We constructed 2 multivariate models of carotid artery stenosis by artery: 1 for all patients and 1 limited to those patients treated with intensity-modulated radiation therapy (IMRT). Recurrent events analysis was performed to adjust for the relationship between 2 events occurring in the same patient.⁸ This model tested the relationship between RT dose parameters and carotid artery stenosis after adjusting for Framingham risk factors and lymph node dissection, another factor that is associated with a greater risk of carotid artery stenosis.⁹ In order to evaluate different fractionation schedules, all RT doses were converted into 2 Gy per fraction equivalents, assuming an α/β of 3.¹⁰ For the all patient artery model, the maximum prescribed radiation dose was the parameter tested.

Radiation dose parameters collected among IMRT patients included maximum, mean, and partial organ volumes receiving 50, 55, 60, 65, or 70 Gy (partial volume doses). These dose parameters were calculated for each carotid artery based on either: (1) the entire carotid from the origin of the common carotid in the low neck, to the carotid bulb, and then following the internal carotid to its exit into the skull base; or (2) the carotid bulb plus 2 cm of the distal common carotid and 2 cm of proximal internal carotid artery. We considered the carotid bulb plus 2 cm as a distinct structure because the greatest atherosclerotic plaque

thickness in both general and irradiated populations occurs in this region.^{4,11} Because of this distribution, carotid artery stenosis screening programs, such as in the Framingham Heart Study, image the carotid bulb plus 2 cm.¹²

RESULTS

Seven hundred thirty-five patients were identified who underwent radiation for head and neck cancer from 2000 to 2009. Of these, 116 patients were excluded: 84 patients who were treated with palliative intent, 14 patients who previously received neck RT, and 18 patients who had a history of carotid artery stenosis or stroke. Among the remaining 619 patients, 524 patients received neck RT, whereas 95 patients did not. During follow-up, 192 patients did not complete screening because of an event within 2 years of RT (head and neck cancer recurrence, $n = 130$; second cancer, $n = 21$; death, $n = 29$; severe comorbid illness, $n = 7$; or CVE, $n = 5$).

Three hundred thirty-two patients were eligible to undergo carotid artery stenosis screening, of whom 224 completed screening. Eligible patients were not screened for the following reasons: follow-up at another institution ($n = 42$), follow-up only with otolaryngology ($n = 43$), or radiation oncology follow-up before initiation of screening practice ($n = 23$). The majority of patients began their screening after 2004 (2000–2004, $n = 80$; 2005–2009, $n = 144$).

Patient characteristics are found in Table 1. Median age was 56 years old at diagnosis (range, 26–85 years). Fourteen percent had stage I to II disease, 23% had stage III, and 63% had stage IV. Primary sites included the oro-pharynx (59%), larynx (17%), oral cavity (10%), naso-pharynx (6%), and other (8%). Radiation technique was 2-dimensional (33%), 3-dimensional (6%), or IMRT (61%). Radiation schedules included conventional, 2 Gy daily doses (56%), hypofractionation (2%), accelerated fractionation (7%), or accelerated hyperfractionation (35%). Patients received cisplatin alone (40%), cisplatin plus another agent (32%), other agents (2%), or no chemotherapy (28%). Lymph node neck dissection was performed in 50% of patients. The subset of patients treated with IMRT had similar characteristics, except that more were treated with conventional fractionation and chemotherapy (Table 1).

Outcomes

The median time from RT completion to the most recent carotid ultrasound was 3.6 years (interquartile range, 1.2–4.8 years). Patients underwent first carotid ultrasound a median of 1.3 years after completing RT. Stenosis was identified in 35 patients and 53 carotid arteries a median of 3 years after completion of RT. In the IMRT subgroup, there were 11 arteries with stenosis among 136 patients. All stenoses were observed to involve all or a portion of the carotid bulb plus 2 cm of distal common carotid and proximal internal carotid. Actuarial rates of carotid artery stenosis at 2, 3, and 4 years were 4% (95% confidence interval [CI], 0% to 9%), 11% (95% CI, 3% to 18%), and 14% (95% CI, 4% to 22%), respectively (Figure 1). Among patients with 0 to 1 Framingham risk factors, the 4-year rate of carotid artery stenosis was 11% (95% CI, 4% to 18%).

Univariate analysis by patient revealed that male sex (HR, 3.0; 95% CI, 1.1–8.3), hypertension (HR, 2.4; 95% CI, 1.2–4.7), cardio/peripheral vascular disease (HR, 3.9; 95% CI, 1.6–9.1), and each additional Framingham risk factor (HR, 1.5; 95% CI, 1.2–2.0) were associated with increased risk of carotid artery stenosis by patient (Table 2). On multivariate analysis, after adjusting for age and receipt of chemotherapy, the Framingham score was associated with an increased risk of carotid artery stenosis by patient (HR, 1.6 per factor; 95% CI, 1.2–2.2; $p = .003$; Table 3).

Based on 272 arteries treated with IMRT, the mean volume of the entire carotid was 6.5 cc (SD, 1.8) and carotid bulb plus 2 cm was 2.4 cc (SD, 0.8) (Table 3). Calculated mean RT dose for the carotid bulb plus 2 cm was 57 Gy. Mean RT dose to the entire carotid was 50 Gy. Three-year carotid artery stenosis rates by artery were higher if the mean RT dose to the carotid bulb plus 2 cm fell above the median value (vs >57 Gy, 5% vs 10%) or within the highest quartile (vs >67 Gy, 4% vs 19%).

On multivariate analysis, adjusting for Framingham score and lymph node dissection, there were no statistically significant RT dosimetric predictors of carotid artery stenosis (Table 4). Each row in Table 4 represents a distinct multivariate model. For every 10 Gy increase in the mean and maximum dose to the carotid bulb plus 2 cm, the HR for carotid artery stenosis was 1.4 (95% CI, 0.8–2.4; $p = .35$) and 1.4 (95% CI, 0.7–2.4; $p = .29$), respectively. When dichotomized at the median value, a V50 for the carotid bulb plus 2 cm of 100% compared to <100% had an HR for carotid artery stenosis of 1.0 (95% CI, 0.3–3.0; $p = .94$). Additionally, when dichotomized at the median value, a V70 of 0 compared to 1% had an HR of 1.2 (95% CI, 0.5–3.2; $p = .66$). In comparison, for every 10 Gy increase in the mean and maximum dose to the entire carotid, the HR for carotid artery stenosis was 1.2 (95% CI, 0.7–2.0; $p = .45$) and 1.3 (95% CI, 0.8–2.0; $p = .08$), respectively. When dichotomized at the median value, a V70 for the entire carotid of 0 vs 1% had an HR for carotid artery stenosis of 0.9 (95% CI, 0.4–2.3; $p = .97$).

Among 35 patients diagnosed with carotid artery stenosis, 27 of them completed multiple imaging studies in follow-up. Of these 27 patients, 9 had stable stenosis on follow-up imaging, whereas 18 patients had either progressive or high-grade (>70%) stenosis. Of the 18 patients with progressive or high-grade stenosis, 9 underwent surgical intervention. Two patients could not undergo surgery because they had unilateral arterial occlusion. One patient, who was not a surgical candidate because of medical comorbid illness, experienced a CVE and had residual hemi-body weakness.

Nine patients underwent surgical intervention; 3 patients with CEA and 6 with carotid artery stenting. Two patients were free from restenosis after unilateral CEA at 1 and 3 years. However, 1 patient underwent bilateral CEA and developed right-sided complete occlusion at 1 year and left-sided high-grade restenosis at 2 years without symptoms. Six patients underwent carotid artery stenting and 4 patients developed restenosis at a median follow-up of 2 years. Of 4 patients with restenosis, 3 patients had stable stenoses, whereas 1 patient had a CVE and died 2 years after carotid artery stenting.

DISCUSSION

Multiple studies demonstrate an increased risk of cerebrovascular events^{1,2,13} and carotid artery stenosis^{3,4} after RT for head and neck cancer. However, the incidence of carotid artery stenosis after RT in asymptomatic patients is not known. Studies that have quantified the prevalence of carotid artery stenosis have included patients with a history of CVE/ carotid artery stenosis or who had neurologic symptoms before undergoing screening. Additionally, it is not clear how many eligible patients were included. The current study includes all asymptomatic patients with head and neck cancer who underwent carotid ultrasound as part of the screening practice at DCI. A total of 68% of potentially eligible patients underwent screening for carotid stenosis.

In our study, the actuarial rate of carotid artery stenosis at 4 years was 14%. For comparison, the prevalence of carotid artery stenosis 50% in the general population was 4.2% (95% CI, 3.1% to 5.7%) in a pooled analysis of 22,636 individuals.¹⁴ Among an irradiated group of patients with head and neck cancer in Taiwan, the reported 2-year carotid artery stenosis (50%) rate of 20% was higher than our rate.⁴ The higher carotid artery stenosis rate might be attributed to the fact that symptomatic patients and those with a history of carotid artery stenosis were included. A study of 40 patients with head and neck cancer who underwent screening 10 years after completing RT reported carotid artery stenosis in 40% of patients, 7.5% of whom had sustained a previous stroke.¹⁵ We expect that the incidence of carotid artery stenosis will similarly increase among our patients with longer follow-up time.

Two retrospective series reported 8-year rates of carotid artery stenosis (50% to 60%) of 15% to 18% in patients undergoing unilateral head and neck RT.^{5,9} Even with longer follow-up times, these studies had rates of carotid artery stenosis similar to our series. Lower than expected carotid artery stenosis rates might be explained by the fact that only 55% received RT targeted to the neck in 1 series⁹ and 35% of patients had lymphoma and were treated to lower doses of RT (30–35 Gy) in the other series.⁵

Our study suggests that RT dose may be correlated with increasing risk of hemodynamically significant carotid artery stenosis. There was a higher risk of carotid artery stenosis with an increase in multiple dosimetric parameters, although none was statistically significant. There were only 11 stenotic arteries among 136 IMRT patients, which limited the power to establish a statistically significant RT dose effect. For every 10 Gy increase in mean RT dose to the carotid bulb plus 2 cm, the HR of carotid artery stenosis was 1.4. A previous study found that RT dose predicted for a worse overall carotid plaque score (HR, 1.001 per cGy; $p < .001$),⁴ but did not relate it to hemodynamically significant carotid artery stenosis.

There is suggestion of an RT dose effect for cerebrovascular events. In a Surveillance, Epidemiology, and End Results-Medicare analysis, patients who underwent RT alone were at a higher risk than those who underwent both surgery and RT (HR, 1.42; 95% CI, 1.14–1.8).² Higher rates of CVE could have been related to larger volumes of carotid arteries treated and/or higher RT doses used. Although RT doses of 60 to 66 Gy are often used in the postoperative setting,¹⁶ definitive RT doses are typically 70 Gy in 2 Gy per fraction.¹⁷

Unfortunately, it is not possible in most clinical scenarios to eliminate RT dose to the carotids, even with IMRT, because much of the carotid artery is included in the neck nodal target volumes representing areas at risk of subclinical disease.¹⁸ However, judicious use of IMRT may facilitate RT dose reduction to the carotid arteries for early staged larynx cancer or when planning RT boost volumes to gross disease. Future studies should investigate the techniques for and impact of reducing RT doses to carotid arteries. It is important to further characterize the optimal RT avoidance structure and dosimetric constraint. In our study, the HRs of carotid artery stenosis for multiple dosimetric parameters for the carotid bulb plus 2 cm were higher than those for the entire carotid. Additionally, the HR of carotid artery stenosis above the median cutoff for the V70 was higher than for the V50 of the carotid bulb plus 2 cm.

The number of Framingham stroke risk factors was associated with an increased risk of carotid artery stenosis with an HR of 1.6 per each additional factor. These factors are known to increase the risk of asymptomatic carotid artery stenosis in the general population, with a similar relative risk of 2 to 3 per additional factor.¹⁹ Given that medical management of risk factors reduces carotid artery stenosis incidence and progression in the general population,²⁰ similar interventions should be considered in patients with head and neck cancer.

For the general population, the United States Preventive Task Force does not recommend screening for asymptomatic carotid artery stenosis because the prevalence of carotid artery stenosis is low, as is the risk of developing progressive stenosis (5% per year) or CVE (<1% per year) given asymptomatic carotid artery stenosis.^{20,21} Additionally, surgical complication rates vary widely and can outweigh the benefits of CEA or carotid artery stenting. Considering that patients with head and neck cancer after RT have higher rates of developing asymptomatic and progressive carotid artery stenosis, and cerebrovascular events, screening and risk factor reduction programs that carefully evaluate associated risks and benefits warrant future investigation. The fact that our study and others²² demonstrate high rates of restenosis after surgical intervention for carotid artery stenosis further supports prevention strategies for patients with head and neck cancer.

CONCLUSIONS

The risk of carotid artery stenosis in irradiated head and neck cancer survivors increases with increasing RT dose and number of Framingham risk factors. Posttreatment prevention and screening programs should be considered for head and neck cancer survivors.

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FIGURE 1.
Incidence of carotid artery stenosis by patient.

TABLE 1

Patient and treatment characteristics.

Characteristic	All patients	IMRT
	<i>n</i> = 224 (%)	<i>n</i> = 136 (%)
Sex		
Male	76	81
Female	23	19
Median age, y	56	56
Stage		
I–II	14	14
III	23	19
IV	63	67
Primary site		
Oropharynx	59	60
Larynx	17	13
Oral cavity	10	12
Nasopharynx	6	5
Other	8	10
RT fractionation		
Conventional	56	64
Accelerated	7	12
Accelerated hyper	35	22
Hypo	2	2
Chemotherapy regimen		
CDDP	40	52
CDDP + other	32	21
Other	2	25
None	28	2
Neck dissection	50	49
Framingham score, median	1	1
Framingham risk factors		
Smoking	70	68
Diabetes	11	12
Hypertension	37	37
Hyperlipidemia	10	25
Vascular disease	12	14
Atrial fibrillation	2	2

Abbreviations: IMRT, intensity-modulated radiation therapy; RT, radiation therapy; CDDP, cisplatin.

TABLE 2

Univariate analysis for carotid artery stenosis.

Factor	HR	95% CI	p value
Age, per 10 y	1.06	0.8–1.5	.7
Sex, male	3.0	1.1–8.3	.04*
Smoking	2.0	0.8–4.8	.13
Diabetes	1.8	0.7–4.6	.24
Hypertension	2.4	1.2–4.7	.01*
Hyperlipidemia	1.2	0.5–2.7	.7
Vascular disease	3.9	1.6–9.1	.002*
Framingham risk score, per factor	1.5	1.2–2.0	.002*
Neck dissection	0.6	0.3–1.2	.16
Chemotherapy	0.8	0.4–1.6	.5

Abbreviations: HR, hazard ratio; CI, confidence interval.

*
p value < .05.

TABLE 3
Dosimetric parameters: mean doses and partial volumes receiving specified doses (mean $\pm$ SD).

Structure	Volume cc	Max Gy	Mean Gy	V50 %	V55 %	V60 %	V65 %	V70 %
Entire artery	6.5 $\pm$ 1.8	64 $\pm$ 15	50 $\pm$ 15	67 $\pm$ 32	44 $\pm$ 27	34 $\pm$ 27	22 $\pm$ 27	15 $\pm$ 22
Carotid bulb *	2.4 $\pm$ 0.8	63 $\pm$ 15	57 $\pm$ 16	81 $\pm$ 34	68 $\pm$ 39	55 $\pm$ 41	37 $\pm$ 42	25 $\pm$ 37

* Carotid bulb + 2 cm, as defined in text.

TABLE 4

Multivariate analysis for carotid artery stenosis.

	HR	95% CI	p value
Factor by patient (all patients) adjusted for age and chemotherapy			
Framingham score per factor	1.6	1.2–2.2	.003*
Factor by artery (all patients) adjusted for Framingham score and lymph neck dissection			
Max prescribed dose per 10 Gy	1.01	.99–1.04	.35
Factor by artery (IMRT patients) adjusted for Framingham score and lymph neck dissection			
Entire carotid			
Mean dose per 10 Gy	1.2	0.7–2.0	0.45
Max dose per 10 Gy	1.3	0.8–2.0	0.08
V50, < vs 82% [†]	1	0.3–2.8	0.97
V70, 0 vs 1% [†]	0.9	0.4–2.3	0.84
Carotid bulb + 2 cm			
Mean dose per 10 Gy	1.4	0.8–2.4	0.35
Max dose per 10 Gy	1.4	0.7–2.4	0.29
V50, < vs = 100% [†]	1	0.3–3.0	0.94
V70, 0 vs 1% [†]	1.2	0.5–3.2	0.66

Abbreviations: HR, hazard ratio; CI, confidence interval; IMRT, intensity-modulated radiation therapy.

*
p value < .05 in multivariate analysis.[†]
Dichotomized at the median value.