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The risk of carotid stenosis in head and neck cancer patients after radiation therapy

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ABSTRACT

Objectives: Head and neck radiotherapy (RT) is a risk factor for cerebrovascular disease. We performed a retrospective cohort study to evaluate carotid artery stenosis (CAS) incidence in head and neck cancer (HNC) patients undergoing RT, characterizing associated risk factors.

Materials and methods: Records were retrospectively reviewed for HNC patients undergoing carotid ultrasound screening after definitive or adjuvant RT between January 2000 and May 2016. CAS was defined as ≥50% stenosis on imaging, stroke, or transient ischemic attack. Actuarial CAS rates were calculated by Kaplan-Meier method. Univariate and multivariate analyses predicted CAS risk based on carotid dosimetric and clinical parameters.

Results: 366 patients met inclusion criteria. Median time from RT completion to last follow-up was 4.1 yr. Actuarial risk for CAS was 29% (95% CI 22–36%) at 8 years. Univariate analysis showed that smoking (HR 1.7; 95% CI 1.1–2.7), hyperlipidemia (HR 1.6; 95% CI 1.03–2.6), diabetes (HR 2.8; 95% CI 1.6–4.8), coronary artery disease (HR 2.4; 95% CI 1.4–4.2), and peripheral artery disease (HR 3.6; 95% CI 1.1–11.6) were significantly associated with increased CAS. In multivariate analysis, diabetes was predictive of time to CAS (HR 1.9; 95% CI 1.1–3.4). Carotid dose parameters were not significantly associated with CAS.

Conclusions: CAS incidence is high after head and neck radiotherapy, gradually rising over time. No clear dose-response effect between carotid dose and CAS was identified for HNC patients. Carotid artery screening and preventative strategies should be employed in this high-risk patient population.

Introduction

The role of post-treatment screening for asymptomatic carotid artery stenosis (CAS) in the head and neck cancer (HNC) population is unclear. The United States Preventive Task Force does not recommend CAS screening in the general population due to low CAS prevalence (< 5%) [1]. Addressing higher risk populations, guidelines from the Society of Vascular Surgeons and the American Society of Neuroimaging determined CAS screening to be cost-effective for reducing stroke when CAS prevalence is ≥20%, and potentially cost-effective when CAS prevalence is between 5% and 20% [2,3]. Reports supporting these guidelines differ in their definitions of CAS, ranging from 50% to 80% luminal reduction [4,5]. In those defining CAS as ≥50% luminal reduction, independent predictors of high CAS prevalence (9–21%) include age, diabetes mellitus (DM), coronary artery disease (CAD), smoking, and history of stroke or transient ischemic attack (TIA) [5–9]. Current CAS screening recommendations do not include patients undergoing radiation therapy (RT) for HNC.

Head and neck RT is an independent risk factor for stroke and asymptomatic CAS. RT correlated with high rates of stroke in two retrospective series comparing HNC patients to matched controls from population-based stroke registries (relative risk 2.1–10.1) [10,11]. Several Surveillance, Epidemiology, and End Results analyses of HNC patients showed that, compared to surgery alone, RT use was associated

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with an increased 10-year risk of stroke [12,13], and 15-year risk of fatal stroke [14]. RT also correlated with high rates of asymptomatic stenosis in multiple cross-sectional studies of HNC patients, with CAS prevalence ranging from 11.7% at a mean of 72 months post-RT to 19.8% at a mean of 24 months post-RT [15–19].

CAS screening post-RT for HNC began at our institution in 2000. Doppler ultrasound (US) is typically performed 12–18 months following RT completion with subsequent screening every 3 years where CAS is < 50%. Patients with ≥ 50% CAS are screened annually and referred to vascular surgery for further evaluation and management. Our initial report of 224 asymptomatic HNC patients revealed a 14% actuarial rate of CAS at 4 years post-RT [19]. The current study assesses asymptomatic CAS and symptomatic cerebrovascular disease in an expanded cohort with longer follow-up.

Methods

Subject selection

Records were retrospectively reviewed under an institutional review board-approved protocol for all adult patients who underwent carotid screening following definitive curative-intent or post-operative RT for non-metastatic HNC at Duke University Medical Center between January 2000 and May 2016. Exclusion criteria included previous CAS, stroke, or RT to the neck, or failure to obtain baseline carotid screening within 2 years after RT completion (Fig. 1).

Patient demographics, disease stage, primary disease site, histology, smoking status, hypertension (HTN), hyperlipidemia (HLD), DM, CAD, peripheral artery disease (PAD), congestive heart disease, atrial fibrillation, receipt of chemotherapy, neck dissection status, and occurrence of stroke or TIA were obtained by chart review. The following RT parameters were recorded: technique (intensity modulated radiation therapy [IMRT], 2D, or 3D conformal radiation therapy), total dose, schedule (conventional [1.8–2.0 Gy/fraction,5treatments/week], accelerated [1.8–2.0 Gy/fraction, > 5 treatments/week], accelerated hyperfractionation [< 1.25 Gy/fraction, 10 treatments/week], or hypofractionation [> 2 Gy/fraction once daily]), and sidedness (bilateral or unilateral). Baseline carotid artery imaging (within 2 years of RT completion) and follow-up carotid artery imaging results were reviewed. CAS screening practice evolved empirically from its inception in 2000. By 2005, most patients underwent post-treatment screening by doppler US within 1–2 years post-RT followed by surveillance carotid US approximately every 3 years or more frequently if indicated by abnormal imaging results or symptoms. Patients with clinically significant or worsening CAS were referred to vascular surgery for further evaluation and management.

Carotid artery stenosis and dosimetric parameters

CAS was analyzed as a composite outcome including both asymptomatic carotid stenosis and cerebrovascular events (CVEs). Asymptomatic carotid stenosis was defined as ≥ 50% reduction in luminal diameter of common and/or internal carotid artery on carotid artery imaging (ultrasound, arteriogram, computed tomography angiogram, and/or magnetic resonance angiogram). CVEs were defined as stroke and/or TIAs. Patients not undergoing US screening within 2 years post-RT due to CVEs during that timeframe (n = 6) were excluded due to the high likelihood of pre-existing asymptomatic CAS. Carotid arteries (extending from clavicle to entry into temporal bone) and carotid bulbs (2 cm above and below carotid bifurcation) were contoured on the radiation treatment planning computed tomography (CT) scan. The following dosimetric parameters were calculated for each carotid artery and bulb: maximum dose, mean dose, and partial organ volumes receiving 40, 50, 60, or 70 Gy (V40, V50, etc.). Maximum and mean carotid doses were analyzed in 10 Gy increments.

Statistical analysis

Actuarial rates of composite CVEs and asymptomatic CAS following RT completion were calculated by Kaplan-Meier product limit method. The time interval was calculated from the completion of RT until development of carotid artery stenosis detected on imaging. Patients were censored for composite CAS at death or last follow-up appointment. Asymptomatic CAS was censored at CVE onset or date of last carotid imaging. Univariate Cox proportional hazards regression analyses were used to predict time to composite CAS development using the following factors: age, sex, smoking, HTN, HLD, DM, CAD, PAD, neck dissection, receipt of chemotherapy, and RT sidedness. Univariate analysis per patient included total RT dose. Analysis per individual carotid artery included maximum dose, mean dose, V40, V50, V60, and V70 values for the entire carotid and the carotid bulb. Multivariate Cox proportional hazards models were constructed per patient. Variables were retained in the model based on the following criteria: univariate p-value (1) < 0.05 or (2) < 0.07 for variables significantly associated with carotid artery stenosis in previous reports. Statistical analyses were conducted using SAS v 9.4 (SAS Institute, Inc., Cary, NC), and actuarial plots were created using Spotfire S + v. 8.1 (TIBCO, Palo Alto, CA).

Results

A total of 1295 patients underwent RT for non-metastatic HNC between January 2000 and May 2016. Three hundred sixty-one patients did not undergo baseline carotid US screening within two years due to HNC recurrence, death, second malignancy, severe comorbid illness, or CVE. Additionally, 458 patients did not undergo baseline carotid screening within two years of RT completion for other reasons while 110 patients underwent baseline screening > 24 months post-RT completion without a documented reason for delayed screening. The remaining 366 patients met inclusion criteria (Fig. 1A). As our institutional screening practice evolved over time, an increasing proportion of patients completed baseline screening within 2 years: 3% (4/156) from 2000 to 01, 31% (64/206) from 2007 to 08, and 40% (77/193) from 2013 to 2014.

Table 1 shows baseline patient characteristics. Patients were predominantly male (80%) with a mean age of 59.6 years (range: 23–97). Squamous cell carcinoma comprised 95% of cases with oropharynx being the most common primary tumor site (63%). Most patients had locally advanced disease (16% stage III; 71% stage IV). Median time from RT completion to last follow-up was 4.1 years (interquartile range, 2.3–6.8).

Table 2 summarizes treatment characteristics, carotid imaging studies, and outcomes (asymptomatic CAS, stroke, TIA). IMRT was used for 91% of patients, and RT was administered to bilateral neck in 77% of cases. Most patients underwent conventionally fractionated radiation therapy (72%) and received concurrent chemotherapy (75%). Neck dissection was performed in 30% of cases. Patients underwent an average of two carotid imaging studies (range, 1–8) after RT. Carotid ultrasound was the predominant imaging modality (95%).

Stroke occurred in 18 patients (5%), and TIA in 13 patients (4%). Asymptomatic CAS was documented prior to 6 of 18 S. CAS management beforehand for these patients included carotid stenting (n = 1), medical management (n = 2), or observation alone (n = 3). Asymptomatic CAS was documented prior to 7 of 13 TIAs. These patients underwent carotid stenting (n = 1), carotid endarterectomy (n = 1), medical management (n = 3), or observation alone (n = 2) after CAS diagnosis on imaging.

Asymptomatic CAS was observed in 58 patients (16%). Fourteen of 58 patients (24%) with asymptomatic CAS were prescribed a new or higher aspirin dose or other anti-coagulant medication, 13 patients (22%) were prescribed a new anti-hypertensive or lipid-lowering medication, 7 patients (12%) underwent carotid stent placement, and 2 patients (3%) underwent carotid endarterectomy.