Carotid Intima-Media Thickness Measurement Promises to Improve Cardiovascular Risk Evaluation in Head and Neck Cancer Patients

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ABSTRACT

Background: Radiation-treated head and neck cancer (HNC) patients are at high risk for developing radiation vasculopathy, as evidenced by an increased stroke risk. The benefits of screening and assessing the cardiovascular (CV) risk of HNC patients using carotid intima-media thickness (CIMT) ultrasound are not known. Our objective was to determine the prevalence of high CV risk in patients without known CV diseases who received radiation for HNC, determine the percentage of screened patients who had a change in clinical management as a result of an increased CIMT, and to compare this risk-assessment tool to patients' risk classification using the Framingham Risk Score (FRS) and Pooled Cohort Atherosclerotic Cardiovascular Disease (ASCVD) Risk Equation (recommended by American College of Cardiology/American Heart Association Guidelines on the Assessment of Cardiovascular Risk).

Hypothesis: Risk calculators may not accurately predict risk in this population with a unique risk factor. Carotid IMT may be used to detect radiation vasculopathy in HNC patients.

Methods: Retrospective medical chart review was conducted on 134 radiation-treated HNC patients. The main outcome measures were CV risk (as determined by CIMT) and clinical management. Also, the FRS and the Pooled Cohort ASCVD Risk Equation were used to compare classification with CIMT.

Results: Approximately 74% of the cases were at high CV risk using CIMT technique. Approximately half of the HNC patients screened had a change in clinical management characterized by recorded initiation of aspirin and recorded initiation or increase of statin therapies. The FRS and the Pooled Cohort ASCVD Risk Equation failed to detect 40% to 50% of cases found to be at high risk using the CIMT technique.

Conclusions: Carotid IMT identified a much greater percentage of radiation-treated HNC patients at high CV risk compared with standard CV-risk calculators. By more accurately identifying the patients at high risk, this may lead to more effective prevention, and therefore a reduction in CV events.

Introduction

Patients who undergo radiation therapy are at high risk for developing a type of vascular disease called radiation vasculopathy.¹ Injury from radiation therapy is believed to be the key mechanism for the accelerated atherosclerosis.^{2,3} The vascular changes that take place within the carotid artery are believed to be the result of radiation-induced endothelial-cell loss, leading to an abnormal cell proliferation and fibrosis. Though the time from radiotherapy to clinically evident cardiovascular disease (CVD) can often exceed

10 years,^{4–6} short-term effects of radiotherapy can be seen. A recent study demonstrated that vascular changes post-radiation therapy can take place as soon as 90 days after the end of radiation treatments.⁷ Even though research on the long-term stroke risk from radiation vasculopathy is scarce, it has been demonstrated in the literature that high-dose radiotherapy to the head and neck was associated with an increased risk of stroke when compared with the expected rate.^{8,9} A recent systematic review of the literature examined the effect of radiation therapy to the head and neck on incidence of transient ischemic attack and stroke. There was a significantly increased risk of stroke among patients with head and neck injury with a residual risk of

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5.6, compared with a residual risk of 1.12 in patients who received radiation therapy to treat breast cancer.¹⁰

Although there is established knowledge on the risk of vasculopathy after radiation, the standard of care currently does not include preventive CV management strategies for radiation-treated head and neck cancer (HNC) patients. Carotid intima-media thickness (CIMT) in this study was used as a CVD risk-stratification measure and was examined in terms of its role in changing clinical management.

The purpose of this retrospective study was 3-fold: to determine the prevalence of high CV risk among patients who received radiation therapy for HNC, to determine the percentage of screened patients who had a change in clinical management (adding aspirin, adding or intensifying statin therapy) as a result of an increased intima media thickness (IMT) or the presence of carotid plaque, and to compare CIMT to the standard CV-risk calculators recommended in the Adult Treatment Panel III guidelines¹¹ and in the most recent 2013 American College of Cardiology/American Heart Association (ACC/AHA) Guideline on the Assessment of Cardiovascular Risk.¹²

Methods

This study is a retrospective chart review of all radiation-treated adult HNC patient visits to the preventive cardiology clinic at a main university hospital in Philadelphia, Pennsylvania, over a period of 6 years (2006–2012).

Our electronic medical record was queried for patients who were treated by one of our head and neck radiation oncologists and who obtained CIMT to screen for radiation vasculopathy. Patients were referred to our preventive cardiology clinic purely because they had a head and neck injury from radiation exposure. There was no direct referral bias.

A total of 130 cases (out of 134 medical records retrieved) met the inclusion criteria; these included patients with HNC who received radiation therapy, without a known history of CVD (coronary artery disease, vascular disease, myocardial infarction [MI], or stroke), and who had CIMT for CV risk stratification. Of note, subjects received their first screening with CIMT on average 3 years after radiation therapy (mean, 3.4 years; standard deviation, 4.3; range, 0–27 years, with 11 of 130 patients screened >9 years after treatment).

This study was approved by the ethics committee at the University of Pennsylvania.

Data Collection

Based on results of the CIMT, subjects were classified as either high risk or no evidence of high risk. Subjects' CV risk was also assessed using 2 risk-calculation methods: the Framingham Risk Score (FRS) and Pooled Cohort Atherosclerotic Cardiovascular Disease (ASCVD) Risk Equation.

Measures

Carotid intima-media thickness is an ultrasound-based technique that measures the intima and media thickness and examines the presence of carotid plaque. Carotid

intima-media thickness is considered an independent assessment of coronary risk, able to detect subclinical atherosclerosis and an increased CV risk before the emergence of atherosclerosis, simply because thickening precedes the development of atherosclerotic plaque.^{13–17} An increase in the IMT thickness is correlated with an increase in the risk of MI and stroke.^{2,18,19}

Both the technique and classification of CIMT follow standards set forth in the consensus statement from the American Society of Echocardiography (ASE) Carotid Intima-Media Thickness Task Force.¹⁷ The carotid ultrasound was performed by a sonographer in the vascular laboratory and was interpreted by a noninvasive cardiologist specializing in prevention.

Consistent with the ASE CIMT Task Force, age, sex, and ethnicity were used to determine the 75th percentile of risk. The database most frequently used to establish this adjusted risk was the Atherosclerosis Risk In Communities (ARIC) database.

Patients are considered at high risk for developing a CV event when the IMT measurement is >75th percentile or in the presence of a carotid plaque. On the other hand, a patient whose IMT falls below the 75th percentile and without carotid plaque is not considered at high risk.

The FRS is a risk-assessment tool that is designed to calculate risk of MI in an adult (age >20 years) in the next 10 years. A score $\leq 10\%$ is considered low risk. Scores of 10% to 20% and >20% are considered intermediate and high risk, respectively.²⁰

The Pooled Cohort ASCVD Risk Equation was recommended by the AHA/ACC and published in the 2013 Guideline on the Assessment of Cardiovascular Risk. This risk equation estimates the risk of atherosclerotic CV events in the next 10 years (MI and stroke). The Pooled Cohort ASCVD Risk Equation was recently validated and was found to have moderate to good discrimination of high vs low CV risk.³

Sociodemographic and clinical data were collected, and they are summarized in Table 1.

Statistical Analysis

A comprehensive descriptive analysis of the sociodemographic characteristics and pertinent health history of the participants was performed. Separate χ^2 independence tests were used to determine any significant association between the risk-assessment classification between the FRS and the CIMT scales and between the Pooled Cohort ASCVD Risk Equation and CIMT assessment scales. Test of significance was set at $\alpha = <0.05$.

Results

A total of 134 medical charts were retrieved, and 130 met the inclusion criteria. Of these, 74% were at high risk for developing a CV event using the CIMT method of risk classification. Approximately 44% of high-risk individuals were classified as high risk based on the presence of both plaque and IMT >75th percentile. About 38% had plaque and about 18% were classified as high risk given thickness of >75th percentile. Seventy-three percent of the high-risk patients received a change in their clinical management. The

Table 1. Clinical Characteristics and Sociodemographic Data of Participants (N = 130)

Variable	Mean (SD)
Age, y	56.91 (0.9)
Female sex, n (%)	34 (21)
Cancer diagnosis, n (%)	
Tongue	44 (34)
Neck	13 (10)
Tonsil	30 (23)
Nose/pharynx	7 (5)
Other	36 (28)
BMI, kg/m ²	25.3 (4.4)
Cholesterol, mg/dL	
Total	186 (40.9)
HDL-C	55.4 (18.4)
LDL-C	109.8 (36.02)
Triglycerides, mg/dL	104.8 (58.7)
BP, mm Hg	
Systolic	125.15 (16.7)
Diastolic	77.7 (11.01)
Heart rate, bpm	72.71 (12.6)
Framingham Risk Score	6.64 (5.7)
Risk factors, n (%)	
Smoking (former, never)	50, 67 (36, 49)
HTN	59 (43)
Dyslipidemia	74 (54)
DM	11 (8)
Family history of premature CAD	43 (31)
CIMT, mm	0.77 (0.19)
Pooled Cohort score	7.08 (7.02)
Abbreviations: BMI, body mass index; BP, blood pressure; CAD, coronary artery disease; CIMT, carotid intima-media thickness; DM, diabetes mellitus; HDL-C, high-density lipoprotein cholesterol; HTN, hypertension; LDL-C, low-density lipoprotein cholesterol; SD, standard deviation.	

change in clinical management implemented on the high-risk patients was established by recorded initiation of aspirin and initiation or increase in dose of statin therapies. Fifty-one percent of the high-risk subjects had a statin initiated, 13% had their statin therapy intensified, and 2% were started on a second cholesterol agent in addition to their high-intensity statin. Furthermore, 25% of the high-risk subjects initiated aspirin therapy for primary prevention given the presence of carotid plaques.

Table 2. Agreement Between the FRS and CIMT Assessments

		CIMT High Risk	Not High Risk	Total
FRS	High risk	35	7	42
	Not high risk	24	15	39
	Total	59	22	81
Abbreviations: CIMT, carotid intima-media thickness; FRS, Framingham Risk Score.				

Out of 130 patients, 81 patients were candidates to have their risk score calculated for the following reasons: Patients were not on statin therapy, did not have known diabetes mellitus, and had their lipid profile in our record. Of these 81 patients, approximately 2%, 49%, and 48% were high risk, intermediate risk, and low risk, respectively. The CIMT results on the same 81 patients demonstrated a remarkably different result. Using the CIMT, 73% were high risk and 27% had no evidence of increased risk. The Pooled Cohort ASCVD Risk Equation was also remarkably different. Approximately 38% and 61% were found to be high risk ($\geq 7.5\%$) and low risk ($< 7.5\%$), respectively.

Results from the test of agreement between the FRS and CIMT assessment are presented in Table 2. Of the 81 cases assessed, the CIMT and FRS are in agreement that the patient is at risk of developing a CV event in 35 cases. In addition, in 15 out of 81 cases, both assessments indicated low risk of a CV event. Although the level of agreement between the FRS and CIMT was statistically significant ($P = 0.02$), it is the other 24 subjects (30%) that the FRS classified as low risk and for which the CIMT found enough evidence to classify as at risk that may be of clinical concern. Based on the CIMT findings, it is this group of patient that may be at heightened risk of developing a CV event due to the physiological changes to the arterial wall that would otherwise not be eligible to receive any preventive intervention because the FRS failed to recognize them as at risk. Using the Pooled Cohort ASCVD Risk Equation, 39 subjects (48%) were classified as at risk or no risk, in agreement with the CIMT (Table 3). There was disagreement on the remaining 42 subjects (52%) between the 2 assessment techniques whereby the overall association between the 2 techniques also failed to reach statistical significance ($P > 0.05$). Once again, of concern are the 35 cases (43%) that the Pooled Cohort ASCVD Risk Equation failed to classify as at sufficient risk to warrant treatment but who truly had premature atherosclerosis by CIMT. Our findings suggest that both the FRS and the Pooled Cohort ASCVD risk calculators underestimated the level of risk of CV events in this cohort, compared with the CIMT (Table 4).

Discussion

Approximately 74% of radiation-exposed HNC patients were found to be at high CV risk using the IMT technique, and half of the total group had a change in clinical management. Also, the FRS and the Pooled Cohort ASCVD Risk Equation failed to detect about 40% of the cases that would otherwise be treated as at high risk of developing CV events

Table 3. Agreement Between the Pooled Cohort ASCVD Risk Equation Score and CIMT Assessment

		CIMT		Total
		High Risk	Not High Risk	
Pooled cohort score	High risk	24	7	31
	Low risk	35	15	50
Total		59	22	81

Abbreviations: ASCVD, Atherosclerotic Cardiovascular Disease; CIMT, carotid intima-media thickness.

Table 4. Differences Among the Different Risk Categories in Terms of Cardiovascular Risk Factors and IMT Measurements

Risk Factor	High Risk	No Evidence of Risk	P Value
Smoking, %	50	50	0.9
HTN, %	48	41	0.5
Hyperlipidemia, %	51	53	0.8
DM, %	8	9	0.9
IMT, mm, mean	0.83	0.59	<0.001

Abbreviations: DM, diabetes mellitus; HTN, hypertension; IMT, intima-media thickness.

based on subclinical atherosclerosis found on CIMT. This discrepancy in identifying high CV risk between the CIMT and the risk calculators may have multiple explanations. Risk calculators such as FRS and ACC/AHA provide meaningful risk stratification by balancing an individual's standard CV risk factors. Although these tools serve as a useful starting point for risk assessment, they do not perfectly correlate with subclinical atherosclerosis and true cardiac risk. In populations with unique risk factors, such as the HNC patients, additional evaluation, such as with CIMT, enhances the basic calculators to allow more accurate assessment of risk—and, therefore, more individualized treatment. The most important reason for the discrepancy between risk calculators and CIMT may be the unique risk factor of radiation therapy leading to the development of subclinical atherosclerosis. Another contributor to the discrepancy is that risk calculators may underestimate CV risk for the younger population, whereas CIMT is valid in younger populations and directly visualizes the arterial walls.^{21,22}

Although stroke risk and radiation vasculopathy have been established for 3 decades, studies on screening for subclinical atherosclerosis among radiation-treated HNC patients with the goal of changing clinical management do not exist. Similar to other studies that examined the additive values of screening with CIMT,^{23–25} this retrospective study highlighted the additive clinical values of screening patients with carotid-artery injury from irradiation.

Study Limitations

There are several limitations to this pilot study. The nature of this study, a retrospective chart review, is one main

limitation. This pilot study demonstrated that a great percentage of the HNC population had high CV risk. However, future studies should be prospective in nature, aiming to examine the effect of carotid-artery injury after controlling for main risk factors of CVD (eg, hypertension, dyslipidemia, diabetes mellitus, and smoking). The cases were seen in a preventive clinic on average 3 years after radiation therapy. Future studies should follow the HNC patient before the initiation of radiation therapy.

We acknowledge that we are using CIMT as a screening tool to improve CV risk assessment, even though the ACC/AHA 2013 guidelines consider this test to be class 3. The rating of CIMT testing as class 3 has been controversial, and we expect it to return to class 2 during future revisions of the guidelines. Nonetheless, even with a class 3 recommendation for the general population, CIMT for risk assessment in unique populations remains appropriate. The HNC population has known increased CV risk, and there is no better technique to evaluate this population and improve risk modeling than CIMT.

Conclusion

The use of a risk-free, noninvasive screening tool, CIMT, in this patient population demonstrated the potential to improve preventive CV care, with enhanced preventive management in approximately 70% of high-risk HNC patients. Although future trials will continue to reveal more about radiation vasculopathy, this pilot study may favor the need to expand programs that incorporate CV prevention and screening. Future studies are needed to examine the long-term outcomes of this preventive CV screening tool.

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