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Cardiovascular Risk and Prevention in Head and Neck Cancer Patients Treated with Radiotherapy

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Abstract

Background—The underlying contributors to cardiovascular disease (CVD) in patients with head and neck squamous cell carcinoma (HNSCC) are poorly characterized.

Methods—Patients with HNSCC who underwent definitive or adjuvant (chemo)radiation between 2011-2013 were retrospectively reviewed. 10-year risk estimates for a CVD event were calculated according to the Framingham Risk Score (FRS).

Results—115 patients with predominantly stage III/IV HNSCC had a median follow-up of two years. At diagnosis, 23% of patients had CVD. The FRS was higher among patients with laryngeal cancer versus other sites (20.5% versus 14.4%). 24% of all patients had uncontrolled blood pressure at diagnosis. Among patients with CVD, 41% were not taking anti-platelet therapy and 30% were not taking statin therapy. 34% of patients without CVD had indications for initiating statin therapy.

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Conclusions—Patients with HNSCC have a high baseline CVD risk and many do not receive optimal preventive care.

Keywords

Primary Prevention; Cardiovascular Disease; Risk Factors; Head and Neck Cancer; Radiation Therapy

Introduction

Head and neck squamous cell carcinoma (HNSCC) is diagnosed in 42,440 Americans every year ⁽¹⁾. The 5-year survival improved from 55% to 66% over the last 30 years ⁽²⁾ due to advances in multi-modality therapy including radiation therapy (RT), chemotherapy, and surgery ⁽³⁻⁵⁾, as well as the increasing incidence of human papillomavirus (HPV)-related HNSCC, which responds better to therapy ⁽⁶⁾. More than half of deaths after treatment for HNSCC are now due to causes other than recurrent cancer ^(7, 8).

HNSCC patients have an elevated risk of non-HNSCC mortality that persists over their lifetime. Among HNSCC patients, the 5-year incidence of HNSCC-specific mortality is 23.8%, second cancer mortality is 14.6% and non-cancer mortality is 13% ⁽⁹⁾. The most frequent causes of non-cancer mortality were coronary artery disease (28%), chronic obstructive pulmonary disease (8.5%) and cerebrovascular disease (5.6%). Between 5-10 years after treatment, HNSCC-specific mortality dramatically decreased to 5% ⁽¹⁰⁾, while death due to second cancers and non-cancer causes remained 20 to 25% higher in HNSCC patients compared to matched controls ⁽¹¹⁾.

Previous work demonstrates that RT increases the risk for carotid artery stenosis ^(12, 13), which can lead to a stroke in 12-34% of HNSCC patients ⁽¹⁴⁻¹⁶⁾. RT-related carotid stenosis is difficult to treat; HNSCC patients who develop carotid stenosis have a higher rate of progression (66% versus 5% per year) ^(12, 17) and restenosis after stenting (88% versus 27% over 2 years) compared to the general population ^(12, 18).

It is unclear to what degree pre-existing conditions and/or modifiable risk factors both before and after treatment contribute to cardiovascular disease (CVD) including heart attack and stroke. As such, we sought to quantify CVD risk and receipt of primary preventive care among HNSCC patients treated with RT or CRT at our institution.

Materials and Methods

This institutional review board-approved study retrospectively reviewed all HNSCC patients treated with RT from the beginning of 2011 to the end of 2013. Inclusion criteria were defined as patients with HNSCC undergoing definitive or adjuvant (chemo)radiation with curative intent, a population known to have high rates of morbidity and mortality due to CVD ^(9, 14). Patients treated for recurrent or metastatic HNSCC were excluded. Depending on stage and presentation, some patients received concurrent chemotherapy and/or surgery in addition to RT. After completing treatment, patients were evaluated every 2-3 months for the first 24 months, every 4-6 months for the next 3 years, and annually after 5 years.

Demographics were obtained at the time of diagnosis. Median household income was estimated based on zip code using the American Community Survey ⁽¹⁹⁾. Data regarding risk, treatment and primary prevention of CVD was collected and analyzed at two separate time points, pre- and post-RT. Pre-RT data was collected from records available at the time of HNSCC diagnosis; post-RT data was collected at the time of the most recent follow-up visit. In order to minimize the influence of the acute side effects of RT on CVD measures, post-RT data was only collected from patients having longer than 1 year of follow-up time without cancer recurrence. All patients had oncology-specific medical records and patient-reported medical histories available for review. Some patients additionally had records available from primary care providers. Documented CVD of the coronary, carotid, or peripheral arteries was noted. For each patient, the 10-year risk estimate for developing a CVD event was calculated based on the Framingham Point Score (FPS), per 2001 guidelines from the Adult Treatment Panel III (ATP III) ⁽²⁰⁾, and the Framingham Risk Score (FRS), per 2013 guidelines from the American College of Cardiology (ACC) / American Heart Association (AHA) ⁽²¹⁾. These scores incorporate information regarding gender, age, race, total cholesterol, high-density lipoprotein cholesterol, systolic blood pressure (BP), diabetes mellitus (DM), current smoking and use of anti-hypertensive therapy. We relied on patient reports of smoking habits to categorize those who were active smokers and to calculate the number of pack-years smoked. When serum cholesterol values were not available in the medical record, optimal levels were assumed ⁽²¹⁾. The average of 3 readings for systolic blood pressure was used to calculate the Framingham scores ⁽²²⁾. In addition, patients were categorized as high, intermediate or low-risk for cardiovascular events based on the ATP III classification ⁽²⁰⁾. Finally, medications and dosages including anti-hypertensives, anti-platelets, statins, and diabetes drugs were recorded.

Assessment of the quality of CVD prevention included the management of DM and BP, as well as the prescription of statin therapy. Uncontrolled DM was defined as hemoglobin A1c >7%, random total glucose >200 mg/dL, or fasting glucose $\geq$ 126 mg/dL ^(22, 23). BP was considered uncontrolled if values were $\geq$ 140/90 at two or more clinic visits per recommendations of the Joint National Committee; either abnormal systolic and/or diastolic values were considered in this assessment ⁽²⁴⁾. Appropriate statin prescription was based on CVD prevention guidelines from ATP III or ACC/AHA. Both guidelines base recommendations for statin use on serum cholesterol levels and/or the presence of additional CVD risk factors. The ACC/AHA advocates for patients with an AHA FRS $\geq$ 7.5% to engage in a discussion with their physician to consider initiating statin therapy. Additionally, for patients with a known diagnosis of CVD, secondary preventive measures including statin and anti-platelet medications were recorded ⁽²⁵⁾.

T-tests were used to determine associations between the group levels of demographic and cancer-specific factors and AHA FRS, while Fisher's exact tests determined whether they associated with suboptimal management of DM, BP, or hypercholesterolemia. We also hypothesized that suboptimal management of CVD risk factors would decrease from pre- to post-RT time points. In support of this hypothesis, previous studies describe cancer diagnosis as a teachable moment, when there is opportunity to promote positive health behavioral change, such as smoking cessation in HNSCC patients ^(28, 29). McNemar's test compared the proportion with suboptimal management before versus after radiation.

Statistical analysis was completed using SAS software, Version 9.2 of the SAS System for Windows (SAS Institute Inc., Cary, NC, USA).

Results

Patient and Treatment Characteristics

208 patients were treated with RT for HNSCC between 2011 and 2013. Of these, the following patients were excluded: 8 with metastatic disease, 2 undergoing palliative treatment, 8 with recurrent disease, and 75 having non-squamous cell carcinoma histology. In total, 115 patients were identified who met the inclusion criteria and constitute the subject of the present analysis.

Baseline patient and treatment characteristics are outlined in Table 1. Median age was 63 years. The majority of patients were male, white and married or living with a partner. Some patients had limitations in access to care: 12% of patients were uninsured at initial presentation and 20% failed to identify a primary care physician (PCP). The bulk of diagnoses were clinical stage IV HNSCC of the oropharynx, larynx or oral cavity per the 7th edition of the American Joint Committee on Cancer ⁽³⁰⁾. The median clinical follow-up time was 2 years (range: 0-3.7 years).

CVD Risk Assessment

At the time of diagnosis, the most prevalent CVD risk factor was HTN (50%), followed by current smoking (27%) and DM (12%) (Table 2). Twenty-seven patients had known CVD, including coronary artery disease (17 patients), peripheral vascular disease (5 patients), and carotid artery disease (10 patients), all diagnosed prior to treatment for HNSCC. There were no documented CVD events experienced by any patients during the short follow-up period after treatment.

Among the 88 patients without diagnosed CVD, the mean 10-year risk estimate for developing an atherosclerotic cardiovascular event was 9.8% (95% CI: 8.4-11.2) by the ATP III FPS and 13.2% (95% CI: 10.7-15.7) by the AHA FRS. Patients with laryngeal cancer had an AHA FRS of 20.5%, compared to 17.8% among those with HPV– oropharyngeal cancer and 14.7% for those with HPV+ oropharyngeal cancer (Table 3). Compared to HPV+ oropharyngeal cancer patients, more patients with HPV– oropharyngeal or laryngeal cancer were active smokers (58% versus 21%), had HTN (58% versus 48%), poorly controlled BP (33% versus 21%), or indications per statin therapy per AHA guidelines (80% versus 67%) (Table 4). Among HPV+ oropharyngeal cancer patients with a 10 pack-year smoking history, 56% of patients had an AHA FRS 7.5%.

There were no significant differences in AHA FRS by sex, race, income, or educational status (Table 3). Compared to before RT, similar numbers of patients were actively smoking after RT, as well as taking medications for HTN or DM (Table 2).

CVD Prevention

Regardless of anti-hypertensive medication use, the proportion with uncontrolled blood pressure was similar at pre- and post-RT time points (28 versus 26 patients) (Table 2).

Meanwhile, four patients had uncontrolled glucose levels in both the pre- and post-RT setting. A total of 39 patients and 26 patients were taking statins before and after RT, respectively. Among 27 patients with a history of CVD, 16 were not taking anti-platelet therapy and 8 were not taking statin therapy at baseline. An additional 10 patients with CVD should have been taking a higher intensity statin per ACC/AHA guidelines. Patients with CVD not taking statin therapy were less likely to identify a primary care provider than those taking a statin (4 of 8 patients versus 17 of 19 patients). Among 88 patients without CVD at baseline, 30 patients were not currently taking a statin, but had indications for therapy per ACC/AHA guidelines.

Discussion

Our data demonstrate a high prevalence of and risk for CVD at the time of HNSCC diagnosis. Specifically, 15% of HNSCC patients had coronary artery disease and 9% had carotid artery disease. In the general population, the prevalence of coronary artery disease and carotid artery disease increases from 6% and 2% among men aged 40-59 years old to 21% and 7% among men aged 60-79 years old, respectively ^(31, 32). The proportion with CVD in the general population is similar to that among our HNSCC patients, who were composed predominantly of men at a median age of 63 years old. However, many of the remaining HNSCC patients without documented CVD had a high 10-year risk estimate for developing a CVD event, as quantified by an AHA FRS 7.5% (58% of HNSCC patients versus 33% in the general population) ⁽³³⁾.

CVD Preventive Care

In total, 63% of our patients would be recommended to take statin therapy per ACC/AHA guidelines. These complex patients often receive suboptimal preventive care; 20-30% of patients have uncontrolled blood pressures and 30-50% of diabetics have uncontrolled blood glucose levels at both pre- and post-RT time points. If ACC/AHA guidelines were applied to this population, an additional 38% of patients would qualify either for initiation of statin therapy or use of a high-intensity statin. In addition, many HNSCC patients with known CVD received poor secondary preventive care with 59% not taking anti-platelet therapy and 30% not taking statin therapy. Unfortunately, poor secondary CVD preventive care has also been reported in survivors of lung, breast, colon, and renal cancer with less than half of patients with CVD receiving guideline-directed medical therapy (including statins) or referrals to cardiology ⁽³⁵⁾.

Predictors of CVD Risk and Prevention

Unfortunately, we have limited power to detect associations between AHA FRS and demographic or cancer-specific factors due to the small sample sizes of the subgroups. Not surprisingly, the FRS was the highest among our patients with laryngeal cancer, a subgroup known to have high mortality rates⁽³⁶⁾, likely relating to older age and tobacco use ⁽¹⁰⁾. However, significant CVD risk was not confined to larynx cancer patients. Even among the subgroup of HNSCC patients with the most favorable prognosis (HPV+ oropharyngeal cancer with a 10 pack-year smoking history) ⁽²⁶⁾, 56% of patients have an AHA FRS

7.5% and therefore would be recommended to take statin therapy per guidelines. Therefore, it is important to consider CVD prevention among all HNSCC cancer types.

Limitations

Our study is subject to several limitations. There is information bias in retrospective studies given possible underreporting of CVD risk factors in the medical record. In addition, the calculated CVD risk estimates likely underestimate the true risk because we assumed optimal values for missing serum cholesterol data. Furthermore, it is not known whether CVD risk in HNSCC remains stable over time, especially after completing RT. We limited our post-RT analysis to patients with one year or more of follow-up time in order to minimize the effect of acute treatment toxicity on CVD risk. Finally, it is unclear whether the target goals for CVD risk reduction that have been established for the general population are applicable to patients facing a life-altering disease such as HNSCC. However, the fact that there were similar degrees of blood pressure control and statin use at both diagnosis and after one year of follow-up makes these results less likely to be spurious. Future study with more follow-up time is needed to determine how CVD risk and its management affect long-term cardiovascular outcomes in HNSCC patients.

Future Directions

In conclusion, patients with HNSCC have a high risk for CVD and often receive suboptimal preventive care. Strategies to minimize these risks are needed that involve primary care, oncology, and cardiology practitioners. As a first step, it is possible that the application of 2013 ACC/AHA guidelines regarding statin therapy use may improve survival and quality of life in HNSCC patients. The 2013 ACC/AHA guidelines recommend that patients with a 10-year cardiovascular risk $\geq 7.5\%$ discuss initiating statin therapy with their physician, because the benefits of therapy are likely to outweigh the harms ⁽²¹⁾. This recommendation for statin use is based on high-level evidence demonstrating a relative reduction in cardiovascular events of similar magnitude across a wide spectrum of CVD risk and serum cholesterol levels (rate ratio: 0.78; 95% CI: 0.76-0.81) ⁽⁴¹⁾. Future work should investigate whether these guidelines need to be adapted to the special needs of HNSCC patients, who may have a higher risk for drug-drug interactions or competing mortality, barriers to shared decision-making, and/or greater carotid artery injury due to radiotherapy.

Additionally, future work should investigate whether statins or other drugs protect the carotid arteries from RT-related injury. The hypothesis that statins reduce RT-related carotid artery injury by lowering cholesterol levels is suggested by a clinical study which found that the degree of progression in carotid artery intima-media thickness after RT was associated with pre-RT low-density lipoprotein cholesterol levels ($r = 0.66$; $p = 0.03$) ⁽⁴²⁾. If statins are found to be protective, this would lead to an expansion of the indications for statin use to include patients receiving head and neck RT with otherwise low CVD risk. Among our patients, approximately 33% have low CVD risk and would not otherwise be recommended to receive statin therapy.

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TABLE 1

Patient and Treatment Characteristics

Characteristic, n (%)	All patients n = 115
Gender	
Male	84 (73)
Female	31 (27)
Median age, years (range)	63 (40-85)
Race	
White	97 (84)
Black or African American	17 (15)
American Indian	1 (1)
Ethnicity	
Not Hispanic or Latino	114 (99)
Hispanic or Latino	1 (1)
Marital status	
Married or living with partner	60 (52)
Never married	18 (16)
Divorced, separated, or widowed	37 (32)
Highest education	
Less than high school	6 (5)
High school / GED	55 (48)
Some college	9 (8)
Completed college	12 (10)
Graduate / professional degree	7 (6)
Unknown	26 (23)
Median income by zip code, USD (IQR)	50,956 (43,693-64,446)
Insurance type	
Private	49 (43)
Medicare	43 (37)
Medicaid	9 (8)
None	14 (12)
Primary care physician	
Yes	91 (79)
No	24 (21)
Clinical stage, AJCC 7 th edition	
I-II	9 (8)
III	23 (20)
IV	83 (72)
Primary site	
Oropharynx	52 (45)
Larynx	23 (20)
Oral cavity	21 (18)

Characteristic, n (%)	All patients <i>n</i> = 115
Hypopharynx	6 (5)
Nasopharynx	6 (5)
Nasal Cavity / Paranasal Sinus	2 (2)
Unknown Primary Site	5 (5)
Oropharyngeal Cancer HPV status	
Positive	42 (81)
Negative	10 (19)
Treatment modalities	
Definitive RT	6 (5)
Definitive CRT	69 (60)
Surgery and post-operative RT	21 (18)
Surgery and post-operative CRT	19 (17)

Abbreviations: *GED*, General Educational Development; *USD*, United States Dollars; *IQR*, interquartile range; *AJCC*, American Joint Committee on Cancer; *HPV*, human papillomavirus; *RT*, radiation therapy; *CRT*, chemoradiation therapy.

TABLE 2

Cardiovascular Disease (CVD) Risk and Management

Characteristic, n (%)	Pre-Radiation n=115	Post-Radiation n=96*	p-value
BMI (kg/m ²), mean (95% CI)	27.4 (26-29)	26 (25-27)	<0.001 [‡]
Smoking Status			
Never	25 (22)	23 (24)	
Former, 10 Pk-Yr	7 (6)	6 (6)	
Former, >10 Pk-Yr	46 (40)	46 (48)	
Former, unknown Pk-Yr	6 (5)	4 (4)	
Current	31 (27)	17 (18)	0.14 [‡]
Hypertension (HTN)			
Taking HTN medication	57 (50)	42 (44)	0.01 [‡]
BP uncontrolled [‡]	28 (24)	26 (27)	
Diabetes (DM)			
Taking DM medication	14 (12)	8 (8)	0.5 [‡]
DM uncontrolled [‡]	4	4	
Patients without CVD	88 (77)	74 (77)	
ATP III CVD risk category			
Low	32	32	
Intermediate	44	33	
High	12	9	
10-year risk estimate for CVD event, %			
ATP III FPS, mean (95% CI)	9.8 (8.4-11.2)	8.5 (7.1-9.8)	0.01 [‡]
AHA FRS, mean (95% CI)	13.2 (10.7-15.7)	12.6 (10-15)	0.01 [‡]
Statin use per ACC/AHA guidelines [‡]			
Age >75: no recommendation	10	9	
Appropriate: correct statin	12	9	
Appropriate: no statin	33	27	
Inappropriate: should be taking statin	30	26	
Inappropriate: statin intensity too low	3	3	
Patients with CVD	27 (23)	22 (23)	
Coronary artery disease	17	16	
Peripheral vascular disease	5	4	
Carotid artery disease	10	7	
Taking aspirin or anti-platelet therapy	11	12	
Statin use per AHA guidelines [‡]			
Appropriate: high-intensity statin	4	4	
Appropriate: Age >75 and moderate-intensity statin	4	5	
Inappropriate: statin intensity too low	10	6	

Characteristic, <i>n</i> (%)	Pre-Radiation <i>n</i> =115	Post-Radiation <i>n</i> =96 [*]	p-value
Inappropriate: should be taking statin	8	8	

Abbreviations: *BMI*, Body Mass Index; *CI*, confidence interval; *Pk-Yr*, pack-year; *BP*, blood pressure; *FPS*, Framingham Point Score; *FRS*, Framingham Risk Score; *AHA*, American Heart Association; *ATP III*, Adult Treatment Panel III.

^{*} Number of patients with at least 1 year of follow-up time.

^f See manuscript for definition of uncontrolled BP or DM and appropriate statin use per AHA guidelines.

[‡] Indicates statistical test was performed to compare groups.

TABLE 3

Predictors of the Framingham Risk Score

Characteristic	Mean Score 1 (n)	Mean Score 2 (n)	Mean Difference	95% CI	p-value
Male vs. Female	16.4 (84)	13.5 (31)	2.9	−2.3 – 8.1	0.27
Black Race vs. Other	20.2 (18)	14. 8 (97)	5.3	−1 – 11.7	0.1
Zip Code < Median Income vs. > Median Income	18.2 (46)	13.9 (69)	4.30	−0.37 – 9.0	0.07
Education HS or Less vs. Beyond HS	16.2 (87)	13.9 (28)	2.3	−3.1 – 7.7	0.40
Partnered vs. Single	17.2 (60)	14 (55)	3.2	−1.4 – 7.8	0.17
Larynx vs. Other Site	20.5 (23)	14.4 (92)	6.1	0.4 – 11.8	0.036
HPV− Oropharynx vs. HPV+ Oropharynx	17.8 (10)	14.7 (42)	3.1	−4.9 – 11.2	0.44
None or Medicaid Insurance vs. Other	11.6 (23)	16.7 (92)	−5.1	−10.8 – 0.6	0.08

Abbreviations: *HS*, high school; *HPV*, human papillomavirus.

TABLE 4

Cardiovascular Disease Risk at Baseline by Cancer Subsite

Characteristic, <i>n</i> (%)	Oropharynx: HPV positive <i>n</i> =42	Oropharynx: HPV negative <i>n</i> =10	Larynx <i>n</i> =23
BMI (kg/m ²), mean (95% CI)	29 (27-31)	22 (18-26)	28 (25-31)
Smoking Status			
Never	13	0	0
Former, 10 Pk-Yr	3	0	0
Former, >10 Pk-Yr	18	4	7
Former, unknown Pk-Yr	2	1	2
Current	6 (14)	5 (50)	14 (61)
Hypertension (HTN)			
Taking HTN medication	20 (48)	6 (60)	13 (57)
BP uncontrolled *	9 (21)	3 (30)	8 (35)
Diabetes (DM)			
Taking DM medication	6 (14)	1 (10)	3 (13)
Patients without CVD	30 (71)	7 (70)	17 (74)
Statins recommended per AHA *	16	5	13
Statins not used per AHA *	12	3	9
10-year risk for CVD event, %			
ATP III FPS, mean (95% CI)	9.9 (7.5-12.2)	9.3 (3.5-15)	11.2 (7.6-14.8)
AHA FRS, mean (95% CI)	11 (7.6-14.4)	14 (5.6-22.5)	17.6 (11.2-24)
Patients with CVD	12 (29)	3 (30)	6 (26)
Statins not used per AHA *	10	2	3
No aspirin or anti-platelet therapy	9	2	4

Abbreviations: *BMI*, Body Mass Index; *CI*, confidence interval; *Pk-Yr*, pack-year; *BP*, blood pressure; *CVD*, cardiovascular disease; *ATP III*, Adult Treatment Panel III; *AHA*, American Heart Association; *FPS*, Framingham Point Score; *FRS*, Framingham Risk Score.

* See manuscript for definition of uncontrolled BP and appropriate statin use per AHA guidelines for patients with AHA FRS ≥ 7.5% or history of CVD.