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ORIGINAL REPORT

Cerebrovascular Disease Risk in Older Head and Neck Cancer Patients After Radiotherapy

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ABSTRACT

Purpose
Cerebrovascular disease is common in head and neck cancer patients, but it is unknown whether radiotherapy increases the cerebrovascular disease risk in this population.

Patients and Methods
We identified 6,862 patients (age > 65 years) from the Surveillance, Epidemiology, and End Results (SEER) –Medicare cohort diagnosed with nonmetastatic head and neck cancer between 1992 and 2002. Using proportional hazards regression, we compared risk of cerebrovascular events (stroke, carotid revascularization, or stroke death) after treatment with radiotherapy alone, surgery plus radiotherapy, or surgery alone. To further validate whether treatment groups had equivalent baseline risk of vascular disease, we compared the risks of developing a control diagnosis, cardiac events (myocardial infarction, percutaneous coronary intervention, coronary artery bypass graft, or cardiac death). Unlike cerebrovascular risk, no difference in cardiac risk was hypothesized.

Results
Mean age was 76 ± 7 years. Ten-year incidence of cerebrovascular events was 34% in patients treated with radiotherapy alone compared with 25% in patients treated with surgery plus radiotherapy and 26% in patients treated with surgery alone ($P < .001$). After adjusting for covariates, patients treated with radiotherapy alone had increased cerebrovascular risk compared with surgery plus radiotherapy (hazard ratio [HR] = 1.42; 95% CI, 1.14 to 1.77) and surgery alone (HR = 1.50; 95% CI, 1.18 to 1.90). However, no difference was found for surgery plus radiotherapy versus surgery alone ($P = .60$). As expected, patients treated with radiotherapy alone had no increased cardiac risk compared with the other treatment groups ($P = .63$ and $P = .81$).

Conclusion
Definitive radiotherapy for head and neck cancer, but not postoperative radiotherapy, was associated with excess cerebrovascular disease risk in older patients.

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INTRODUCTION

In various cancer populations, radiotherapy is associated with development of vascular disease.[1-3] For example, radiotherapy in Hodgkin's disease patients is associated with significantly increased risk of cerebrovascular and cardiac events 10 or more years after treatment.[1] In addition, radiotherapy in breast cancer patients treated in earlier eras has been associated with a higher risk of cardiac-related death.[2,3]

Previous single-institution studies suggest that head and neck cancer patients who undergo radiotherapy have higher incidence of carotid stenosis and stroke compared with controls in the general population.[4,5] However, these studies have not definitively established the independent contribution of radiotherapy to cerebrovascular disease risk because analyses have not compared head and neck cancer patients who underwent radiotherapy with patients did not undergo radiotherapy. Therefore, it remains unknown whether the high cerebrovascular event rate observed in head and neck cancer patients represents long-term treatment toxicity or merely reflects the increased prevalence of traditional risk factors in this population, such as history of smoking and male sex.

Establishing the effect of radiotherapy on cerebrovascular risk in head and neck cancer patients is important for helping to define the role of screening for vascular disease and secondary prevention of stroke in this high-risk group. In addition, determining risks associated with radiotherapy

is important for identifying whether newer treatment techniques, such as more conformal techniques, alternative fractionation schemes, or use of radioprotective agents, could potentially modify cerebrovascular morbidity and mortality.

We sought to determine the incidence of cerebrovascular events in a cohort of older head and neck cancer patients identified through the Surveillance, Epidemiology, and End Results (SEER) –Medicare database. We compared the risk of developing cerebrovascular events in patients who underwent radiotherapy alone (more likely to receive higher radiation doses to the carotid),[6] surgery plus radiotherapy (more likely to receive slightly lower radiation doses),[7,8] or surgery alone (no radiation). Given that treatment fields in head and neck cancer patients typically spare coronary vessels and other cardiac structures, we additionally compared the risk of developing a validating control diagnosis, cardiac events. We hypothesized that radiotherapy to the neck would increase cerebrovascular risk but not affect cardiac risk.

PATIENTS AND METHODS

SEER-Medicare Cohort

The SEER-Medicare database includes a population-based cohort of Medicare beneficiaries with incident cancer identified through SEER tumor registries. Until 1999, SEER included 11 registries, accounting for 14% of the US population; in 2000, the program included an additional five registries, accounting for 26% of the US population.[9]

Study Sample and Exclusions

The study population included 40,200 participants with International Classification of Diseases, Ninth Revision diagnosis of head and neck cancer (diagnosis codes 142, 144 to 149, 160, 190, 193, or 194) from 1986 to 2002 identified in SEER-Medicare records. Tumors of the larynx were not included based on International Classification of Diseases, Ninth Revision code screening criteria. From our study population, we derived a sample of 6,862 patients based on pathologic and clinical exclusion criteria (Appendix, online only).

Outcomes

Our primary outcome was development of cerebrovascular events, including stroke, carotid revascularization, or stroke death. Patients hospitalized for stroke or transient ischemic attack were identified based on Medicare Part A and B claims in the SEER-Medicare linked database, and stroke (cerebrovascular) deaths were identified from the SEER-Medicare cause of death data. All claims codes are listed in the Appendix. This algorithm for identifying cerebrovascular events is a modified combination of algorithms used in prior studies with high sensitivity and specificity for identifying events.[3,10] Time to event was calculated from date of cancer diagnosis.

Our secondary, validating outcome was development of cardiac events, including hospitalization for myocardial infarction, percutaneous coronary intervention, or coronary artery bypass graft (based on Medicare Part A and B claims) or cardiac death (based on SEER-Medicare cause of death). This algorithm for identifying cardiac events is modified from prior studies of SEER-Medicare patients.[2,11] Because an increased risk of cerebrovascular but not cardiac events was expected, this validating control diagnosis was designed to help exclude the possibility of residual confounding in the association between radiotherapy and cerebrovascular events.

Treatments

We determined radiotherapy and/or surgery treatment using SEER records and Medicare claims (Appendix). Patients were categorized as undergoing cancer-directed surgery (total or partial tumor resection) or not undergoing cancer-directed surgery (including biopsy alone). Patients were considered to have undergone radiotherapy and/or surgery treatments if a claim was recorded within 9 months of cancer diagnosis. In addition, sensitivity analyses were conducted using claims within 6 and 4 months of diagnosis.

We compared outcomes for patients who underwent radiotherapy alone, surgery plus radiotherapy, or surgery alone. The two radiotherapy groups were analyzed separately to account for the likelihood that patients who undergo radiotherapy alone may receive higher radiation doses (and higher dose to the carotid) than patients undergoing postoperative radiotherapy.[6-8] We also present combined outcomes for patients who underwent any radiotherapy (radiotherapy alone or radiotherapy plus surgery) versus patients who underwent surgery alone. Finally, we present results for the more restrictive outcome of stroke or stroke death because carotid revascularization is an elective procedure and unmeasured factors affecting selection for this procedure may also influence cancer treatment selection.

For all patients, additional treatment with chemotherapy within 6 months of diagnosis (determined from Medicare claims) and surgical treatment to the neck (determined from Medicare claims and SEER records) were considered covariates. Treatment definitions have been used in previously published studies of SEER-Medicare.[12,13]

Other Covariates

Patient characteristics including age and race were obtained from SEER records. Severity of comorbid disease was based on a modified Charlson comorbidity score validated in prior studies (0 = no comorbidity, 1 = mild to moderate, and 2 = severe).[14] This score combined comorbidities from Medicare claims between 12 months and 1 month before cancer diagnosis. To enhance specificity, patients must have had at least one hospital diagnosis (Part A) claim or at least two outpatient (Part B) claims more than 30 days apart.[14] History of stroke and myocardial infarction were considered separate covariates in the primary and validating analyses, respectively. Tumor characteristics included size, extent of disease (level of pretreatment primary tumor invasion into adjacent structures based on clinical and pathologic assessment for each tumor site[15]), extent of positive lymph nodes, grade, and histology, obtained from SEER records. Socioeconomic characteristics included median income of census tract, urban/rural residence, geographic region, and year of treatment, obtained from SEER records. Number of physician visits (characterizing frequency of patients' interactions with the health care system) between 12 months and 1 month before cancer diagnosis was determined from Medicare claims.

Statistical Analysis

Bivariate associations between the three treatment groups (radiotherapy only, radiotherapy plus surgery, or surgery only) and covariates were tested using the Pearson χ^2 test for categoric variables and the Wilcoxon rank sum test for continuous variables. Incidence of cerebrovascular events in each treatment group was calculated using Kaplan-Meier survival function estimates and compared using the log-rank test. Multivariate Cox proportional hazards models tested whether associations between treatment groups and risk of cerebrovascular events or risk of cardiac events was significant after adjustment for covariates. Covariate selection was based on clinical significance in prior studies or statistical significance in bivariate analyses. Proportionality assumptions were assessed using log-log complementary plots. In multivariate models, we censored patients who died of other causes (nonstroke death in the primary analysis and noncardiac death in the validation analysis) or were lost to follow-up. Finally, for the primary outcome of cerebrovascular events, we tested the potential modifying effects of covariates selected a priori, including age, sex, race, comorbidity, chemotherapy, tumor sites with higher likelihood of receiving radiotherapy to the bilateral neck (nasopharynx, tonsil, oropharynx, hypopharynx, and pharynx), and number of positive nodes, using interaction terms to determine whether a high-risk patient group could be identified.

Finally, to validate the strength and magnitude of the association between treatment group and cerebrovascular risk, we conducted a subsidiary propensity score analysis using the Mayo Greedy Match algorithm (without replacement) with 1:1 matching.[16] Balance of measured variables between treatment groups considered all nontreatment covariates listed earlier (plus chemotherapy), and the propensity score (probability of treatment assignment) was based on a logistic regression model. Cox proportional hazards

models estimated treatment effect after accounting for propensity scores, with matched pairs stratified by case-control status. This analysis was intended to account for residual confounding associated with treatment selection.

Analyses were conducted using SAS version 9.1.3 (SAS Institute, Cary, NC), and all statistical tests assumed a two-tailed $\alpha = .05$. The University of Texas M. D. Anderson Cancer Center Institutional Review Board approved use of the SEER-Medicare database.

RESULTS

Patient Characteristics

In 6,862 patients, the median follow-up time was 2.4 years (interquartile range, 1.4 to 4.4 years). This corresponded to median follow-up time of 3.2 years (range, 2.0 to 5.8 years) for patients who survived and 1.8 years (range, 1.1 to 3.4 years) for patients who died. Mean age of the entire cohort was 76 years (standard deviation, 7 years), 54% were men, and 85% were white. At diagnosis, 57% of patients had localized disease, 42% had primary tumor extension into adjacent regional structures, 54% were node negative, and 77% had squamous histology. The most common tumor sites occurred in the oral cavity and oropharynx. The majority of oral cavity tumors were treated with surgery (alone or plus radiotherapy), whereas most oropharynx tumors were treated with radiotherapy alone (Table 1).

Treatment Characteristics

Among the entire cohort, 29% of patients underwent radiotherapy alone, 41% underwent surgery plus radiotherapy, and 30% underwent surgery alone. In addition, 18% received chemotherapy. As expected based on standard practice patterns, patients who underwent radiotherapy were more likely to have greater tumor involvement (larger tumors, regionally invasive disease, and positive lymph nodes) and more severe comorbid disease than patients who underwent surgery alone (Table 2).

Risk of Cerebrovascular Events

The incidence of events was highest in patients who underwent radiotherapy alone compared with any other treatment group ($P < .001$). Specifically, by 5 years after diagnosis, actuarial incidence of cerebrovascular events was 19% in patients who underwent radiotherapy alone compared with 14% in patients who underwent surgery plus radiotherapy and 14% in patients who underwent surgery alone; the corresponding actuarial incidences by 10 years after diagnosis were 34%, 25%, and 26%, respectively (Table 3, Fig 1). However, there was no significant difference between incidence of cerebrovascular events in the combined group of patients who underwent any radiotherapy (with or without surgery; 29%) and patients who underwent surgery alone (26%; Appendix Fig A1, online only).

On multivariate analysis, patients who underwent radiotherapy alone again had significantly higher risk of developing a cerebrovascular event than did those who underwent surgery plus radiotherapy (hazard ratio [HR] = 1.42; 95% CI, 1.14 to 1.77) and those who underwent surgery alone (HR = 1.50; 95% CI, 1.18 to 1.90; Table 4). The combined group of patients who underwent any radiotherapy (with or without surgery) were not at significantly higher risk for a cerebrovascular event compared with patients treated with surgery alone (HR = 1.17; 95% CI, 0.97 to 1.41). The interaction term between any radiotherapy and surgery was significant ($P = .002$). No other factors modifying this association were identified, including positive lymph nodes or tumor sites more likely to receive bilateral neck radiotherapy (Appendix Table A1, online only).

Risk of Cardiac Events

There was no significant difference in incidence of cardiac events between the three treatment groups (5-year incidence of 20% in each group, $P = .62$). On multivariate analysis, patients who underwent radiotherapy were no more likely to experience cardiac events, even when patients who underwent radiotherapy alone were compared with the surgery plus radiotherapy and surgery alone treatment groups ($P = .81$ and $P = .63$, respectively; Table 4).

Subsidiary Analyses

Effect size of the association between treatment group and cerebrovascular events was validated in the propensity score analysis, with

Table 1. Head and Neck Cancer Sites by Treatment Groups (N = 6,862)

Site	Total Patients		% of Patients by Treatment		
	No.	%	RT Alone (n = 1,983)	Surgery + RT (n = 2,823)	Surgery Alone (n = 2,056)
Oral cavity	3,106	45	16	35	49
Anterior tongue	1,006	15	10	31	58
Floor of mouth	566	8	15	39	46
Gingiva or buccal mucosa	1,534	22	20	36	44
Oropharynx	1,342	20	56	36	8
Base of tongue	604	9	54	36	10
Tonsil	569	8	68	27	5
Other oropharynx	169	2	59	34	8
Nasopharynx	256	4	79	20	2
Hypopharynx	576	8	59	37	4
Nasal cavity and sinus	496	7	17	59	25
Salivary gland	934	14	6	68	26
Other	152	2	45	41	14

Abbreviation: RT, radiotherapy.

Table 2. Patient Characteristics by Treatment Group

Characteristic	% of Patients			*P**
	RT Alone (n = 1,983)	Surgery + RT (n = 2,823)	Surgery Alone (n = 2,056)	
Demographics				
Age, years				< .0001
Mean	75	75	77	
SD	7	6	7	
White	80	85	89	< .0001
Men	62	57	44	< .0001
Tumor characteristics				
Extent of disease				< .0001
Localized	42	50	80	
Extends into regional structures	55	48	20	
Unknown	3	2	< 1	
Size, cm†				< .0001
< 2	14	28	44	
2 to < 4	27	36	22	
> 4	11	13	5	
Unknown	48	24	28	
No. of positive nodes				< .0001
None	41	48	74	
1 ipsilateral, ≤ 3 cm	10	8	2	
1 ipsilateral, > 3 cm to ≤ 6 cm or bilateral/contralateral ≤ 6 cm	30	29	4	
Any, at least 1 > 6 cm	2	1	< 1	
Unknown	17	14	20	
Grade				< .0001
Well differentiated	8	11	27	
Moderately differentiated	37	37	40	
Poorly or undifferentiated	35	36	11	
Unknown	20	16	21	
Squamous histology	88	73	73	
Other clinical characteristics				
Charlson comorbidity score				< .0001
None (0)	57	62	64	
Mild to moderate (1)	22	21	20	
Severe (2)	14	10	11	
Unknown	8	7	5	
Other treatment				
Chemotherapy	39	14	2	< .0001
Socioeconomic variables				
Married	50	55	47	
Location of residence				.0004
Large metropolitan area	62	58	57	
Metropolitan area	25	27	27	
Urban area	6	7	6	
Less urban area	5	7	8	
Rural area	1	2	2	
Income, quartile				.15
First (median = $23,419)	24	24	23	
Second (median = $36,513)	23	24	23	
Third (median = $47,377)	25	23	23	
Fourth (median = $76,440)	28	29	31	
No. of doctor visits in past year				.31
Mean	15	14	15	
SD	14	12	12	

Abbreviations: RT, radiation therapy; SD, standard deviation.
*P values reflect the comparison of the three treatment groups.
†Size refers to measurement of greatest diameter, as reported in the Surveillance, Epidemiology, and End Results database.

Table 3. Actuarial Incidence of Cerebrovascular Events by Treatment Group

Treatment	No. of Events per 1,000 Person-Years	Incidence of Cerebrovascular Events (%)		
		1 Year	5 Years	10 Years
RT alone	42.8	4	19	34
Surgery + RT	28.0	3	14	25
Any RT	33.6	3	16	29
Surgery alone	30.7	3	14	26

NOTE. *P* values were as follows: RT alone *v* surgery + RT, $P < .001$; RT alone *v* surgery alone, $P < .001$; surgery + RT *v* surgery alone, $P = .56$; and any RT *v* surgery alone, $P = .20$.
Abbreviation: RT, radiotherapy.

radiotherapy alone still associated with significantly higher cerebrovascular risk than surgery plus radiotherapy (HR = 1.37; 95% CI, 1.09 to 1.72) or surgery alone (HR = 1.51; 95% CI, 1.12 to 2.05; Appendix Table A2, online only). Sensitivity analyses restricting treatment claims to those identified within 6 months and 4 months did not significantly alter associations.

DISCUSSION

Our study demonstrated that older head and neck cancer patients who underwent radiotherapy alone were at increased risk for subsequent cerebrovascular events. Of patients who did not succumb to other causes, approximately one third of patients who underwent radiotherapy alone experienced a cerebrovascular event within 10 years of cancer diagnosis. In contrast, only approximately one quarter of patients who underwent surgery plus radiotherapy or surgery alone experienced an event.

Our study adds several novel insights on the association between radiotherapy and cerebrovascular events in head and neck cancer patients. This study was conducted on a large, representative sample that included patients who received treatment with or without radiotherapy, thus delineating the independent effect attributable to radiotherapy. This association between treatment with radiotherapy and subsequent cerebrovascular events was maintained after thorough adjustment for covariates. Furthermore, the validating finding that no significant cardiac risk was associated with radiotherapy suggested that the increased cerebrovascular risk was less likely to be attributable to unmeasured confounding affecting patients' treatment assignment.

Vascular risks have been explored in various cancer populations, including head and neck cancer patients.[1-5,11,17-24] Dorresteijn et al[4] reported a 12% 15-year incidence of stroke in younger head and neck cancer patients treated with radiation. Haynes et al[5] reported a 12% 5-year incidence in patients who received a median dose of 64 Gy to the neck, similar to the 5-year incidence rate of 14% to19% reported in our study.

Stroke risks in previously studied head and neck cancer cohorts clearly exceeded risks in comparable healthy populations by 2 to 9 times.[4,5] Similarly, the stroke incidence of 28.0 to 42.8 per 1,000 person-years in our sample exceeded incidences of 9.8 to 16.6 per 1,000 person-years found in an elderly community-based cohort.[25] Prior studies included detailed information on the course of radiotherapy in head and neck cancer patients who suffered stroke[4,5,19,23]

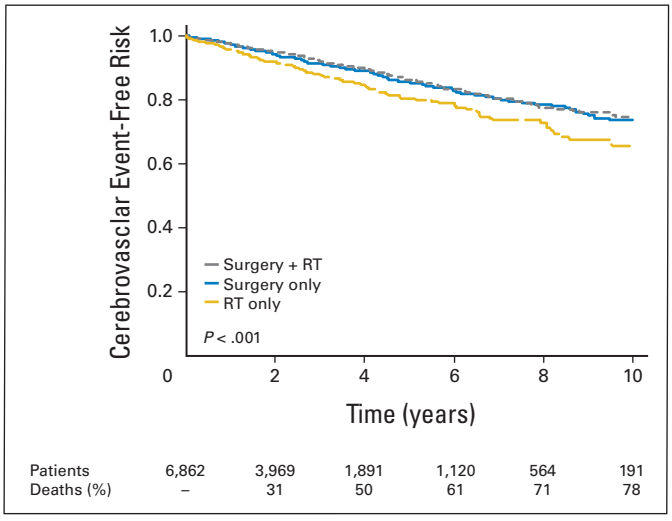

Fig 1. Cerebrovascular event-free risk over time by treatment groups. RT, radiotherapy.

Table 4. Adjusted Risk of Cerebrovascular and Cardiac Events by Treatment Group

Comparison of treatment groups*	HR	95% CI	*P*
Risk of cerebrovascular events			
RT alone *v* surgery + RT	1.42	1.14 to 1.77	.002
RT alone *v* surgery alone†	1.50	1.18 to 1.90	.0009
Any RT *v* surgery alone	1.17	0.97 to 1.41	.10
Risk of stroke or stroke death only			
RT alone *v* surgery + RT	1.44	1.14 to 1.82	.003
RT alone *v* surgery alone	1.59	1.22 to 2.06	.0005
Any RT *v* surgery alone	1.23	1.00 to 1.51	.05
Risk of cardiovascular events			
RT alone *v* surgery + RT	1.02	0.84 to 1.25	.81
RT alone *v* surgery alone	0.95	0.76 to 1.18	.63
Any RT *v* surgery alone	0.93	0.80 to 1.09	.38
Risk of MI or cardiac death only			
RT alone *v* surgery + RT	1.08	0.88 to 1.31	.48
RT alone *v* surgery alone	1.01	0.81 to 1.25	.93
Any RT *v* surgery alone	0.96	0.81 to 1.12	.58

Abbreviations: HR, hazard ratio; RT, radiotherapy; MI, myocardial infarction.
*Models were adjusted for age, sex, race, history of stroke (or MI for control diagnosis), other comorbid disease, chemotherapy, surgery, tumor size, extent, positive lymph nodes, grade, squamous histology, tumor site, socioeconomic status variables, year of treatment, and geographic region.
†Comparison of risk of cerebrovascular events for surgery alone *v* surgery + RT shows no significant difference ($P = .60$).

Table 5. Comparison of Effect Sizes Reported in Prior Studies and Our Study

Measure	Dorresteijn et al[4]	Haynes et al[5]	Present Study
Year of publication	2002	2002	2008
No. of patients	367	413	6,862
Site	Head and neck	Head and neck	Head and neck
Actuarial incidence of event	12% over 15 years	12% over 5 years	14%-19% over 5 years
Comparison (relative risk or hazard ratio)			
Any RT (± surgery) *v* general population	5.1 to 8.5	2.1	1.7 to 4.4*
Any RT (± surgery) *v* no RT	Analysis not performed	Analysis not performed	1.17 to 1.23†
RT only *v* surgery + RT	Analysis not performed	Analysis not performed	1.42 to 1.44†
RT only *v* surgery only	Analysis not performed	Analysis not performed	1.50 to 1.59†

Abbreviation: RT, radiotherapy.
*Range is based on comparing incidence rates of 28.0 to 42.8 events per 1,000 person-years in our study cohort with 9.8 to 16.6 events per 1,000 person-years in a comparable elderly cohort.[25]
†Ranges reflect primary outcome of stroke, carotid revascularization, or stroke death and restrictive outcome of stroke or stroke death.

but lacked data on stroke outcomes in head and neck cancer patients who did not undergo radiotherapy. Thus, the magnitude of independent contribution of radiotherapy to stroke events has required further clarification. Our study reported a magnitude of increased cerebrovascular risk of up to 50% in patients who underwent radiotherapy alone compared with patients who underwent surgery (Table 5). This finding is consistent with the independent effect of radiotherapy on cerebrovascular and cardiac sequelae reported in other cancer patient populations, including Hodgkin's disease,[1] leukemia,[17] and breast cancer.[20]

Unexpectedly, patients who underwent surgery plus radiotherapy did not show increased cerebrovascular risk. This finding could have been attributable to these patients potentially having tumor sites less likely to receive comprehensive radiotherapy to the neck including significant portions of carotid vessels. Specifically, although we adjusted for tumor site in multivariate analysis, our study cannot rule out residual confounding from this important source.

In addition, head and neck cancer patients who received postoperative radiotherapy in this era typically received total doses of approximately 57.6 to 66 Gy[7,8] (or up to 70 Gy boost), whereas patients treated definitively typically received 70 to 72 Gy.[6] One interesting hypothesis is that a dose threshold for developing clinically significant cerebrovascular events could occur between 60 and 70 Gy. However, dose data were unavailable for our cohort, and prior population-based studies of head and neck cancer patients have not adequately investigated dose-response effects on vascular outcomes in this range. Notably, one study of older breast cancer patients reported no increased risk of stroke in patients more likely to receive radiotherapy to a supraclavicular field (with doses typically between 45 and 50 Gy).[3] Furthermore, in head and neck cancer patients, a threshold effect could be biologically plausible given evidence for an additional one to two logs of vascular cell killing over this range.[26] In contrast, studies of Hodgkin's disease patients report adverse cardiovascular events with doses as low as 38 to 40 Gy.[27,28] Our study cannot rule out a more subtle effect of lower radiation doses in this cohort of older patients with relatively short survival, given that such an effect could require a longer latency period for development of clinically significant events compared with higher dose treatments. Alternatively, it is important to note that unidentified confounders may still exist for the association with cerebrovascular events in patients treated with radiotherapy alone. Thus, an alternative interpretation of our data would suggest that the true magnitude of association in patients treated with radiotherapy alone could be lower than that found in our cohort.

If independently validated, however, our findings could have important implications for evaluating cerebrovascular risks associated with newer radiotherapy strategies in head and neck cancer, including conformal therapy, which may spare carotid vessels, and alternative fractionation schemes.[29] Additionally, benefits of screening, stroke preventive therapies, and intervention with carotid endarterectomy in these patients are unknown; prior studies suggest that screening of high-risk patients for asymptomatic carotid stenosis could be cost effective,[30] and patients undergoing definitive radiotherapy may represent a subset that could benefit from noninvasive assessment including routine carotid bruit auscultation and imaging (with ultrasonography, magnetic resonance angiography, or computed tomographic angiography) within several years after treatment. Future studies may also evaluate whether stricter goals for blood pressure, lipids, and hemoglobin A1c (such as those applied to high-risk patients with diabetes and chronic kidney disease) could improve outcomes.

Our study has several limitations. Because only older patients (age $\geq$ 65 years) were included, results require validation in younger cohorts, particularly because patients with longer survival could manifest significant risks with lower radiation doses. SEER-Medicare does not have information on specific radiation fields or dosages available, and thus, treatment groups may not reflect completely homogeneous treatment strategies. Of note, a prior study of compliance in head and neck cancer radiotherapy trials found that nearly 90% of patients fully received prescribed radiation doses.[31] However, potential heterogeneity would have likely biased results toward the null if some patients were not fully treated to standard doses. Future studies with more detailed radiotherapy and comorbidity data may seek to further rule out potential residual confounding, particularly given our finding of no association with surgery plus radiotherapy.

In this cohort of older head and neck cancer patients, patients who underwent radiotherapy alone had increased cerebrovascular risk compared with patients who underwent surgery with or without radiation (19% *v* 14% at 5 years and 34% *v* 26% at 10 years after therapy, respectively). Further study of the impact of evolving radiotherapy techniques that could minimize dose to carotid arteries may be warranted, particularly in patients undergoing definitive radiotherapy.

AUTHORS' DISCLOSURES OF POTENTIAL CONFLICTS OF INTEREST

The author(s) indicated no potential conflicts of interest.

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Acknowledgment

The Acknowledgment is included in the full-text version of this article, available online at www.jco.org. It is not included in the PDF version (via Adobe® Reader®).

Appendix

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