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Race and competing mortality in advanced head and neck cancer

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SUMMARY

Objectives: Black patients with head and neck cancer (HNC) have poorer survival and disease control compared to non-black patients, but disparities in death from non-cancer causes (i.e., competing mortality) are less well-studied.

Materials and methods: We conducted an analysis of 538 patients (169 black, 369 non-black) with stage III–IV HNC treated on one of six multi-institutional protocols between 1993 and 2004 involving multi-agent chemoradiotherapy with or without surgery. Competing mortality was defined as death due to intercurrent comorbid disease, treatment-related morbidity, or unknown cause in the absence of disease recurrence, progression, or second malignancy. Cox proportional hazards and competing risks regression were used to estimate the effect of black race on competing mortality.

Results: Black race was associated with increased rates of comorbidity, smoking, heavy alcohol use, advanced tumor stage, and poorer performance status ($p < .001$ for all). Compared to non-black patients, black HNC patients had a higher 5 year cumulative incidence of disease progression (31.4%; 95% CI, 24.4–38.5% vs 23.4%; 95% CI, 19.1–28.1%) and competing mortality (28.1%; 95% CI, 21.2–35.3% vs 14.5%; 95% CI, 11.0–18.5%). When adjusting for age, male sex, body mass index, distance traveled, smoking and alcohol use, performance status, comorbidity, and tumor stage, the black race was associated with death from comorbid disease (Cox hazard ratio 2.13; 95% CI, 1.06–4.28, $p = 0.033$).

Conclusions: Black patients with advanced HNC are at increased risk of both disease progression and death from competing non-cancer mortality, particularly death from comorbid disease. Improved strategies to manage comorbid disease may increase the benefit of treatment intensification in black patients.

Introduction

Racial disparities in treatment outcomes are a widely recognized problem in head and neck cancer (HNC). Studies have shown that black HNC patients have worse rates of overall survival, relative survival, HNC mortality, and disease recurrence compared to non-black HNC patients [1–5]. A better understanding of modifiable risk factors contributing to survival disparities is needed to design strategies to mitigate these disparities.

Previous studies have identified that lower socioeconomic status (SES), poorer access to health care, higher rates of comorbidity, later stage at presentation, and lower rates of surgical treatment are associated with both black race and poorer survival in HNC [3–8]. These studies have analyzed racial disparities in HNC using composite endpoints, such as overall survival or disease-free survival, which are comprised of both cancer-specific (e.g., disease recurrence) and non-cancer events (e.g., death from any cause). A limitation of composite endpoints is that they can obscure whether survival differences are due to cancer-specific events, non-cancer events, or both [9].

In addition to being undesirable events in their own right, deaths from competing causes diminish the clinical benefit of cancer therapies and reduce the efficiency of cancer clinical trials [9–13]. We have previously shown that black race is associated with increased risk of HNC specific mortality and non-cancer mortality in a population-based analysis [12], though the study did not directly compare black and non-black patients and lacked important prognostic data on tobacco and alcohol use, comorbidity, performance status, and treatment techniques. Therefore, with the addition of these covariates, we sought to determine the effect of race on competing mortality in advanced HNC using a multi-institutional cohort.

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Methods

Patients

The study design was a secondary analysis of 538 patients (168 black; 369 non-black) with American Joint Committee on Cancer stage III–IV HNC, treated on a series of six multi-institutional protocols between August 1993 and November 2004. Patients were treated at one of four institutions: University of Chicago, Northwestern Memorial Hospital, University of Illinois Chicago, and Weiss Memorial Hospital. Protocol treatment details have been previously described (Appendix Table A1) [10,14–17].

Treatment techniques

All patients were treated with concurrent multi-agent chemoradiotherapy (CRT). Select patients received induction chemotherapy with paclitaxel and carboplatin preceding CRT. Limited initial organ-sparing surgery was used in selected patients preceding CRT and was used at the primary site for persistent or recurrent disease after CRT. Neck dissection was recommended for patients with N2 or N3 disease.

CRT was given in five cycles on alternating weeks and RT was given in 1.5 Gy fractions twice daily. Gross disease was treated to total dose of 70–75 Gy, while postoperatively treated patients received 60–66 Gy. High-risk areas of the neck were treated to 51–60 Gy and standard-risk areas were treated to 36–45 Gy. Chemotherapy consisted of fluorouracil plus hydroxyurea concurrent with RT. Additional chemotherapy depended on the protocol and consisted of cisplatin, paclitaxel, or oral ZD1839 (Iressa; AstraZeneca, Wilmington, DE).

Patients were evaluated 1 month after the completion of CRT, every 3 to 4 months in the first year, every 6 months in the second and third year, and annually thereafter. Computed tomography of the head, neck, and chest, was obtained at each follow-up evaluation. All locoregional and distant recurrences were biopsy proven whenever possible and clinically indicated. Follow-up continued until November 2004.

Statistical analysis

Disease-free survival was defined as disease progression, second malignancy, or death due to any cause. Competing mortality was defined as death due to intercurrent comorbid disease, treatment-related morbidity, or unknown cause in the absence of disease recurrence, progression, or second malignancy. Examples of death from comorbid disease included stroke, myocardial infarction, arrhythmia, pneumonia, hepatic failure, and diabetic ketoacidosis. Treatment-related mortality included death from any cause within two months of treatment and death immediately after surgery or late complications. Examples included surgical complications, sepsis, and pulmonary embolism within two months of treatment, in accordance with previously described methods [18]. As the patients in this study were treated at tertiary referral centers on a set of multi-institutional protocols, cause of death ascertainment was collectively reviewed and confirmed in multidisciplinary tumor boards [10].

Chi-squared and *t*-tests were used to test differences in covariates for black and non-black patients. Cumulative incidence

Table 1
Patient Characteristics.

	Black (n = 169) No. (%)	Non-Black (n = 369) No. (%)	P value
Institution			
University of Chicago	113 (66.9)	225 (61.0)	
Northwestern Memorial Hospital	12 (7.1)	98 (26.6)	
University of Illinois Chicago	44 (26.0)	40 (10.8)	
Weiss Memorial Hospital	0	5 (1.4)	
Missing	0	1	
Age (mean)	56.1	57.1	0.33
Age > 65	37 (21.9)	100 (27.1)	0.24
Male sex	122 (72.2)	281 (76.2)	0.38
Body Mass Index (mean)	23.4	25.9	<.001
Smoking history > 20 pack years	134 (79.3)	225 (61.0)	<.001
Alcohol use > 1 drink per day	117 (69.2)	196 (53.1)	<.001
Distance traveled > 15 miles	30 (17.8)	237 (64.2)	<.001
Unknown	24 (14.2)	35 (9.5)	
Charlson comorbidity index			
0	100 (59.2)	233 (63.1)	0.016
1	16 (9.5)	37 (10.0)	
2	23 (13.6)	29 (7.9)	
⩾3	13 (7.7)	8 (2.2)	
Unknown	62 (3.7)	17 (4.6)	
ECOG performance status			<.001
0	53 (31.4)	196 (53.1)	
1	86 (50.9)	156 (42.3)	
2	30 (17.8)	17 (4.6)	
T stage 3/4	138 (81.5)	216 (58.5)	<.001
Unknown	7 (4.1)	9 (2.4)	
Nodal stage			
N2c	36 (21.4)	60 (16.3)	0.12
N3	31 (18.5)	50 (13.6)	0.17
Unknown	7 (4.1)	9 (2.4)	
Site			
Hypopharynx	16 (9.5)	43 (11.7)	
Larynx	42 (24.9)	44 (11.9)	
Oropharynx	67 (39.6)	167 (45.3)	

ECOG = Eastern Cooperative Oncology Group.