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Original Article

Undertreatment of Women With Locoregionally Advanced Head and Neck Cancer

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BACKGROUND: It is difficult to predict whether a patient with head and neck cancer (HNC) is more likely to die of the cancer or another comorbidity. Competing event models can help to identify individual patients or groups of patients who may be undertreated or overtreated in clinical practice. **METHODS:** Patients with HNC (n = 884), aged 18 to 85 years and diagnosed from 2000 to 2015 with stage II to IVB disease according to the seventh edition of the American Joint Committee on Cancer system, were identified. With a generalized competing event (GCE) model that controlled for age, sex, tumor site, surgical treatment, and Charlson Comorbidity Index (CCI), the association between these factors and the relative hazard for cancer mortality was determined. Logistic regression models were used to estimate the odds of receiving platinum-based chemoradiotherapy or a less intensive therapy, with adjustments made for age, sex, tumor site, CCI, stage, smoking, and alcohol abuse history. **RESULTS:** Compared with men, women had an increased relative hazard ratio for death from HNC versus other causes, which was reported as an adjusted ω^+ ratio comparing women with men (ω^+ ratio, 1.95; 95% CI, 1.09-3.49), even though they were less likely to receive intensive chemoradiotherapy than men (adjusted odds ratio, 0.69; 95% CI, 0.48-0.99). **CONCLUSIONS:** These findings indicate that women in this cohort may be undertreated in clinical practice and potentially miss the opportunity for their HNC to be aggressively treated. This study supports the use of GCE models to identify patients who are potentially undertreated and may also help to guide future research in health disparities. ***Cancer* 2019;0:1-7**. © *2019 American Cancer Society.*

KEYWORDS: chemotherapy, head and neck cancer, health care disparities, morbidity.

INTRODUCTION

Head and neck cancer (HNC) accounts for approximately 4% of all cancers diagnosed in the United States.[1] The incidence rates for cancers of the oral cavity and pharynx, as reported by the American Cancer Society in 2017, were more than twice as high in men as in women.[2] The treatment for patients with HNC varies by the primary site and by the stage of the disease. Curative treatment for locally advanced HNC often involves a combination of modalities, including surgery, radiation, and/or chemotherapy. Organ-sparing approaches for locally advanced, nonmetastatic HNC have shown that patients benefit from the addition of chemotherapy to radiation,[3-6] although the addition of concurrent chemoradiotherapy is not clearly associated with an incremental advantage in older patients.[7,8] Indeed, in clinical practice, many patients, especially older patients and those with significant comorbidities, may be treated with less intensive treatments such as cetuximab with radiation[9] and radiation therapy alone or even no treatment.[10] The optimal selection of patients for intensive treatment is not standardized and remains controversial.

Several health disparities in patients with HNC have been identified previously. Higher socioeconomic status and health insurance status have been associated with improved survival.[11,12] Racial disparities have also been described in patients with HNC.[11,13-18] However, sex disparities and patient outcomes remain less clearly delineated. Some studies have demonstrated no difference in survival between women and men,[11,19-21] whereas other studies have found differences in survival. For example, Choi et al[11] reported that women had better survival, whereas others found that outcomes for men improved over time.[22,23]

Generalized competing event (GCE) modeling is a useful and relatively novel method for analyzing effects of treatment and risk factors on outcomes.[21,24,25] This approach has been validated for several cancers, including head and neck, endometrial, prostate, and breast cancer.[24,26] The GCE model differentiates patients according to their hazard for an event of interest, such as cancer recurrence or mortality, with respect to competing events, such as death from noncancer causes, and this makes it useful for identifying individual patients who may benefit from intensive treatment

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and groups of patients who may be undertreated.[24] The advantage of GCE models over standard prognostic models lies in assessing the extent to which a factor affects the ratio of a primary event to a competing event (ie, ω^+) or the proportion of an overall event hazard attributable to a primary event (ie, ω). A recent publication has also found that the GCE model can reduce the cost and duration of cancer clinical trials through better risk stratification.[27] In this study, we applied the GCE model to evaluate a large cohort of patients in Northern California with HNC with the goal of comparing cause-specific survival between women and men while controlling for differences in age, sex, tumor site, surgical treatment, and Charlson comorbidity scores.

MATERIALS AND METHODS

Study Design, Setting, and Population

We conducted a retrospective cohort analysis with data from Kaiser Permanente Northern California (KPNC), a large integrated health care system. KPNC provides medical care to more than 4 million members in Northern California and maintains clinical, demographic, and socioeconomic data for more than 10 million past health care plan members.[28,29] The Institutional Review Board at KPNC approved the study, providing a waiver of informed consent.

Outcome Measurement

Patients with HNC, aged 18 to 85 years and diagnosed with squamous cell carcinoma between 2000 and 2015, were included. Patients at stage I or IVC according to the seventh edition of the American Joint Committee on Cancer system or at Surveillance, Epidemiology, and End Results (SEER) summary stage 1, 7, or 9 were excluded, as were those who were diagnosed or treated outside of KPNC. The date of death was determined from hospital records, California state death certificates, and Social Security Administration data. The cause of death was determined from patients' linked state death certificates. If a known death could not be linked to a primary cause of death, the patient chart was manually reviewed by the study's clinical investigators. Cause-specific death was defined as death from cancer, whereas death from any other cause was considered a competing event. Treatment information, including chemotherapy, radiation, and surgery, was collected from the medical record. Intensive therapy was defined as concurrent therapy with cisplatin and radiation. Each patient's age, race/ethnicity (non-Hispanic white, Asian, black, non-Asian/nonblack Hispanic, or other), sex, cancer site, cancer stage, self-reported smoking history, and alcohol abuse diagnostic history were also collected from the medical record. As for the census-based socioeconomic status, each patient's address at the time of diagnosis was used to determine his or her neighborhood median income. A patient's diagnosis and utilization history in the year before the HNC diagnosis were used to calculate the Charlson Comorbidity Index (CCI; modified to exclude cancer in the calculation).[30]

Statistical Analysis

Our primary interest was to compare cancer mortality and treatment outcomes between women and men. Baseline characteristics, stratified by patient sex, were calculated and compared with chi-square tests. The cumulative incidence of cancer-specific and noncancer deaths through the first 5 years of follow-up, stratified on patient sex, was plotted with the cumulative incidence function. Patients were censored at the end of the study (December 2016) or if they disenrolled from KPNC. Disenrollment was defined as the end of membership or a gap in membership exceeding 3 months.

We used a multivariable GCE model (the gcerisk package in R) to estimate effects of covariates on the (adjusted) ratio of the hazard for cancer death to the hazard for competing mortality (the ω^+ ratio). An ω^+ ratio greater than 1 indicates that a covariate category has a higher mean ω^+ with respect to the baseline category. We used a GCE model based on Cox proportional hazards regression, verified by inspection for proportional hazards, and controlling for age, sex, tumor site, surgical treatment, and CCI (binary: 0 vs 1 or more comorbidities).[24,31]

We then used logistic regression to estimate the odds of receiving intensive treatment (ie, cisplatin with radiation), any radiation, or surgery, adjusting for the same covariates used in the GCE model plus cancer stage, smoking, and alcohol abuse history. For sensitivity analyses, all GCE and logistic regression models, stratified by oropharyngeal HNC versus other HNC sites, were repeated. Because the magnitude and direction of the main effects were consistent and the power was low on account of the small sample sizes, the results from the sensitivity analyses are not presented here.

RESULTS

Between 2000 and 2015, we identified 884 patients diagnosed with HNC who met the inclusion and exclusion criteria (Fig. 1 and Table 1). The median follow-up was

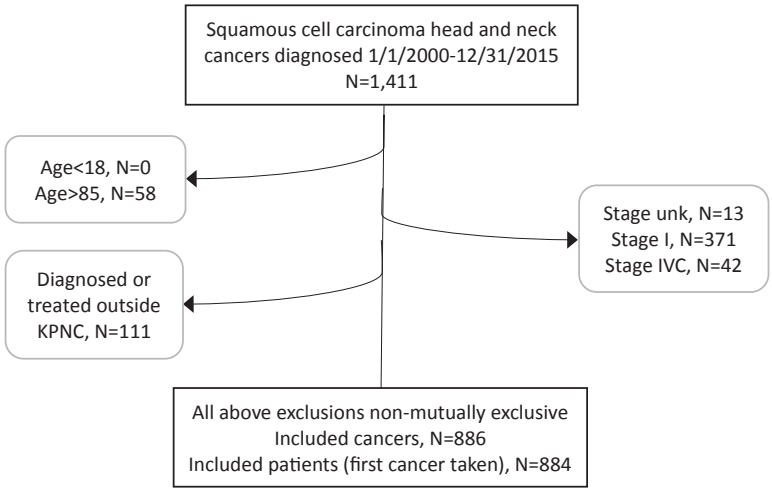

Figure 1. Cohort of patients with squamous cell carcinoma of the head and neck. KPNC indicates Kaiser Permanente Northern California; unk, unknown.

2.9 years with a maximum follow-up of 16.8 years. Two hundred seventy one patients died of cancer (82 women and 189 men), and 93 patients died of noncancer causes (19 women and 74 men). One hundred six patients (12%) were censored because of disenrollment. In comparison with men, the cumulative incidence of cancer-specific death was higher for women ($P = .03$), whereas the cumulative incidence of noncancer death was slightly lower ($P = .10$; Fig. 2A,B).

In our cohort, the male-to-female ratio was 3:1 (661 men and 223 women; Table 1). The median age was higher for women at 64 years than for men at 60 years ($P < .001$). There was also a difference in the distribution of cancer sites between women and men ($P < .001$), with a higher incidence of oropharyngeal cancer in men than women (55% vs 38%). Men also had a lower incidence of oral cavity cancer (13% vs 28%). The distributions for race, neighborhood median income, smoking status, alcohol abuse history, and CCI were similar between women and men (Table 1).

The mean ω^+ for women was 7.0, whereas the mean ω^+ for men was 3.8; this indicated that compared with men, women had a higher hazard for cancer mortality with respect to death from competing events. Because the ω^+ scores for women and men were both greater than 1, both populations were more likely to die of their HNC than other causes. However, the ratio or difference between the cancer and noncancer death proportions was smaller for men than women. A higher ω^+ could be explained by presentation with a more advanced or aggressive malignancy, a better baseline health status, a lower propensity to die of competing causes, undertreatment, or a combination of these factors. After we had controlled for other baseline covariates, the adjusted ω^+ ratio comparing women with men was 1.95 (95% CI, 1.09-3.49). The ω^+ ratio was lower for patients with increasing age per 10 years (0.77; 95% CI, 0.61-0.98) and for those who had surgery (0.52; 95% CI, 0.30-0.89). Patients with oral cavity primaries had a higher adjusted ω^+ ratio (1.82; 95% CI, 0.92-3.58), but this effect only reached borderline significance (Fig. 3).

Compared with men, women were less likely to receive cisplatin concurrently with radiation (34% vs 44%; $P = .008$) and radiation (60% vs 70%; $P = .008$; Table 1). With adjustments for covariates, women had lower odds of receiving cisplatin concurrently with radiation (adjusted odds ratio [OR], 0.69; 95% CI, 0.48-0.99) and borderline lower odds of receiving any radiation (adjusted OR, 0.79; 95% CI, 0.56-1.12). Similarly, those with a CCI ≥ 1 (OR, 0.72; 95% CI, 0.51-1.00), oral cavity cancer (OR, 0.43; 95% CI, 0.23-0.80), and increasing age (per 10 years; OR, 0.83; 95% CI, 0.71-0.96) were less likely to receive cisplatin with radiation. We also found that with increasing age, fewer patients received radiation (adjusted OR, 0.90; 95% CI, 0.77-1.04) or surgery as part of their treatment (OR, 0.69; 95% CI, 0.58-0.82). Patients with oral cavity cancer were less likely to receive radiation than the cohort as a whole (OR, 0.32; 95% CI, 0.19-0.52) but more likely to receive surgery (9.90; 95% CI, 5.61-17.97; Table 2).

DISCUSSION

Our principal findings from a large, diverse cohort of patients from KPNC with HNC were the following: 1)

TABLE 1. Characteristics of Patients With Head and Neck Cancer From Kaiser Permanente Northern California

Characteristic	Women, No. (%)	Men, No. (%)	P[a]
Total cases	223 (25.2)	661 (74.8)	
Age at diagnosis			.0002
21-40 y	12 (5.4)	21 (3.2)	
41-50 y	18 (8.1)	94 (14.2)	
51-60 y	61 (27.3)	218 (33.0)	
61-70 y	64 (28.7)	214 (32.3)	
71-80 y	53 (23.8)	95 (14.4)	
81-85 y	15 (6.7)	19 (2.9)	
Race/ethnicity			.84
White	145 (65.0)	440 (66.6)	
Black	16 (7.2)	40 (6.0)	
Asian/Pacific Islander	38 (17.0)	98 (14.8)	
Hispanic	15 (6.7)	54 (8.2)	
Other/unknown	9 (4.1)	29 (4.4)	
Census-based income[b]			.57
Lower income	72 (32.3)	200 (30.3)	
Higher income	151 (67.7)	461 (69.7)	
Prior smoking	143 (64.1)	448 (67.8)	.31
Prior alcohol abuse	40 (17.9)	123 (18.6)	.82
CCI			.98
0	140 (62.8)	412 (62.3)	
1	43 (19.3)	132 (20.0)	
≥2	40 (17.9)	117 (17.8)	
Cancer stage[c]			.003
IIA/IIB	52 (23.3)	94 (14.2)	
III	56 (25.1)	159 (24.1)	
IVA/IVB	115 (51.6)	408 (61.7)	
Cancer site			<.0001
Hypopharynx and larynx	32 (14.3)	106 (16.0)	
Lip and oral cavity	62 (27.8)	88 (13.3)	
Nasopharynx	45 (20.2)	95 (14.4)	
Oropharynx	84 (37.7)	362 (54.8)	
Salivary gland	0 (0)	10 (1.5)	
Cisplatin chemotherapy + radiation	76 (34.1)	292 (44.2)	.008
Any radiation	134 (60.1)	461 (69.7)	.008
Radiation alone	39 (17.5)	114 (17.3)	.93
Any surgery	96 (43.1)	270 (40.9)	.56
Surgery alone	47 (21.1)	101 (15.3)	.05

Abbreviation: CCI, Charlson Comorbidity Index.
[a]*P* values are based on the chi-square test.
[b]A lower income census tract was defined as a median neighborhood income less than $60,000.
[c]American Joint Committee on Cancer system, seventh edition.

the cumulative incidence of cancer-specific death was higher for women than men, but women had a lower rate of competing mortality in comparison with men (Fig 2A,B); 2) the ratio or difference of cancer death to noncancer death was greater for women; and 3) women were less likely to receive intensive treatment than men. Taken together, these findings indicate that women with HNC in our cohort appear to be undertreated. Our findings also provide support for the use of GCE analysis to identify disparities in the care of patients with cancer.

Our findings on GCE analysis accounted for established risk factors, including age, site of the primary tumor, surgical treatment, and comorbidities. The ω^+ ratio (ie, ω^+ for women over ω^+ for men) was approximately 2 times higher for women in comparison with men, and this finding indicates an increased hazard of cancer death along with a concurrent decreased hazard of noncancer death, regardless of the primary cancer location.

Our finding that fewer women received intensive therapy in comparison with men remained significant even though we controlled for age, site of the primary tumor, surgical treatment, comorbidities, stage, smoking history, and alcohol history. Thus, when we controlled for each of these factors, women had higher cancer-specific mortality and lower competing mortality in comparison with men, and this signified undertreatment. Similar sex disparities in treatment have been reported for other types of cancer, including bladder cancer,[32] pancreatic cancer,[33] kidney cancer,[34] colon cancer,[35] and lymphoma.[36] Regarding the undertreatment of women with HNC, we hypothesize that other unmeasured factors, including an implicit physician bias and variation in patient treatment goals, may contribute to the lower utilization of intensive therapy that we observed.

Unlike prior studies that evaluated sex disparities in HNC mortality,[11,19-23] our study examined the ratio of cancer mortality to noncancer mortality. In addition, our data source, the KNPC database, is advantageous because it has a large, diverse patient population with demographic characteristics similar to those of the larger California community with respect to age, sex, and ethnicity.[29] In contrast, data from clinical trials have less treatment variation, and comorbidity data are typically lacking; SEER-Medicare data are age-skewed and not representative of the overall population; the SEER database lacks sufficient treatment detail, progression, and comorbidity data; the National Cancer Database lacks cause-specific outcomes; the Veterans Affairs database has few women; and single-institution databases often have limited sample sizes, which constrain power for competing event analyses. This lends insight into why other analyses that examine only composite endpoints, such as progression-free survival or overall survival, can easily overlook health disparities when they exist: as shown in Figure 2, although the overall probability of either cancer events or competing events could be similar between groups, their ratio could be quite different.

We acknowledge several limitations of our study. This was a retrospective, observational analysis. There were relatively few noncancer deaths in our population, and this potentially affected the stability of the GCE

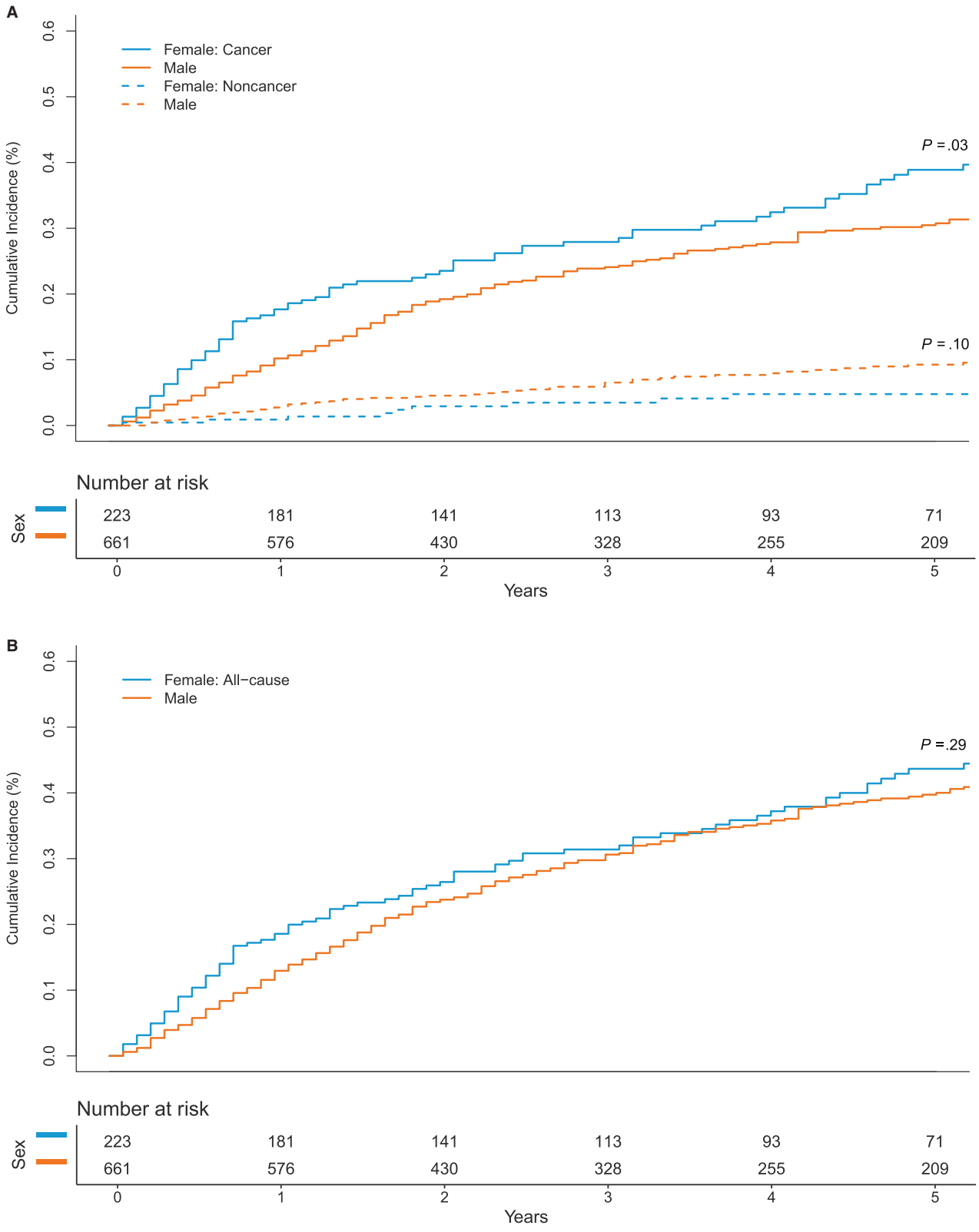

Figure 2. Cumulative incidence of (A) cancer death and noncancer death and (B) all-cause mortality.

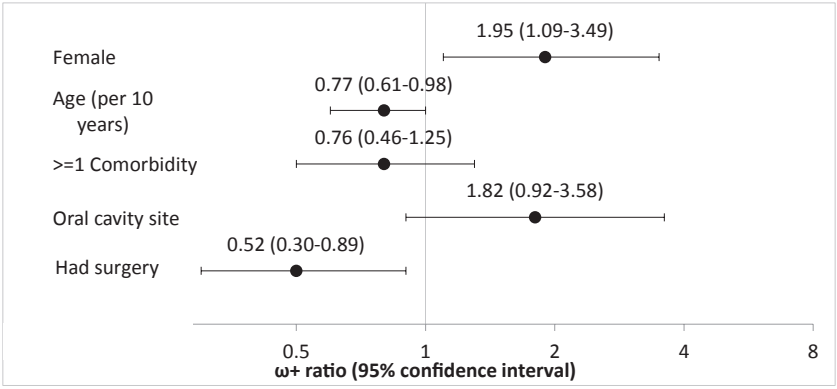

Figure 3. ω^+ ratios comparing between groups.

TABLE 2. Adjusted Odds Ratios of Treatment for Select Covariates

	OR (95% CI)		
Covariate	Cisplatin Chemotherapy + Radiation	Any Radiation	Any Surgery
Women	0.69 (0.48-0.99)	0.79 (0.56-1.12)	1.04 (0.71-1.52)
CCI > 1	0.72 (0.51-1.00)	0.91 (0.65-1.26)	1.09 (0.77-1.54)
Oral cavity site	0.43 (0.23-0.80)	0.32 (0.19-0.52)	9.90 (5.61-17.97)
Age (per 10 y)	0.83 (0.71-0.96)	0.90 (0.77-1.04)	0.69 (0.58-0.82)

Abbreviations: CCI, Charlson Comorbidity Index; OR, odds ratio.

model. The human papillomavirus status and p16 testing for oropharyngeal cancers were not available. We did perform an additional analysis stratified by oropharyngeal cancer versus nonoropharyngeal cancer, and the magnitude and direction of the covariate effects, including sex, were all similar, albeit with a power loss due to the sample size (data not shown). In addition, the determination of the cause of death was based on cancer registry data, which are far superior to death certificate data but remain imperfect.

In summary, we applied the GCE model to evaluate a large cohort of patients in Northern California with HNC with the goal of comparing cause-specific survival between women and men, and we found that women with HNC may be undertreated. Further investigation, particularly from large population-level databases, may be able to confirm our findings and verify that our findings are consistent with the greater HNC population as a whole. If corroborated, our study will hopefully inform patients and physicians when they were considering treatment for HNC. Clinicians must remain vigilant when considering treatment options with their patients to avoid withholding potentially curative treatment because of fear of perceived harms in the face of evidence demonstrating that women may be undertreated.

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CONFLICT OF INTEREST DISCLOSURES

The authors made no disclosures.

AUTHOR CONTRIBUTIONS

Annie Park: Design and implementation of the research, analysis of the results, and writing of the manuscript. **Amy Alabaster:** Design and implementation of the research, analysis of the results, and writing of the manuscript. **Hanjie Shen:** Design and implementation of the research, analysis of the results, and writing of the manuscript. **Loren K. Mell:** Design and implementation of the research, analysis of the results, and writing of the manuscript. **Jed A. Katzel:** Design and implementation of the research, analysis of the results, and writing of the manuscript.

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