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Noncancer-Related Health Events and Mortality in Head and Neck Cancer Patients After Definitive Radiotherapy

A Prospective Study

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Abstract: The survival of patients with head and neck squamous cell carcinoma (HNSCC) can be affected not only by progression of the original cancer or occurrence of a second cancer but also by noncancer health event (NCHE). In this study, we evaluated the prognostic significance of early NCHEs in HNSCC patients after definitive radiotherapy (RT) or chemoradiotherapy (CRT).

The prospective study cohort comprised 190 HNSCC patients who underwent definitive RT (n = 75) or CRT (n = 115). An early NCHE was defined as an event requiring hospital readmission of the patient within 12 months after treatment. Univariate and multivariate analyses were performed to identify clinicopathologic factors associated with early NCHEs, and competing and all-cause mortalities.

Thirty-three patients suffered an NCHE (17.3%) and 8 succumbed to a competing cause of mortality (4.2%). Twenty-two (11.6%) patients had an early NCHE: respiratory (22.8%), cerebrovascular (13.7%), gastrointestinal (13.7%), and others (50.0%). In multivariate analysis, hypoalbuminemia ($P = 0.022$, hazard ratio [HR] = 3.66, 95% confidence interval [CI] = 1.21–11.1), chemotherapy ($P = 0.047$, HR = 3.02, 95% CI = 1.01–8.98), and tumor recurrence ($P = 0.024$, HR = 2.66, 95% CI = 1.14–6.22) were independent predictors of an early NCHE. Patients with early NCHEs were at high risk of competing mortality ($P < 0.001$, HR = 22.6, 95% CI = 4.21–121.00) and all-cause mortality ($P = 0.002$, HR = 4.44, 95% CI = 1.76–11.2).

Early NCHEs are a major contributor to competing and all-cause mortality in HNSCC patients receiving RT or CRT. The risk factors identified could be used to predict early NCHEs.

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Abbreviations: CRT = chemoradiotherapy, HNSCC = head and neck squamous cell carcinoma, NCHE = noncancer health event, RT = radiotherapy.

INTRODUCTION

More than half a million cases of head and neck cancer are diagnosed worldwide each year, making it the eighth most common cancer.[1] Recent advances in the diagnosis and treatment of head and neck squamous cell carcinoma (HNSCC) have mainly focused on the control of the presenting primary (index) cancer.[2] This has brought a slight improvement in overall survival.[3] Although improvement in disease control using the multimodal approach of combined chemoradiotherapy (CRT) has decreased cancer mortality, it has increased the risk of competing mortality in HNSCC patients.[4–6] Overall survival of HNSCC patients can be affected by competing events causing death, as well as by the progression of the index cancer or of a second cancer. Therefore, a better understanding of risk factors for competing mortality could lead to an improved overall survival.

Multiple factors have been suggested to affect the risk of competing mortality in HNSCC. A recent population-based study showed that increasing age, male sex, black race, unmarried status, localized disease, higher socioeconomic status, advanced stage, and nonsurgical treatment are closely associated with increased noncancer-related deaths among these patients.[7] This also suggested that grouping patients according to competing risk would simultaneously provide stratification for risk of all-cause mortality. Furthermore, an impending competing mortality might be predicted from noncancer-associated morbidities that develop after treatment.[8] An elevation in the rate of competing mortality could be caused by the development of competing noncancer health events (NCHEs), defined as readmission after treatment for HNSCC due to noncancer-related causes.[8] An NCHE can also be predicted by several risk factors, such as comorbidity, advanced stage disease, tumor recurrence, and occurrence of a second primary cancer (SPC).[8,9] In particular, respiratory NCHEs are strongly associated with competing mortality in HNSCC.[9]

The incidence of NCHEs and competing mortality is known to increase in patients who undergo nonsurgical treatment, including chemotherapy.[6,9] To evaluate the prognostic significance of early NCHEs (those that required hospital readmission of the patient within 12 months after treatment) in HNSCC patients after definitive radiotherapy (RT) or CRT, we prospectively observed the incidence of NCHEs and cause of death. We hypothesize that early NCHEs after definitive

treatments are major contributors to competing mortality in HNSCC patients and predict survival outcomes in patients with HNSCC. In this study, we evaluated the relationship between early NCHEs and competing and all-cause mortalities in HNSCC patients after definitive RT or CRT, and sought to find predictors of early NCHEs.

METHODS

Patients

A total of 190 patients with head and neck cancer met the inclusion criteria at our tertiary referral center between 2010 and 2013. The inclusion criteria were age >18 years; previously untreated, pathologically proven SCC arising in the oropharynx, larynx, hypopharynx, and/or nasopharynx; initially treated with RT or CRT and completed the treatment; no distant metastasis at initial presentation; and followed for more than a year after the initial treatment. Data were collected prospectively pretreatment, during treatment, and at follow-up. This study was approved by our institutional review board and informed consent from each patient was obtained.

Patients were treated with definitive RT or CRT according to the consensus of the multidisciplinary head and neck oncology team. The RT was intensity modulated. Radiation was administered in daily fractions of 1.8 or 2.0 Gy 5 days each week for 8 weeks. The total radiation dose per patient was 50 to 77.5 Gy. Concurrent chemotherapy consisted of high-dose cisplatin (75–100 mg/m^2) infused on days 1, 22, and 43 of CRT. Salvage surgery was indicated for patients with progressive or residual disease on primary tumor or neck after RT or CRT.

All patients had physical and endoscopic examinations at every clinic visit after the completion of the initial treatment. The patients were evaluated every 1 to 3 months in the first year, every 2 to 4 months in the second and third year, every 6 months in the fourth and fifth year, and annually thereafter. For suspicious lesions suggestive of recurrence of the index cancer or an SPC, biopsies and additional diagnostic tests were performed. Patients with a confirmed recurrence of the index cancer or with an SPC were scheduled for salvage or palliative treatment. Patients requiring symptom management or with other medical problems were seen more frequently and were hospitalized as necessary.

Definition of NCHEs, Early NCHEs, and Competing Mortality

An NCHE was defined as admission to the hospital after completion of initial treatment for any cause unrelated to the index cancer or an SPC.[8,9] Events that resulted in a visit to the emergency department were not included, and nor were admissions for diagnostic workup. Events were recorded during the period from the end date of initial treatment to the last follow-up date and categorized according to the Common Terminology Criteria for Adverse Events.[10] Treatment-related morbidity requiring lengthened hospitalization during definitive treatment was not considered as an NCHE. The incidence of NCHEs during treatment for recurrent index cancer or for a newly developed SPC was not evaluated. To analyze the risk factors and association with mortality, early NCHEs were defined as those developing within 12 months after the completion of definitive treatment. Competing mortality was defined as death from any cause unrelated to the index cancer or an SPC.

Variables

Variables included patient age and gender, smoking history, alcohol consumption, body mass index (kg/m^2), marital status, educational level, residence, occupation, pretreatment serum hemoglobin, and albumin levels, Karnofsky performance status (KPS), tumor site, differentiation, and clinical tumor-node-metastasis stage of the index cancer, treatment modality, occurrence of tumor recurrence and of an SPC, and performance of salvage surgery. Heavy smokers were defined as those with at least 30 pack-years. One drink was defined as 15.6 mL of pure ethanol (100%).[11] Co-existing morbidity was categorized according to the Charlson comorbidity index.[12]

Statistical Analysis

The χ^2 test and Student *t* test were used to compare patients with and without an NCHE after definitive treatment. Cox-proportional hazards model was used to examine the risk factors of early NCHEs, all-cause mortality and competing mortality according to the categorized values of the tested variables. Multivariate Cox-proportional hazard regression was performed with backward elimination of variables with $P < 0.1$ on univariate analysis. The estimated hazard ratio (HR) and 95% confidence intervals (CI) were calculated. The cumulative incidence probabilities of an NCHE and a noncancer-related death in the presence of other competing risks were calculated using the cumulative incidence function. The estimated cause-specific HR and 95% CI were calculated. A two-sided $P \leq 0.05$ was considered statistically significant. The statistical analyses were performed using SPSS version 21.0 (IBM, Armonk, NY) and R version 3.0.1 (R Project for Statistical Computing, http://www.r-project.org).

RESULTS

The study cohort comprised 164 men and 26 women with a median age of 59 years (range, 20–83 years). The most common site of the primary tumor was the larynx (46.3%), followed by the oropharynx (22.6%), the nasopharynx (22.1%), and the hypopharynx (8.9%). Fifty-six patients (29.5%) had tumors of advanced T3–T4 stage, 84 patients (44.2%) had N1–N3 stage disease, and 94 patients (49.5%) were stage III–IV overall. Fifty-five patients (39.5%) received RT, 115 patients (60.5%) underwent CRT, and 37 patients (19.5%) underwent salvage surgery after RT or CRT.

An NCHE developed in a total of 33 (17.4%) patients at a median time of 6 months (range, 0–59 months) after treatment. Of the 33 patients, 22 (66.7%) had early NCHEs that developed within 12 months after treatment. The characteristics of the patients with and without an NCHE were compared and the results are shown in Table 1. The KPS and serum albumin level were lower in the NCHE group than in the no NCHE group ($P \leq 0.05$). The other variables were comparable between the 2 groups.

The median follow-up period of survivors was 39 months (range, 20–65 months). During the follow-up period, 11 patients (5.8%) died from the index cancer, and 12 patients (6.3%) died of noncancer-related causes; none died from an SPC. Local, regional, and distant failures occurred in 30 (15.8%), 24 (12.6%) and 8 (4.2%) patients, respectively. An SPC developed in 10 (5.3%) patients. Posttreatment recurrence was higher in the NCHE group than the no NCHE group (60.6% vs 19.7%, $P < 0.001$). The 3-year cumulative incidence of the index cancer event and of a NCHE was 27.3% and 15.7%, respectively (Figure 1). The 3-year cumulative incidence of

TABLE 1. Characteristics of Patients With or Without NCHE (n = 190)

Characteristics	NCHE N (%)	No NCHE N (%)	*P*
Total number of patients	33 (17.4)	157 (82.6)	
Age, median (range), y	58 (27–79)	59 (20–83)	0.567
Sex, M/F	28/5 (84.8/15.2)	136/21 (86.6/13.4)	0.787
Smoking, pack-years			0.938
Never or <30/≥30	20/13 (60.6/39.4)	94/63 (60.0/40.0)	
Active smoking	18 (54.5)	77 (49.0)	
Alcohol drinking			0.341
Never or social/heavy	28/5 (84.8/15.2)	142/15 (90.4/9.6)	
Active drinking	21 (63.6)	94 (60.0)	
Median BMI (range), kg/m^2	23.5 (17.9–30.9)	23.1 (11.1–32.0)	0.829
Marital status at detection			0.845
Single or divorced	2 (6.1)	11 (7.0)	
Married	31 (93.9)	146 (93.0)	
Education level			0.564
High school or less	21 (63.6)	108 (68.8)	
College or more	12 (36.4)	49 (31.2)	
Hypoalbuminemia, g/dL			0.050
≥3.5	29 (87.9)	152 (96.8)	
<3.5	4 (12.1)	5 (3.2)	
KPS			0.045
100	23 (69.7)	120 (76.4)	
80–90	6 (18.2)	33 (21.0)	
≤70	4 (12.1)	4 (2.5)	
Charlson comorbidity index			0.120
0	19 (57.6)	112 (71.3)	
≥1	14 (42.4)	45 (28.7)	
Tumor location			0.635
Oropharynx	9 (27.3)	34 (21.7)	
Larynx	15 (45.5)	73 (46.5)	
Hypopharynx	4 (12.1)	13 (8.3)	
Nasopharynx	5 (15.2)	37 (23.6)	
Histological differentiation			0.160
G1/G2/G3/G0	5/19/7/2 (15.2/57.6/21.2/6.1)	25/97/34/1 (15.9/61.8/21.7/0.6)	
TNM stage			
T1/T2/T3/T4	10/7/10/6 (30.3/21.2/30.3/18.2)	75/42/22/18 (47.8/26.8/14.0/11.5)	0.059
N0/N1/N2/N3	14/5/14/0 (42.4/15.2/42.4/0)	92/23/39/3 (58.6/14.6/24.8/1.9)	0.177
Overall I/II/III/IV	5/5/9/14 (15.2/15.2/27.3/42.4)	55/31/23/48 (35.0/19.7/14.6/30.6)	0.058
Initial definitive treatments			
RT alone	11 (33.3)	64 (40.8)	0.427
CRT	22 (66.6)	93 (59.2)	
Salvage surgery after RT or CRT	14 (42.4)	23 (14.6)	<0.001
Follow-up			
Last status, NED/AD/DOD/DOC	19/3/3/8 (57.6/9.1/9.1/24.2)	139/6/8/4 (88.5/3.8/5.1/2.5)	<0.001
Median time to follow-up (range), mo	39.3 (20–65)	38.1 (18–65)	
Tumor recurrence, L/R/D	14/11/3 (42.4/33.3/9.1)	16/13/5 (10.2/8.3/3.2)	<0.001
SPC, yes/no	1/32 (3.0/97.0)	9/148 (5.7/94.3)	0.527

AD = alive with disease, BMI = body mass index, CRT = concurrent chemoradiotherapy, D = distant metastasis, DOC = died of other causes, DOD = died of disease, G1/G2/G3/G0 = well/moderate/poorly/undetermined, KPS = Karnofsky performance status, L = local recurrence, NCHE = noncancer health event, NED = no evidence of disease, R = regional recurrence, RT = radiotherapy, SPC = second primary cancer, TNM = clinical tumor-node-metastasis stage (AJCC, 7th ed.).

all-cause and competing mortalities was 9.4% and 4.5%, respectively.

Early NCHEs and Noncancer-Related Deaths

The causes of early NCHEs and noncancer-related deaths are summarized in Supplementary Table S1, http://links.lww.com/MD/A975. Early NCHEs occurred in 22 patients. The most common early NCHEs were from respiratory (n = 5, 22.8%), cerebrovascular (n = 3, 13.7%), and gastrointestinal (n = 3, 13.7%) causes. The most common respiratory and gastrointestinal problems were pneumonia (18.2%) and dysphagia (9.1%), respectively. Major causes of the

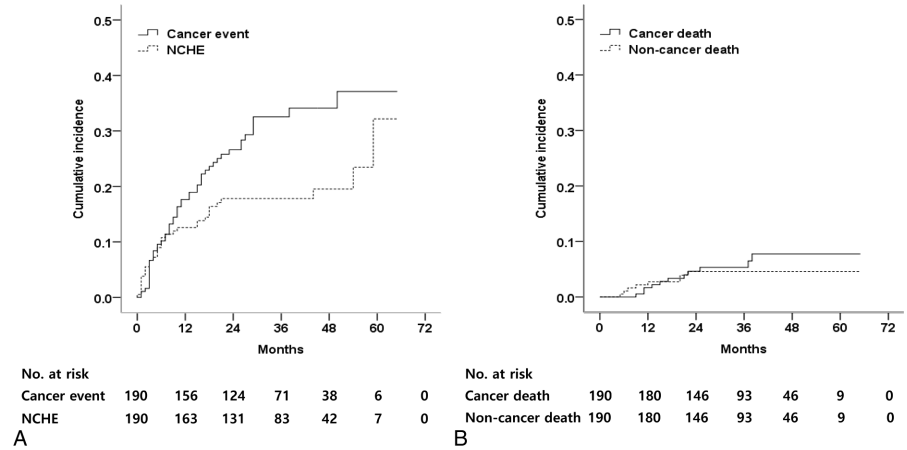

FIGURE 1. Cumulative incidence of (A) cancer events and NCHEs, and (B) index cancer and competing mortalities. An NCHE was defined as hospital readmission due to noncancerous causes after definitive treatment. Competing mortality represents mortality from causes other than the index or second primary cancer. NCHEs = noncancer health events.

noncancer-related deaths were cerebrovascular (n = 3, 37.5%) and respiratory (n = 2, 25.0%) episodes.

Risk Factors of Early NCHEs

In univariate analyses, hypoalbuminemia (<3.5 g/dL), locally advanced tumor (stage T3–T4), positive nodal disease, advanced overall stage (III–IV), chemotherapy, and tumor recurrence were significantly associated with the occurrence of early NCHEs ($P < 0.05$ for each factor; Table 2). Multivariate analysis revealed that hypoalbuminemia ($P = 0.022$, HR = 3.66, 95% CI = 1.21–11.1), chemotherapy ($P = 0.047$, HR = 3.02, 95% CI = 1.01–8.98), and tumor recurrence ($P = 0.024$, HR = 2.66, 95% CI = 1.14–6.22) were independent predictors of development of an early NCHE.

Risk Factors for Competing and All-Cause Mortalities

Table 3 and Supplementary Table S2, http://links.lww.com/MD/A975 show the results of univariate and multivariate analyses for competing mortality and all-cause mortality. The univariate analyses revealed that KPS ($P = 0.013$), tumor recurrence ($P = 0.007$), salvage surgery ($P = 0.008$), and an early NCHE ($P < 0.001$) were significantly associated with competing mortality. In multivariate analysis, patients with an early NCHE were at a higher risk of competing mortality ($P < 0.001$, HR = 22.6, 95% CI = 4.21–121.00; Figure 2). The univariate analyses showed that tumor recurrence ($P < 0.001$), salvage surgery ($P < 0.001$), and an early NCHE ($P < 0.001$) were significantly associated with all-cause mortality. Patients with an early NCHE had an increased all-cause mortality rate ($P = 0.002$; HR = 4.44; 95% CI = 1.76–11.2).

DISCUSSION

Our study has shown that early NCHEs play a central role in increasing both competing and all-cause mortalities. Two-thirds of patients with an NCHE developed it within 12 months after definitive RT or CRT. Adverse effects from chemotherapy or RT can occur in both early and late phases after treatment. The head and neck encompass vital anatomy associated with functions critical for daily life, such as breathing, speaking, and swallowing. Despite recent advances in RT techniques, oral mucositis, oedema, xerostomia, and necrosis significantly affect the vital functions of the upper aerodigestive tract, causing dysphasia and aspiration.[13,14] In addition, side effects of platinum-containing anticancer agents are well known in the oral and pharyngeal mucosa as well as in the kidneys, gastrointestinal tract, immune system, peripheral nerves, and inner ear.[15] Treatment-associated acute or late complications and comorbidities will contribute to deaths, and therefore reducing treatment toxicity is a major goal in the management of HNSCC.[16–19] In addition, adverse effects appear to be more significant within a year of completing such nonsurgical treatments, potentially causing an increase in NCHEs. This is in line with the results of previous studies showing that nonsurgical treatment is an important risk factor for competing mortality.[6,9] NCHEs are reported to be the major cause of noncancer-related deaths,[8,9] and furthermore, our study emphasizes the clinical importance of early NCHEs in HNSCC patients who undergo the nonsurgical treatments of definitive RT or CRT.

A previous study showed that competing mortality may be affected by multiple factors, such as age, sex, race, marital status, socioeconomic status, tumor site and stage, and treatment modality.[7] We have previously shown the role of the NCHE in the development of competing mortality after definitive treatments.[8,9] Significant associations between comorbidities, tumor recurrence, respiratory NCHE, and noncancer-related deaths were shown in a retrospective study of patients with advanced HNSCC arising in the oral cavity, oropharynx, larynx, and/or hypopharynx.[9] One or more comorbidity, tumor recurrence, and occurrence of a second cancer were independent predictors of both NCHEs and noncancer-related mortality in the cohort. The results of the present study also suggested that tumor recurrence and early NCHEs were important risk factors in all-cause mortality. Performance status and salvage surgery were significantly associated with both competing and all-cause mortalities; however, this was only by univariate, not multivariate analysis. This may be explained by the differences in treatment modality, stage, and site of the tumor of the included patients.

Reliable prediction of NCHEs may identify patients at risk and improve competing mortality rates. If patients at risk of an NCHE receive close surveillance during and after treatment, such efforts may lessen the number of deaths from noncancer-related causes. That the early NCHE is closely associated with increased competing and all-cause mortalities indicates that it is

TABLE 2. Univariate and Multivariate Analyses of Risk Factors for an Early Noncancer Health Event After Treatment (n = 190)

	Univariate			Multivariate		
Variable	**HR**	**95% CI**	***P***	**HR**	**95% CI**	***P****
Age, y						
<60	1					
≥60	0.84	0.36–1.93	0.674			
Gender, male/female						
Male	1					
Female	1.00	0.30–3.38	0.999			
Smoking, pack-years						
<30	1					
≥30	1.08	0.46–2.52	0.864			
Alcohol drinking						
Never or social	1					
Heavy	0.82	0.19–3.52	0.793			
BMI, kg/m^2						
≥20	1					
<20	0.924	0.27–3.12	0.898			
Marital status						
Married	1					
Single or divorced	0.63	0.08–4.66	0.648			
Educational level						
High school or less	1					
College or more	1.84	0.79–4.26	0.155			
Residence						
Rural	1					
Urban	1.12	0.47–2.67	0.799			
Occupation						
No	1					
Yes	1.17	0.48–2.87	0.734			
Hemoglobin, g/dL						
≥11.0	1					
<11.0	1.26	0.17–9.34	0.824			
Hypoalbuminemia, 3.5 g/dL						
≥3.5	1			1		
<3.5	5.27	1.78–15.6	0.003	3.66	1.21–11.1	0.022
KPS						
≥80	1					
<80	2.47	0.58–10.6	0.224			
Charlson comorbidity index						
0	1					
≥1	0.85	0.33–2.17	0.730			
Tumor location						
Oropharynx	1		0.685			
Larynx	0.65	0.23–1.88	0.428			
Hypopharynx	1.41	0.35–5.65	0.626			
Nasopharynx	0.86	0.26–2.82	0.802			
Tumor differentiation						
Well or moderately	1		0.997			
Poorly	1.04	0.38–2.81	0.944			
T-classification						
T1–T2	1			1		
T3–T4	2.15	0.93–4.97	0.074	1.24	0.45–3.43	0.686
N-classification						
N0	1		0.064	1		0.764
N1	2.94	0.93–9.27	0.065	1.58	0.43–5.86	0.493
N2–N3	2.92	1.11–7.67	0.030	1.13	0.30–4.18	0.858
Overall TNM stage						
I–II	1			1		
III–IV	3.00	1.18–7.68	0.022	1.63	0.56–4.78	0.374

	Univariate			Multivariate		
Variable	**HR**	**95% CI**	***P***	**HR**	**95% CI**	***P****
Initial treatment						
RT	1			1		
CRT	3.22	1.09–9.53	0.034	3.02	1.01–8.98	0.047
Tumor recurrence						
No	1			1		
Yes	2.89	1.25–6.68	0.013	2.66	1.14–6.22	0.024
Salvage surgery						
No	1					
Yes	1.93	0.79–4.73	0.152			
Second primary cancer						
No	1					
Yes	0.94	0.13–6.96	0.949			

BMI = body mass index, CI = confidence interval, CRT = concurrent chemoradiotherapy, HR = hazard ratio, KPS = Karnofsky performance status, NCHE = noncancer health event, RT = radiotherapy.
*Cox-proportional hazard regression analyses were performed with backward elimination from variables with $P < 0.1$ on univariate analyses.

during the 12 months after treatment that the patient most requires surveillance. Our study showed that hypoalbuminemia, chemotherapy combined with RT, and tumor recurrence were independent factors predictive of an early NCHE. As albumin concentrations are primarily determined by body cell mass and systemic inflammatory reactions in cancer patients with weight loss, the progressive loss of vital body protein components may be the cause of death in patients with cancer.[20] Serum albumin, a marker of malnutrition, is easily measurable and can be used to predict survival in patients with cancers treated with RT or chemotherapy.[21,22] However, the prognostic significance of pretreatment hypoalbuminemia as a predictor of an NCHE or competing mortality has not been studied in head and neck cancer patients. Our present analyses suggest that hypoalbuminemia is an important factor predictive of an early NCHE in HNSCC patients receiving definitive RT or CRT. Furthermore, as a clinical factor affecting NCHEs, patients with index HNSCC recurrence are more likely to experience aggravation by other noncancer competing disease and by the toxic effects of treatments for recurrence. This could

TABLE 3. Univariate and Multivariate Analyses of Risk Factors for Competing Mortality and All-Cause Mortality After Treatment (n = 190)

	Competing Mortality						All-Cause Mortality					
	Univariate			Multivariate			Univariate			Multivariate		
Variable	**HR**	**95% CI**	***P***	**HR**	**95% CI**	***P****	**HR**	**95% CI**	***P***	**HR**	**95% CI**	***P****
Marital status at detection												
Married	1			1			1					
Single or divorced	4.53	0.91–22.4	0.064	5.38	0.97–29.7	0.054	1.68	0.39–7.27	0.489			
Overall TNM stage												
I–II	1					1			1			
III–IV	1.83	0.44–7.66	0.409			2.47	0.94–6.51	0.067	1.58	0.57–4.39	0.378	
KPS												
≥80	1			1			1					
<80	7.53	1.52–37.3	0.013	2.09	0.17–26.0	0.567	2.69	0.62–11.6	0.186			
Tumor recurrence												
No	1			1			1			1		
Yes	9.01	1.82–44.7	0.007	4.30	0.80–23.2	0.090	26.9	6.21–116	<0.001	22.3	5.10–97.6	<0.001
Salvage surgery												
No	1			1			1			1		
Yes	7.04	1.68–29.5	0.008	1.52	0.17–13.9	0.711	7.51	2.95–19.1	<0.001	0.93	0.32–2.66	0.888
Early NCHE												
No	1			1			1			1		
Yes	26.8	5.40–133	<0.001	22.6	4.21–121.00	<0.001	7.12	2.86–17.7	<0.001	4.44	1.76–11.2	0.002

CI = confidence interval, HR = hazard ratio, KPS = Karnofsky performance status, NCHE = noncancer health event, TNM = clinical tumor-node-metastasis stage.
*Cox-proportional hazard regression analyses were performed with backward elimination from variables with $P < 0.1$ on univariate analyses.

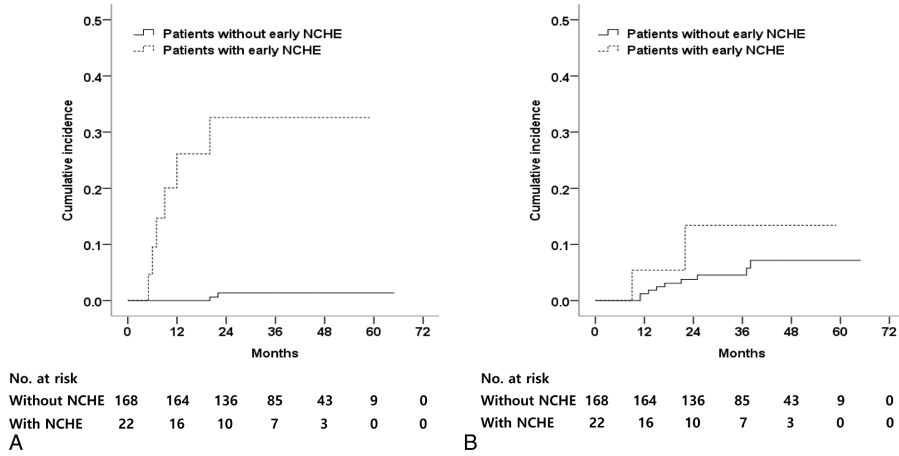

FIGURE 2. Cumulative incidence comparing (A) competing mortality and (B) all-cause mortality between patients with and without an early NCHE. NCHE = noncancer health event.

explain the association between tumor recurrence and NCHEs and all-cause mortality.

Our study has several limitations, including the variety of tumor sites among the cohort and a follow-up period of <5 years. The primary tumor location may affect metastatic potential, the natural course of the disease, clinical behavior, and the delineation of RT fields. Eighty-five of the 190 study patients (44.7%) had oropharyngeal or nasopharyngeal carcinomas, sites commonly associated with a viral etiology (human papilloma virus [HPV] or Epstein-Barr virus) and favorable survival outcomes.[23–25] In addition, a considerable number of patients (50.5%) were in early stages (I–II). Overall, these characteristics could explain the relatively favorable survival outcomes in our patient cohort. Data on p16 and HPV status were only obtained for some patients, we were therefore unable to analyze the utility of these biomarkers.[26] To confirm the results of the present study, a longer follow-up period recording NCHEs and cause of death is now required. The present study included a relatively large cohort of patients with HNSCC who underwent definitive RT or CRT, and the results could help clinicians to identify patients with risk factors for an early NCHE and thereby decrease rates of all-cause mortality.

In conclusion, our study showed that early NCHEs are a major contributor to competing and all-cause mortality in HNSCC patients receiving RT or CRT. The risk factors hypoalbuminemia, chemotherapy, and tumor recurrence predict an early NCHE. Our results may be used to help identify patients at risk and who will need close surveillance and supplementation to lessen the chances of succumbing to a competing mortality.

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