Noncancer health events as a leading cause of competing mortality in advanced head and neck cancer

M. Kwon1, J.-L. Roh1*, J. Song2, S.-W. Lee3, S.-B. Kim4, S.-H. Choi1, S. Y. Nam1 & S. Y. Kim1,5

Departments of 1Otolaryngology; 2Clinical Epidemiology and Biostatistics; 3Radiation Oncology; 4Internal Medicine (Oncology), Asan Medical Centre, University of Ulsan College of Medicine, Seoul; 5Biomedical Research Institute, Korea Institute of Science and Technology, Seoul, Republic of Korea

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Background: The survival of patients with head and neck squamous cell carcinoma (HNSCC) can be affected by noncancer health events (NCHE) as well as by index cancer progression and second primary cancer (SPC). This study aimed to investigate the risk factors for NCHE and noncancer mortality (NCM) in patients with advanced-stage HNSCC.

Patients and methods: This cohort study involved 600 consecutive patients with overall stage III to IV HNSCC who were treated between 2001 and 2010 at our tertiary referral hospital. NCHE was defined as re-admission (i.e. after the primary treatments for the index tumors) due to noncancer-related causes. The incidences of NCHE and NCM and their risk factors were analyzed by using cumulative incidence and cause-specific hazard functions.

Results: During a median follow-up period of 54 months, 224 (37.3%) and 55 (9.2%) of the 600 patients had NCHE and NCM, respectively. The 5-year index cancer mortality, SPC mortality, and NCM rates were 23.8%, 4.2%, and 8.9%, respectively. Multivariate analyses revealed that body mass index <20 kg/m² (P=0.018), Charlson comorbidity index (CCI) ≥ 2 (P=0.001), tumor recurrence (P<0.001), SPC occurrence (P=0.001), and initial chemotherapy (P=0.049) were independent NCHE predictors. Older age (P<0.001), CCI ≥ 1 (P=0.008), tumor recurrence (P<0.001), and SPC occurrence (P=0.047) were independent NCM predictors. Patients with respiratory NCHE were at a higher risk of NCM than patients with other NCHE types (P<0.001).

Conclusions: One or more comorbidities, tumor recurrence, and SPC occurrence were independent predictors of both NCHE and NCM. Patients with respiratory NCHE had a particularly high risk of NCM.

Key words: head and neck squamous cell carcinoma, noncancer health event, comorbidities, competing mortalities, risk factors

introduction

The survival of patients with head and neck squamous cell carcinoma (HNSCC) is largely dictated by the progression or recurrence of the index cancer [1, 2]. However, in recent decades, competing mortality has been recognized to also significantly affect the overall survival of patients with HNSCC [1–4]. Although recent advances in the diagnosis and treatment of HNSCC have slightly improved survival [5, 6], the overall survival of patients with HNSCC could be improved further by a better understanding of the risk factors for competing mortality, as this knowledge could improve the...
identification of at-risk patients and the provision of adequate interventions.

The factors that promote competing mortality in HNSCC cases include the same factors that induce morbidity and mortality in the general population (e.g. patient comorbidities). However, patients with HNSCC may also be more prone to other competing mortality factors, including second primary cancers (SPC) that are present at the initial diagnosis or develop during follow-up [2]. Factors relating to the index cancer and oncological treatments are also likely to increase the competing mortality risk of patients with HNSCC. For example because HNSCC occurs at sites that are critical for breathing and feeding, the cancer itself, the cancer treatments, and/or the treatment-related complications could induce serious functional impairment, particularly in advanced-stage HNSCC [3]. This impairment could result in competing noncancer health events (NCHE) that could in turn elevate the rate of cancer-unrelated death in patients with HNSCC.

Ryu et al., who coined the term NCHE [7], carried out the only study to date on the risk factors for NCHE in patients with HNSCC. They showed that patients with comorbidities and stage III/IV disease may be at higher risk of NCHE [7]. The current large cohort study was carried out to identify the risk factors for NCHEs and noncancer mortality (NCM) in patients with advanced-stage HNSCC. The main NCHE responsible for noncancer death in these patients was also sought. The results of this study may help clinicians to identify, early after diagnosis, those patients who are at particular risk of NCHE and subsequent NCM.

patients and methods

patients

The medical records of all patients who were diagnosed and treated for advanced-stage HNSCC at our tertiary referral hospital between January 2001 and December 2010 were reviewed after retrieval from the hospital cancer registry. Of these patients, 600 met all of the inclusion criteria and none of the exclusion criteria (supplementary Figure S1, available at Annals of Oncology online). The inclusion criteria were (i) age >18, (ii) previously untreated, pathologically proven SCC arising in the oral cavity, oropharynx, larynx, and/or hypopharynx, (iii) overall stage III or IV in accordance with the American Joint Committee on Cancer tumor-node-metastasis (TNM) staging system [8], (iv) no distant metastasis (DM) at initial presentation, and (v) followed for more than 1 year after the initial treatment. This study was approved by the institutional review board of our hospital and informed consent from each patient was waived.

treatments

Tumors were initially treated by primary curative surgery or radiotherapy (RT) with/without chemotherapy, or their combinations. Induction chemotherapy (IC) consisted of two or three 21-day cycles composed of cisplatin (100 mg/m²) on day 1 and 5-fluorouracil (100 mg/m²) on days 1–4 or TS-1 (40–60 mg twice daily) on days 1–14, or docetaxel (75 mg/m²) on day 1, followed by cisplatin (75 mg/m²) on day 1 and 5-fluorouracil (750 mg/m²) on days 1–4. Concurrent chemoradiotherapy (CRT) or RT followed IC. RT consisted of intensity-modulated or 3D conformal radiation and started within 6 weeks of the last cycle of IC. Radiation was administered in daily fractions of 1.8 or 2.0 Gy 5 days each week for 8 weeks. The total radiation dose for the patients was 57–80 Gy. Concurrent chemotherapy consisted of high-dose cisplatin (75–100 mg/m²) infused on days 1, 22, and 43 of CRT. Salvage surgery was indicated for patients with progression of primary tumors after IC or residual diseases on the primary site or neck after RT or CRT.

follow-up

All patients underwent physical and endoscopic examinations at every clinic visit after the completion of the initial treatments. The patients were evaluated every 1–3 months in the first year, every 2–4 months in the second and third year, every 6 months in the fourth and fifth year, and annually thereafter [9]. Any lesions suggestive of recurrences or SPCs were confirmed by biopsies and specific additional diagnostic tests. Patients with confirmed recurrence or SPC were scheduled for salvage or palliative treatment. Patients who had troubling symptoms or medical problems initiated extra visits; whether to be hospitalized was decided by the treating physicians.

definition of NCHE

NCHE was defined as admission to the hospital after the initial treatments for any cause that did not directly relate to the index cancer or a newly developed SPC [7]. Events that resulted in emergency room visits but did not result in hospital admission were not included along with admissions for diagnostic evaluation. The events were categorized according to the Common Terminology Criteria for Adverse Events (CTCAE, version 4.0) [10]. The causes and incidences of post-treatment noncancer-associated morbidities were analyzed. Treatment-related morbidity requiring prolonged hospitalization during the initial HNSCC treatments was not considered to be a NCHE. However, the noncancer-related morbidities that arose during recurrent tumor treatment and required admission were considered to be NCHEs and their incidences were calculated. Noncancer-associated mortality was defined as death from any cause that bore no definite relationship to the index cancer or an SPC [3, 4]. Causes of death were determined by assessing the clinical data, phone calls to the patients’ families, and/or reviews of the national databases. A NCHE was defined as the initial occurrence of either noncancer-associated morbidity or mortality.

variables

The data obtained from the medical records included patient age and gender, the site and TNM stage of the primary tumor, and the underlying comorbidities, smoking status, alcohol consumption, initial body mass index (BMI, kg/m²), educational level, occupation, residence, religion, and initial treatment modalities. Heavy smokers were defined as those with ≥50 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 (CCI) [12]. Patient age at the time of diagnosis was converted to 10-year categorical intervals. The patients who were planned to undergo surgery with/without IC as the initial definitive treatment were allocated to the surgery group. The patients who were initially planned to undergo nonsurgical treatments were allocated to the nonsurgical group. The patients were also divided into two other groups according to whether they were treated with chemotherapy or with IC.

statistical analysis

The cumulative incidence functions were used to calculate the cumulative incidence probabilities of NCHE and noncancer deaths in the presence of other competing risks [13]. To identify predictors of NCHEs or noncancer deaths, the cause-specific proportional hazards model was used based on the cause-specific hazard function that represents the instantaneous rate of failures of a specific type at time t given the x(t), covariate, and in the presence of all other failure types [13]. Since the status of some covariates (e.g. cancer recurrence or SPC) changed during the follow-up period, the proportional hazards model was used for the time-varying covariates. To evaluate main
NCHE responsible for noncancer death, a subgroup analysis was conducted by comparing respiratory NCHE to other NCHE types and time to events were from the first day of NCHE occurrence to the day of death or the last follow-up. The estimated cause-specific hazard ratio (HR) and 95% confidence intervals (CI) were calculated. R version 3.0.1 (R Project for Statistical Computing, http://www.r-project.org) and package ‘cmprsk’ and ‘survival’ in R were used. A two-sided P value of <0.05 was considered to indicate statistical significance.

results

patient characteristics

The characteristics of the 600 eligible patients with advanced-stage HNSCC are summarized in supplementary Table S1, available at Annals of Oncology online. Of 600 patients, 103 (17.2%) had one or more comorbidities at the time of index tumor diagnosis. The primary tumors were most frequently located in the larynx (n = 240). Of the 600 patients, 373 (62.2%) were in the T3–4 stage, 446 (74.3%) were in the positive nodal stage, and 446 (74.3%) were in the overall stage IV. Primary surgery was carried out in 371 patients (61.8%) and primary nonsurgical treatments were carried out in the remaining 229 patients (38.2%). Chemotherapy was carried out in a total of 295 (49.2%) patients; of these, 236 underwent IC.

The median follow-up duration for survivors was 54 (range, 12–136) months. During follow-up, 123 patients (20.5%) died of the index cancer, 25 (4.2%) died of SPCs, and 55 (9.2%) died of noncancer causes. The 2- and 5-year overall survival rates were 83.3% and 63.2%, respectively. After index HNSCC treatment completion, locoregional failure (LRF) and DM were observed in 134 (22.3%) and 88 (14.7%) patients, respectively. Cancer events, defined as LRF and/or DM, were observed in 189 (31.5%) patients. The 2- and 5-year cumulative incidence probabilities of index cancer events were 24.5% and 33.8%.

Figure 1. Cumulative incidence functions of events and deaths. (A–C) Cumulative incidence curves of cancer events (A), second primary cancer (SPC) events (B), and noncancer health events (NCHE) (C). Note that competing mortality each represents mortality from other causes than index cancer or SPC events. (D) Cumulative incidence probabilities for the different causes of death as time progressed.
respectively (Figure 1). The cumulative 2- and 5-year index cancer-specific mortality rates were 11.0% and 23.8%, respectively.

occurrence of synchronous and metachronous SPCs

Of the 600 patients, 94 (15.7%) had SPCs at the time of index HNSCC diagnosis \( [i.e. \text{synchronous}; \ n = 31 (5.2\%)] \) or developed an SPC later \( [i.e. \text{metachronous}; \ n = 63 (10.5\%)] \). The metachronous SPCs were detected at a median of 31 (range, 6–113) months after index HNSCC diagnosis. The most frequent SPC site was the lung \( (n = 22) \), followed by the esophagus \( (n = 18) \), colorectal tract \( (n = 16) \), stomach \( (n = 15) \), thyroid \( (n = 8) \), another head and neck area \( (n = 6) \), genitourinary area \( (n = 2) \), and hepatobiliary area \( (n = 2) \) (supplementary Table S2, available at \textit{Annals of Oncology} online). The cumulative 2- and 5-year incidences of synchronous and metachronous SPC were 9.2% and 16.5%, respectively. The cumulative 2- and 5-year SPC-related mortality rates were 1.2% and 4.2%, respectively.

occurrence of NCHEs and noncancer deaths

The causes and incidences of NCHEs and noncancer deaths in the study population are summarized in supplementary Table S3, available at \textit{Annals of Oncology} online. In total, 224 patients (37.3%) had at least one NCHE. The total number of events was 277 and 41 patients (6.8%) experienced multiple NCHEs or had several different kinds of NCHEs. Respiratory events such as pneumonia or dyspnea were the most common NCHEs \( (42.0\%) \), followed by gastrointestinal NCHEs \( (18.8\%) \), wound problems \( (8.9\%) \), cerebro-/cardiovascular accidents \( (5.8\%) \), and others.

Noncancer deaths were observed in 55 of the 600 patients \( (9.2\%) \). The most common causes of noncancer deaths were similar to the common causes of NCHEs: respiratory events \( (72.7\%) \) were the most frequent cause of noncancer death. The cumulative 2- and 5-year incidences of NCHEs after the initial index HNSCC treatments were 24.6% and 37.3%, respectively. The cumulative 2- and 5-year NCM rates were 4.6% and 8.9%, respectively.

risk factors for NCHEs

To identify risk factors for NCHEs, univariate and multivariate analyses were carried out by using the cause-specific proportional hazards model (Table 1). The univariate analyses revealed that BMI <20 kg/m\(^2\) \( (P = 0.002) \), smoking ≥30 pack-years \( (P = 0.023) \), CCI ≥1 \( (P < 0.001) \), tumor recurrence \( (P < 0.001) \), SPC occurrence \( (P < 0.001) \), and chemotherapy in the initial treatment \( (P = 0.036) \) associated significantly with NCHEs. The surgery and nonsurgery groups did not differ significantly in terms of NCHE occurrence \( (P = 0.208) \). Multivariate analyses showed that BMI <20 kg/m\(^2\) \( (HR = 1.31, 95\% \ CI 1.06–1.49, P = 0.018) \), CCI ≥1 \( (HR = 1.71, 95\% \ CI 1.30–2.25, P < 0.001) \), tumor recurrence \( (HR = 6.92, 95\% \ CI 5.17–9.26, P < 0.001) \), SPC occurrence \( (HR = 2.57, 95\% \ CI 1.78–3.71, P < 0.001) \), and chemotherapy in the initial treatment \( (HR = 1.29, 95\% \ CI 1.01–1.68, P = 0.049) \) remained independent predictors of NCHEs.

risk factors for noncancer deaths

Table 2 shows the results of univariate and multivariate analyses for NCM-associated risk factors. The univariate analyses revealed that an older age \( (P < 0.001) \), no occupation \( (P < 0.001) \), CCI ≥1 \( (P < 0.001) \), tumor recurrence \( (P < 0.001) \), and SPC occurrence \( (P = 0.052) \) associated significantly with noncancer deaths. Neither the primary treatment modality nor the use of chemotherapy associated significantly with NCM \( (P > 0.1) \). Multivariate analyses showed that an older age \( (HR = 2.23, 95\% \ CI 1.61–3.09, P < 0.001) \), CCI ≥1 \( (HR = 2.09, 95\% \ CI 1.21–3.61, P = 0.008) \),

\begin{table}[h]
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\begin{tabular}{|l|lll|lll|}
\hline
\textbf{Variables} & \textbf{Univariate} & & & \textbf{Multivariate\textsuperscript{a}} & & \\
 & \textbf{HR} & \textbf{95\% CI} & \textbf{P} & \textbf{HR} & \textbf{95\% CI} & \textbf{P} \\
\hline
Age, per 10 years\textsuperscript{b} & 1.13 & 0.99–1.29 & 0.072 & 1.10 & 0.95–1.27 & 0.192 \\
Sex, female & 1.05 & 0.71–1.56 & 0.812 & 1.31 & 1.06–1.49 & 0.018 \\
BMI <20 kg/m\(^2\) & 1.38 & 1.16–1.34 & 0.002 & 1.29 & 0.98–1.70 & 0.074 \\
Smoking ≥30 pack-years & 1.37 & 1.04–1.80 & 0.023 & 1.27 & 0.97–1.66 & 0.192 \\
Alcohol use ≥1 drink per day & 1.36 & 0.92–2.00 & 0.199 & 1.36 & 0.90–1.67 & 0.187 \\
CCI ≥1 & 1.70 & 1.30–2.22 & <0.001 & 1.71 & 1.30–2.25 & <0.001 \\
Primary tumor site, hypopharynx & 1.23 & 0.90–1.67 & 0.187 & 1.23 & 0.90–1.67 & 0.187 \\
Tumor recurrence\textsuperscript{c} & 6.94 & 5.20–9.27 & <0.001 & 6.92 & 5.17–9.26 & <0.001 \\
Second primary cancer\textsuperscript{d} & 2.40 & 1.67–3.47 & <0.001 & 2.57 & 1.78–3.71 & <0.001 \\
Initial treatment, nonsurgery & 1.27 & 0.97–1.66 & 0.085 & 1.27 & 0.97–1.66 & 0.085 \\
Initial treatment, including chemotherapy & 1.33 & 1.02–1.73 & 0.036 & 1.29 & 1.01–1.68 & 0.049 \\
Initial treatment, including induction chemotherapy & 1.16 & 0.89–1.51 & 0.271 & & & \\
\hline
\end{tabular}
\caption{Univariate and multivariate analyses of factors associated with noncancer health events}
\end{table}

\textsuperscript{a}The covariates with \textit{P} < 0.1 in the univariate analyses were selected for the multivariate analyses.

\textsuperscript{b}Calculated at 10-year intervals.

\textsuperscript{c}BMI, body mass index; CCI, Charlson comorbidity index; CI, confidence interval; HR, cause-specific hazard ratio.
tumor recurrence (HR = 6.12, 95% CI 3.38–11.06, P < 0.001), and SPC occurrence (HR = 2.17, 95% CI 1.01–4.65, P = 0.047) remained independent risk factors for noncancer deaths. The occurrences of one or more NCHEs associated significantly with noncancer death (P < 0.001). In addition, a history of respiratory NCHE significantly increased the risk of noncancer death compared with other NCHE types (adjusted HR = 2.67, 95% CI 1.52–4.69, P = 0.001) (Figure 2).

Table 2. Univariate and multivariate analyses of factors associated with noncancer deaths

<table>
<thead>
<tr>
<th>Variables</th>
<th>Univariate</th>
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<td></td>
<td>HR</td>
<td>95% CI</td>
<td>P</td>
<td>HR</td>
<td>95% CI</td>
<td>P</td>
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<tr>
<td>Age, per 10 yearsb</td>
<td>2.11</td>
<td>1.50–2.97</td>
<td>&lt;0.001</td>
<td>2.23</td>
<td>1.61–3.09</td>
<td>&lt;0.001</td>
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<td>Sex, female</td>
<td>0.97</td>
<td>0.41–2.27</td>
<td>0.937</td>
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<tr>
<td>BMI &lt;20 kg/m²</td>
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<td>0.50–1.96</td>
<td>0.969</td>
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<td>Occupation, none</td>
<td>1.62</td>
<td>1.33–1.78</td>
<td>&lt;0.001</td>
<td>1.29</td>
<td>0.70–1.61</td>
<td>0.269</td>
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<td>Smoking ≥30 pack-years</td>
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<td>0.75–2.27</td>
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<td>Alcohol use ≥1 drink per day</td>
<td>1.12</td>
<td>0.48–2.62</td>
<td>0.799</td>
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<tr>
<td>CCI ≥1</td>
<td>2.04</td>
<td>1.18–3.52</td>
<td>&lt;0.001</td>
<td>2.09</td>
<td>1.21–3.61</td>
<td>0.008</td>
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<td>Primary tumor site, hypopharynx</td>
<td>1.37</td>
<td>0.75–2.53</td>
<td>0.308</td>
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<tr>
<td>Tumor recurrencec</td>
<td>4.64</td>
<td>2.64–8.16</td>
<td>&lt;0.001</td>
<td>6.12</td>
<td>3.38–11.06</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Second primary cancerc</td>
<td>2.11</td>
<td>0.99–4.47</td>
<td>0.052</td>
<td>2.17</td>
<td>1.01–4.65</td>
<td>0.047</td>
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<td>Initial treatment, nonsurgery</td>
<td>0.68</td>
<td>0.36–1.30</td>
<td>0.243</td>
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<tr>
<td>Initial treatment, including chemotherapy</td>
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<td>0.43–1.26</td>
<td>0.261</td>
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<tr>
<td>Initial treatment, including induction chemotherapy</td>
<td>0.62</td>
<td>0.34–1.11</td>
<td>0.105</td>
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</table>

aThe covariates with P < 0.1 in the univariate analyses were selected for the multivariate analyses.
bCalculated at 10-year intervals.
cTime-varying covariates in the proportional hazards model.
BMI, body mass index; CCI, Charlson comorbidity index; CI, confidence interval; HR, cause-specific hazard ratio.

Figure 2. Cumulative incidence function of index cancer-specific, second primary cancer (SPC)-specific, and noncancer-related deaths stratified by respiratory (n = 94) or other types (n = 130) of NCHE.
**discussion**

Our study revealed that NCM was more common in older patients. This may reflect the fact that elderly cancer patients are likely to have serious comorbidities that could lead directly to mortality; moreover, these comorbidities can affect treatment decisions, which could indirectly lead to death [14]. Indeed, older cancer patients may often be under-treated because of their age and potential biases against treatment by patients, families, and physicians [14, 15]. However, a previous population-based study showed that patients older and younger than 70 years did not differ significantly in terms of survival after adjustments for cancer and treatment factors were made [16]. Therefore, the effect of age on survival should be interpreted carefully. Nevertheless, in our study, the patients who were older and younger than 70 years did not differ in terms of comorbidity ($\chi^2$ test, $P = 0.100$) or treatment modality ($P = 0.784$). This suggests that patient age is a true independent risk factor for noncancer death in HNSCC.

In the present study, the presence of one or more patient comorbidities was a significant risk factor for both NCHEs and noncancer deaths. This may reflect the fact that patients with HNSCC have a higher prevalence of comorbidities than the general population [17] and that cancer patients with severe comorbidities have a higher incidence of complications and mortality secondary to cancer treatment [18, 19]. Indeed, the cancer treatment itself may increase the risk of comorbidities even after 1 year of treatment, particularly in patients undergoing chemotherapy [1]. Our study revealed that preexisting comorbidities increased the health events that required re-admission of the patients after they completed treatment, and that this elevated the frequency of subsequent noncancer deaths.

Index HNSCC recurrence was a clinical factor that very clearly affected both the NCHEs and noncancer deaths in our study. During the past two decades, better multimodality therapies have improved the survival of patients with HNSCC, especially those with advanced-stage disease [5, 6]. However, compared with patients without recurrences, cancer survivors with recurrent tumors are more likely to experience aggravation of other noncancer competing diseases and the toxic effects of the treatments for recurrences. This explains why cancer recurrence events associate not only with ultimate cancer-specific survival but also with NCM and NCHEs.

In our study, SPC occurrence was a significant risk factor of both NCHEs and noncancer deaths. The risk of SPCs in patients with HNSCC is elevated because of field cancerization, namely, the development of multiple synchronous and metachronous tumors after the aero-digestive tract has received a carcinogenic insult [20]. SPCs are important for survivors of aggressive multimodality therapy for advanced HNSCC because SPCs have been reported to adversely affect the survival of patients with HNSCC [21, 22]. Consequently, SPCs themselves could act as competing risk factors for mortality along with NCHEs.

The present study only involved patients with advanced-stage HNSSC. Such patients are at high risk of various medical events that affect cancer-related and noncancer-related mortality and will often simultaneously have many clinical factors that could promote either or both types of mortality. To identify the factors that specifically affect the competing disease pathway, we sought to identify the competing health event that associated most frequently with noncancer death. This analysis revealed that respiratory NCHEs were the leading cause of noncancer death.

The definition of NCHE seems a little arbitrary and has a risk of underestimating the probability of competing health events. However, it should be noted that it is very difficult to identify all health events and to determine their severity. Therefore, we thought that a possible indicator of the significance of the health

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**Figure 3.** Schematic depiction of the major clinical event pathways in patients with head and neck cancer. This is a modification of the suggestion by Mell et al. [3]. The present study showed that there were significant associations between comorbidities, tumor recurrence, respiratory noncancer health events, and noncancer deaths. HNC, head and neck cancer; SPC, second primary cancer.
event is requirement for hospitalization, which causes the event to fall into the CTCAE grade 3 category. In our study, the competing health events included the NCHEs that developed after the initial treatment was completed, regardless of cancer recurrence events. This may be a more reliable indicator of competing mortality because treatment-related complications during initial treatments can vary depending on the regimen(s) used.

We sought to refine the clinical pathways proposed by Mell et al. [3] by closely analyzing the interrelationships between the three competing mortalities (i.e. the index cancer mortality, SPC mortality, and NCM) and their causative risk factors. As shown in Figure 3, one or more patient comorbidities associated significantly with NCHEs, and respiratory events were the leading cause of noncancer deaths. Moreover, we found that the initial or salvage treatments for the index cancer (including chemotherapy) affected the NCHE rate. In addition, index tumor recurrence associated significantly with NCM as well as with cancer-specific mortality, probably because the treatments for the recurrences affected the general condition and health events of the patients. Finally, SPC occurrence and its treatment also promoted NCHEs and noncancer deaths. It should be emphasized that at this stage, this risk model may only be applicable to patients with advanced-stage HNSCC. Further validation in other cohorts from different centers or by multicenter studies in different countries and ethnic groups is required.

In conclusion, our study showed that patients with advanced-stage HNSCC have a significant risk of NCHEs and noncancer deaths, and that both NCHEs and noncancer deaths in this population are significantly promoted by the presence of comorbidities, tumor recurrence, and SPC occurrence. Of the patients who had NCHEs, those with respiratory events were at particularly high risk of noncancer death. Therefore, patients with respiratory health events should be properly managed to avoid unexpected NCM. Our results may help clinicians to identify, at an early stage, those patients who are at high risk of NCHE and subsequent NCM. This will facilitate their management and reduce their risk of NCM.

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**disclosure**

The authors have declared no conflicts of interest.

**references**


