



Original Article

Long-term Survivorship and Non-cancer Competing Mortality in Head and Neck Cancer: A Nationwide Population-Based Study in South Korea

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Purpose As the survival of head and neck cancer (HNC) improves, survivors increasingly confront non-cancer-related deaths. This nationwide population-based study aimed to investigate non-cancer-related deaths in HNC survivors.

Materials and Methods Data from the Korean Central Cancer Registry were obtained to characterize causes of death, mortality patterns, and survival in patients with HNC between 2006 and 2016 (n=40,890). Non-cancer-related mortality relative to the general population was evaluated using standardized mortality ratios (SMRs). The 5- and 10-year cause-specific competing risks probabilities of death (cumulative incidence function, CIF) and subdistribution hazards ratios (sHR) from the Fine-Gray models were estimated.

Results Comorbidity-related mortality was frequent in older patients, whereas suicide was predominant in younger patients. The risk of suicide was greater in patients with HNC than in the general population (SMR, 3.1; 95% confidence interval [CI], 2.7 to 3.5). The probability of HNC deaths reached a plateau at 5 years (5-year CIF, 33.9%; 10-year CIF, 39.5%), whereas the probability of non-HNC deaths showed a long-term linear increase (5-year, CIF 5.6%; 10-year CIF, 11.9%). Patients who were male (sHR, 1.56; 95% CI, 1.41 to 1.72), diagnosed with early-stage HNC (localized vs. distant: sHR, 1.86; 95% CI, 1.58 to 2.21) and older age (65-74 vs. 0-44: sHR, 6.20; 95% CI, 4.92 to 7.82; ≥ 75 vs. 0-44: sHR, 9.81; 95% CI, 7.76 to 12.39) had an increased risk of non-cancer mortality.

Conclusion Non-HNC-related deaths continue increasing. HNC survivors are at increased risk of suicide in the younger and comorbidity-related death in the older. Better population-specific surveillance awareness and survivorship plans for HNC survivors are warranted.

Key words Head and neck neoplasms, Competing risk, Non-cancer death, Mortality, Suicide, Cancer surveillance, Survivorship

Introduction

Competing mortality is becoming more important in cancer survivors. Comorbidities, treatment-related morbidities, frailty, and old age are often related to 'non-cancer' competing mortalities in cancer patients, including patients with head and neck cancer (HNC) [1,2]. As the survival of HNC has recently been improving [3-5], an increasing number of survivors constitutes the aged population [6]. An in-depth understanding of competing non-cancer causes of death (COD) and corresponding mortality risks in survivors of HNC became necessary.

Patients with HNC may experience a higher risk of competing (non-HNC) mortalities than the general population [2,7-11], and the survivors frequently experience comorbidities such as pneumonia and lower respiratory disease and are at an increased risk of competing mortalities [1,7,12-17]. Advanced stage diseases require intensive combined treat-

ments, which could cause related morbidities, usually in the frail elderly, in various cancers, such as human papilloma-virus-positive, -negative oropharyngeal carcinoma, and oral carcinoma [17-21]. Furthermore, HNC is often accompanied by psychosocial morbidities, leading to intentional self-harm (suicide) [22]. Meanwhile, a recent report has debated that HNC did not have the greatest risk of suicide, especially after the emergence of human papillomavirus-associated HNC [23]. These features have yet to be clarified in Korea.

Despite the importance of a comprehensive study on competing mortality, previous nationwide population-based studies, focused mainly on the incidence trends, have not sufficiently highlighted non-cancer competing mortalities and their long-term survival statistics in patients with HNC, especially in the Asian population, for example, in South Korea [24,25]. Moreover, several western population-based studies [2,6,8] and single institute-based clinic studies exist [26,27]; however, these were only focused on the risk factor

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assessment, but not age-specific long-term competing mortality patterns. Therefore, we aimed to investigate the survivorship and non-cancer-related COD in HNC survivors in Korea and provide age-specific non-cancer mortality patterns and long-term survival statistics. We also included the impact of the human papillomavirus (HPV) association on non-cancer mortality. Detailed knowledge about the pattern of non-cancer COD in HNC patients could enhance current survivorship and surveillance strategy, important for reasonable survivorship guidelines.

Materials and Methods

1. Study population

We obtained data from the Korea Central Cancer Registry (KCCR), a population-based cancer registry. The KCCR is a nationally representative, population-based cancer registry including more than 99% of cancer patients in South Korea and contains the nationwide cancer incidence and survival data dating back to 1999. The KCCR registry is linked to the mortality and COD statistics provided by Statistics Korea, a National Statistics Office in South Korea [28]. The COD statistics were obtained from death certificates and classified according to the *International Statistical Classification of Diseases and Related Health Problems, 10th revision (ICD-10)*, recommended by the World Health Organization (WHO) [29,30].

Patients diagnosed with malignant primary head and neck tumors between January 1, 2006, and December 31, 2016, were included in this study and followed until December 31, 2017. We included the first primary HNC (HNC only or first of multiple primaries, both male and females, all ages). We defined HNC based on the *International Classification of Diseases for Oncology (ICD-O, 3rd edition)* codes, including C000-C009 (lip), C019-C029 (tongue), C079-C089 (salivary gland), C040-C049 (floor of mouth), C030-C039, C050-C059, C060-C069 (gum and other mouth), C110-C119 (nasopharynx), C090-C099 (tonsil), C100-C109 (oropharynx), C129, C130-C139 (hypopharynx), C140, C142, C148 (other oral cavity and pharynx), C300-C301, C310-C319 (nose, nasal cavity, and middle ear), and C320-C329 (larynx). HNC was further classified as HPV-associated sites (C090-C099, C019, C051-C052, and C100-C109), HPV-unrelated sites (C020-C069, C129-C139, and C320-C329), and other sites (C000-C009, C058-C059, C079-C089, C110-C119, C300-C301, C310-C319, and C140-C148). The exclusion criteria for this study were as follows: (1) cases with missing COD information (< 1%) or with death certificate only; (2) cases with multiple primary tumors; and (3) cases lost to follow-up. The study protocol was approved by the Institutional Review Board of the National Cancer Center (NCC2016-0041) of Korea.

2. Cause of death classification

We used underlying COD recorded as ICD-10 codes and applied the cause-specific death classification algorithm to reclassify COD in patients with cancer. This algorithm was developed and validated in the United States National Cancer Center Institute's Surveillance Epidemiology and End Results (SEER) program to improve the accuracy of COD information and correct possible misclassifications [31,32]. In our study, we classified the COD as either HNC or other causes, where the latter category included cancers other than HNC and non-cancer causes. To determine COD rankings in cancer patients and estimate non-cancer mortality risks relative to the general population, we classified 56 COD selected from a set of 80 COD recommended by the WHO and used by Statistics Korea [30].

3. Statistical analysis

Descriptive statistics were used to analyze the demographics, tumor characteristics, and proportion of deaths according to COD among patients with HNC. The distribution of COD was analyzed by sex, age group (0-44, 45-54, 55-64, 65-74, ≥ 75), and tumor stage (localized, regional, and distant) at diagnosis. We estimated standardized mortality ratios (SMRs) and 95% confidence intervals (CIs) to compare non-cancer mortality risks in patients with HNC relative to the general South Korean population. The 95% CI for the SMR was calculated using the method described by Kahn and Sempos [33]. Observed all-cause survival probabilities were estimated using Kaplan-Meier methods. To estimate the probability of death by HNC compared to death by other competing causes under the competing risks, we used the cumulative incidence function (CIF) [34]. Survival probabilities and CIFs were estimated over the follow-up years (up to 12 years) stratified by age groups (0-44, 45-54, 55-64, 65-74, and ≥ 75) and tumor stages (localized, regional, and distant). Gray's test was used for the CIF comparisons [35]. Fine-Gray competing risks survival models were fitted [36]. The subdistribution hazard ratios were used to evaluate the association between patient characteristics, including sex, age group, tumor stage, and HPV association with the risk of death from HNC or other causes. All statistical analyses were performed using SAS ver. 9.4 (SAS Institute Inc., Cary, NC). p-values less than < 0.05 were considered statistically significant.

Results

1. Causes of death

Of the 40,890 patients included in the study, 16,730 (41%) died (males: 13,596; females: 3,134). Of these, 13,767 patients (82%) died from HNC, and 2,963 patients (18%) died from

Table 1. Patient characteristics and distribution of causes of death by sex, age group, and tumor stage, KCCR 2006-2016

Characteristic	Total (n=40,890)	Sex		Age group (yr)					Tumor stage		
		Male (n=31,670)	Female (n=9,220)	0-44 (n=4,753)	45-54 (n=7,768)	55-64 (n=10,991)	65-74 (n=10,960)	≥ 75 (n=6,418)	Localized (n=16,825)	Regional (n=16,094)	Distant (n=3,298)
Alive^{a)}	24,160 (59.1)	18,074 (57.1)	6,086 (66.0)	3,873 (81.5)	5,518 (71.0)	7,252 (66.0)	5,530 (50.5)	1,987 (31.0)	12,460 (74.1)	8,541 (53.1)	797 (24.2)
Death^{a)}	16,730 (40.9)	13,596 (42.9)	3,134 (34.0)	880 (18.5)	2,250 (29.0)	3,739 (34.0)	5,430 (49.5)	4,431 (10.8)	4,365 (10.7)	7,553 (18.5)	2,501 (6.1)
Cause of death^{b)}											
Head and neck cancer	13,767 (82.3)	11,111 (81.7)	2,656 (84.7)	802 (91.1)	1,968 (87.5)	3,132 (83.8)	4,328 (79.7)	3,537 (79.8)	3,023 (69.3)	6,568 (87.0)	2,344 (93.7)
Other causes	2,963 (17.7)	2,485 (18.3)	478 (15.3)	78 (8.9)	282 (12.5)	607 (16.2)	1,102 (20.3)	894 (20.2)	1,342 (30.7)	985 (13.0)	157 (6.3)
Distribution of other causes^{c)}											
Cancer of other sites ^{d)}	807 (27.2)	723 (29.1)	84 (17.6)	35 (44.9)	94 (33.3)	210 (34.6)	322 (29.2)	146 (16.3)	345 (25.7)	271 (27.5)	55 (35.0)
Heart diseases	265 (8.9)	220 (8.9)	45 (9.4)	-	14 (5)	44 (7.2)	113 (10.3)	92 (10.3)	143 (10.7)	83 (8.4)	-
Intentional self-harm	256 (8.6)	229 (9.2)	27 (5.6)	14 (17.9)	53 (18.8)	71 (11.7)	74 (6.7)	44 (4.9)	99 (7.4)	111 (11.3)	13 (8.3)
Cerebrovascular diseases	227 (7.7)	179 (7.2)	48 (10.0)	-	13 (4.6)	41 (6.8)	84 (7.6)	84 (9.4)	110 (8.2)	66 (6.7)	-
Pneumonia	185 (6.2)	156 (6.3)	29 (6.1)	-	14 (5)	27 (4.4)	61 (5.5)	83 (9.3)	89 (6.6)	60 (6.1)	-
Chronic lower respiratory diseases	109 (3.7)	94 (3.8)	15 (3.1)	-	-	11 (1.8)	42 (3.8)	53 (5.9)	42 (3.1)	37 (3.8)	-
Other non-cancer causes	1,114 (37.6)	884 (35.6)	230 (48.1)	29 (37.2)	94 (33.3)	203 (33.4)	406 (36.8)	392 (43.8)	514 (38.3)	357 (36.2)	89 (56.7)

Values are presented as number (%). Percentages are rounded to an integer. Patients diagnosed with primary head and neck cancer from January 1, 2006, to December 31, 2016, followed up to December 31, 2017. Results of patients whose tumor stage is unknown are not included. -, less than 10 cases; KCCR, Korea Central Cancer Registry. ^{a)}Percentage among each column of sex, age group, and tumor stage. ^{b)}Percentage among the total number of deaths. ^{c)}Percentage among non-head and neck cancer deaths. ^{d)}Cancer from other sites include cancer of the lung (n=238) and stomach (n=97) as the most frequent.

Table 2. Standard mortality ratios of the most frequent non-cancer causes of death in cancer patients relative to the general population

Rank ^{a)}	All sex		Male		Female	
	Cause of death	SMR ^{b)} (95% CI)	Cause of death	SMR ^{b)} (95% CI)	Cause of death	SMR ^{b)} (95% CI)
1	Heart diseases	1.0 (0.9-1.1)	Intentional self-harm	2.3 (2.0-2.6)	Cerebrovascular diseases	0.7 (0.5-0.9)
2	Intentional self-harm	3.1 (2.7-3.5)	Heart diseases	0.9 (0.8-1.0)	Heart diseases	0.7 (0.5-0.9)
3	Cerebrovascular diseases	0.8 (0.7-0.9)	Cerebrovascular diseases	0.7 (0.6-0.8)	Pneumonia	1.2 (0.7-1.6)
4	Pneumonia	1.7 (1.4-1.9)	Pneumonia	1.3 (1.1-1.5)	Intentional self-harm	2.5 (1.5-3.4)
5	Chronic lower respiratory disease	1.3 (1.1-1.6)	Chronic lower respiratory disease	0.9 (0.7-1.1)	Chronic lower respiratory disease	1.1 (0.5-1.6)

Patients diagnosed with primary head and neck cancer from January 1, 2006, to December 31, 2016, followed up to December 31, 2017. CI, confidence interval; SMR, standard mortality ratio. ^{a)}Rank by the number of deaths for the top five leading causes of death in head and neck cancer patients, ^{b)}SMRs for a specific cause of death were calculated as the average ratio of observed deaths in cancer patients from 2006 to 2017 to the expected deaths in the Korean general population from 2006 to 2017.

other causes (Table 1). Of all non-HNC-related COD, cancer of other sites comprised 27% (n=807), whereas the other 73% were non-cancer-related causes. The most frequent non-cancer-related COD was heart disease (n=265, 9%), followed by suicide (n=256, 9%), cerebrovascular diseases (n=227, 8%), pneumonia (n=185, 6%), and chronic lower respiratory diseases (n=109, 4%). Death by medical comorbidities, such as pneumonia and heart and cerebrovascular disease, were more predominant in older patients. In contrast, suicide was the most frequent non-cancer-related COD in younger patients (< 65 years).

2. Standardized mortality ratio

The SMRs of the most frequent non-HNC-related COD are shown in Table 2. The SMRs of suicide (SMR, 3.1; 95% CI, 2.7 to 3.5), pneumonia (SMR, 1.7; 95% CI, 1.4 to 1.9), and chronic lower respiratory diseases (SMR, 1.3; 95% CI, 1.1 to 1.6) were significantly higher in patients with HNC than the general population of South Korea. Notably, the risk of suicide was higher in both males and females (SMR in males, 2.3 [95% CI, 2.0 to 2.6]; SMR in females, 2.5 [95% CI, 1.5 to 3.4]). Additionally, in male patients with HNC, suicide was the most frequent non-cancer-related COD (n=229).

3. Survival and competing mortality risks: HNC versus non-HNC-related

The proportions (probabilities) of surviving patients and those who died from HNC and competing non-HNC (other) causes are shown in Fig. 1. Although the proportion of surviving patients declined for all COD, non-HNC mortality gradually increased for prolonged follow-up periods and increased more rapidly in older populations. In the presence of competing risks, the probability of death by HNC tended to reach a plateau at approximately 5 years, where-

as death from causes other than HNC maintained a steady linear increase up until 10 years, with significantly higher mortality in the elderly ($p < 0.001$). In the elderly with early-stage HNC, the risk of death from non-HNC-related causes became comparable to the probability of dying from HNC (Figs. 1 and 2). The chances of competing non-HNC (other) deaths were higher in older than in younger patients. Non-HNC death was more predominant in localized SEER stage patients than in the advanced, most of whom died from HNC (Fig. 2). Meanwhile, the HNC was constantly the most common COD in all age groups. Non-HNC mortality linearly increased throughout the follow-up, and this pattern did not change by HPV status (S1 Fig.).

The 5- and 10-year survival and probability of death by HNC and other competing causes are shown in Table 3. In both males and females, the 5- and 10-year survival probabilities were 60.5% and 48.6%, respectively. The probability of death by HNC was 33.9% in 5 years and 39.5% in 10 years of follow-up, whereas the probability of death by competing non-HNC causes was 5.6% in 5 years and increased to 11.9% in 10 years of follow-up. For patients with early-stage cancer, the probability of non-HNC mortality increases as they survive. For example, in patients with a localized tumor, the 5- and 10-year probabilities of non-HNC mortality were 6.1% and 14.0%, respectively. However, for a patient with advanced SEER stage cancer, regardless of age group, the 5- and 10-year probabilities of death by HNC were higher (5-year, 72.4%; 10-year, 77.8%), whereas probabilities of death by non-HNC causes were lower (5-year, 4.1%; 10-year, 6.2%).

The Fine-Gray competing risks modeling results in Table 4 showed that the risks of death were elevated in the male and older ages for both HNC (male vs. female: subdistribution hazards ratio [sHR], 1.19 [95% CI, 1.14 to 1.25]; age 65-74 vs. 0-44: sHR, 2.64 [95% CI, 2.45 to 2.84]) and non-HNC deaths

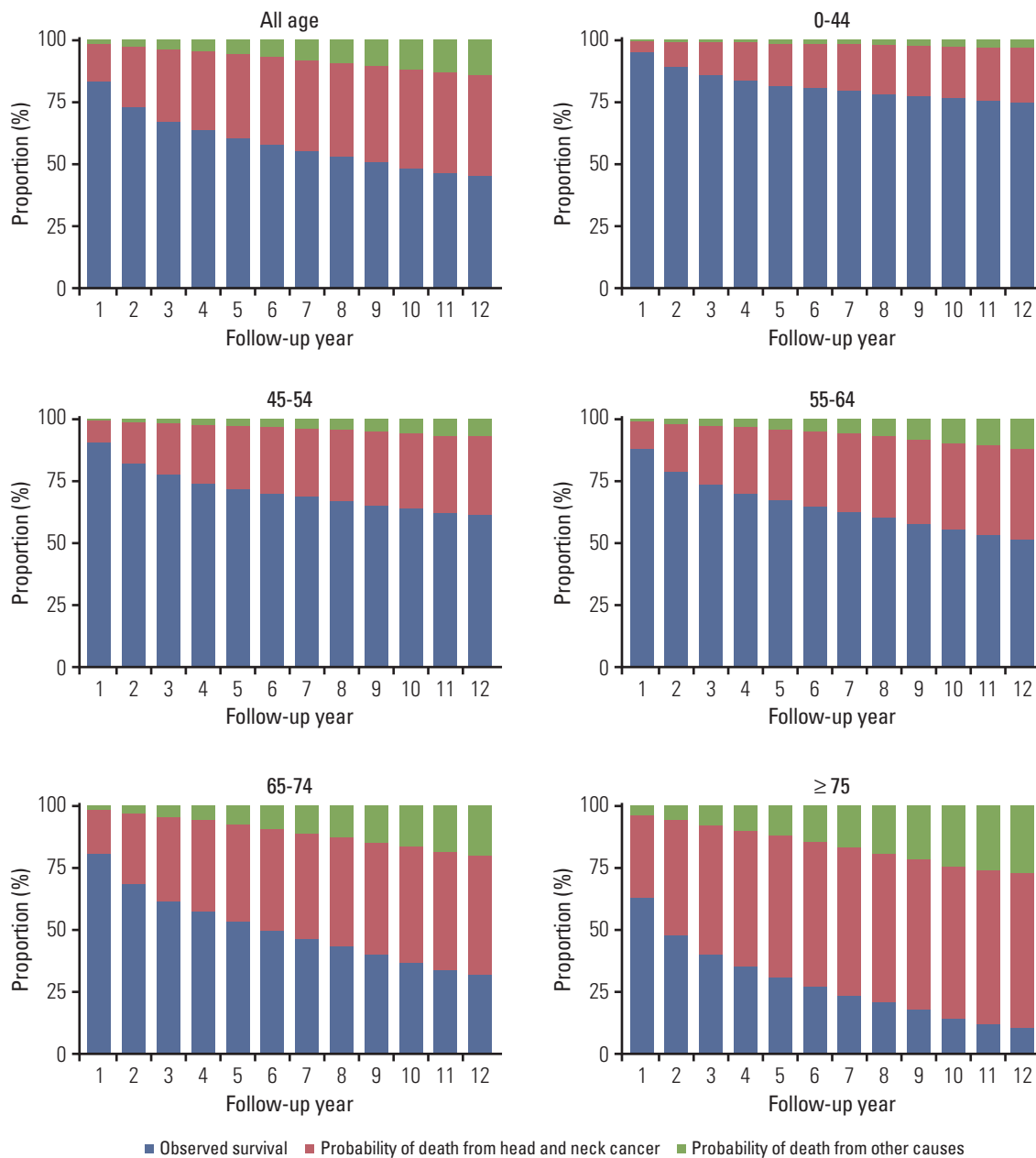


Fig. 1. Probabilities of survival, death from head and neck cancer and competing other causes by age group (yr). The probabilities of death were estimated by the cumulative incidence function.

(male vs. female: sHR, 1.56 [95% CI, 1.41 to 1.72]; age 65-74 vs. 0-44: sHR, 6.20 [95% CI, 4.91 to 7.82]). Age had a substantial impact on non-HNC mortality. Patients diagnosed with early-stage tumors had an increased risk of non-cancer mortality (localized vs. distant: sHR, 1.86 [95% CI, 1.58 to 2.21]). Whereas, for patients diagnosed with a distant stage, the hazard of HNC death was more substantial (distant vs. localized: sHR, 6.71 [95% CI, 6.34 to 7.11]). HPV association was related to the risks of HNC deaths ($p < 0.001$) but not to the

risks of non-HNC deaths ($p=0.683$).

The probability and risks of suicide were provided in S2 and S3 Tables. In both males and females, the 5- and 10-year probability of suicide was 0.6% and 0.8%, respectively. In the males, the probability of suicide was elevated up to 1% in 10 years (S2 Table). The risks of suicide were 2 times higher in males (male vs. female: sHR, 2.35 [95% CI, 1.57 to 3.50]) and patients diagnosed with regional stage (regional vs. distant: sHR, 1.78 [95% CI, 1.00 to 3.15]) (S3 Table).

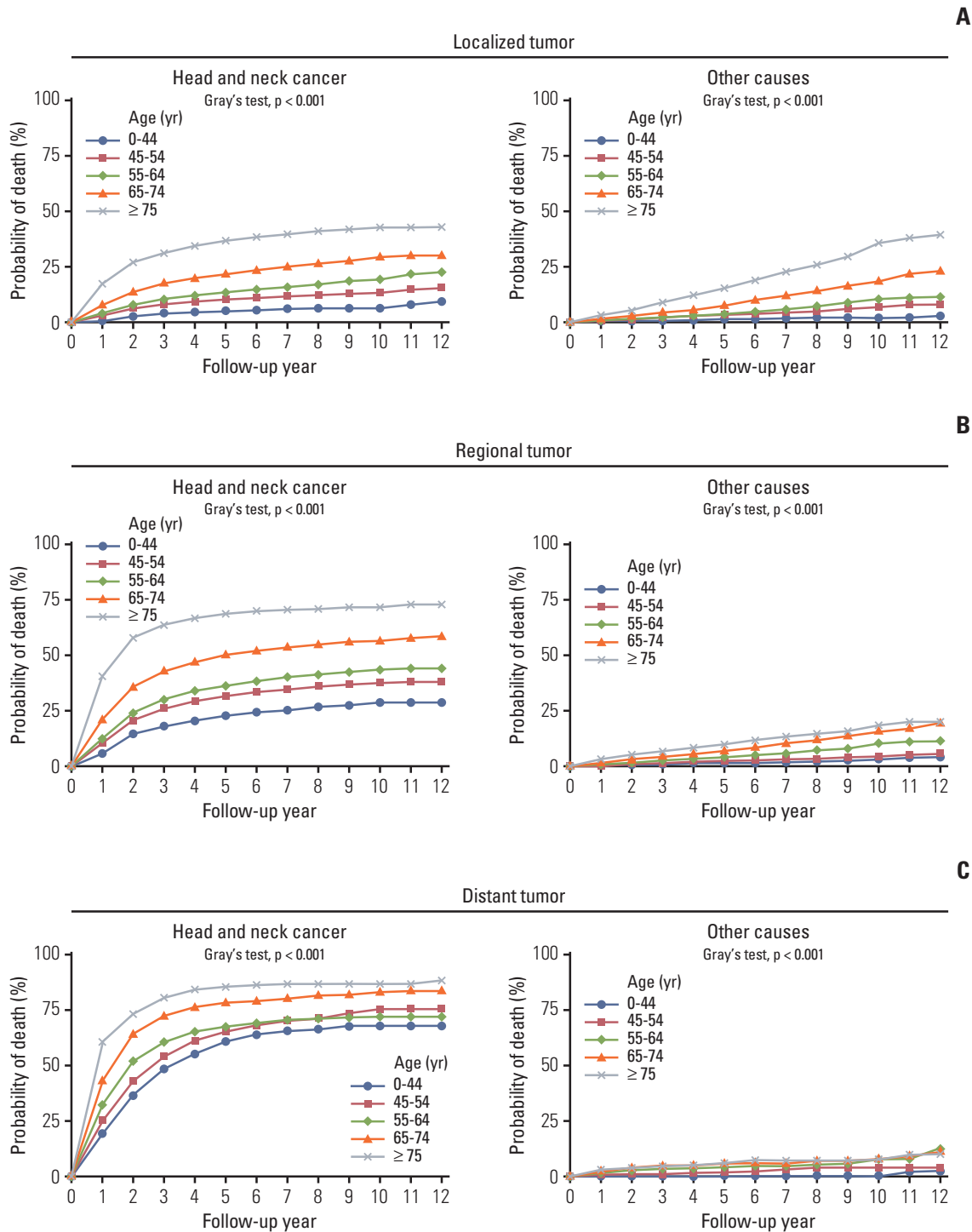


Fig. 2. (A-C) Competing risks probabilities of death from the head and neck cancer and other causes by age and tumor stage.

Discussion

We herein described survival statistics and competing mortality patterns, particularly non-cancer-related deaths

in HNC, using nationwide population-based data in South Korea. In patients with HNC, the risk of cancer deaths was still high, but non-cancer deaths were continuously increasing. Non-cancer deaths associated with comorbidities were

Table 3. Five and 10-year survival and probability of death from the head and neck cancer and competing other causes, KCCR 2006-2016

Characteristic	Observed survival probability ^{a)} (%) (95% CI)		Probability of death ^{b)} (%) (95% CI)			
	5-Year	10-Year	Head and neck cancer		Other causes	
			5-Year	10-Year	5-Year	10-Year
Total^{c)}	60.5 (59.9-61.0)	48.6 (47.9-49.3)	33.9 (33.4-34.4)	39.5 (38.9-40.1)	5.6 (5.4-5.9)	11.9 (11.4-12.4)
Sex						
Male	58.5 (58.0-59.1)	46.0 (45.3-46.8)	35.4 (34.8-35.9)	41.1 (40.5-41.8)	6.1 (5.8-6.4)	12.8 (12.3-13.4)
Female	67.1 (66.0-68.1)	57.6 (56.2-58.9)	28.9 (27.9-29.9)	33.9 (32.7-35.1)	4.1 (3.6-4.5)	8.5 (7.7-9.4)
Age (yr)						
0-44	81.7 (80.5-82.9)	76.7 (75.1-78.2)	16.9 (15.8-18.0)	20.8 (19.4-22.2)	1.4 (1.0-1.8)	2.5 (1.9-3.2)
45-54	71.8 (70.7-72.9)	64.0 (62.6-65.4)	25.3 (24.3-26.4)	30.4 (29.2-31.7)	2.8 (2.5-3.3)	5.6 (4.9-6.4)
55-64	67.3 (66.3-68.2)	55.4 (54.1-56.7)	28.5 (27.6-29.4)	34.8 (33.6-35.9)	4.3 (3.9-4.7)	9.8 (8.9-10.7)
65-74	53.2 (52.2-54.2)	37.0 (35.7-38.3)	39.4 (38.5-40.4)	46.5 (45.3-47.7)	7.3 (6.8-7.9)	16.5 (15.5-17.6)
≥ 75	30.9 (29.7-32.2)	14.3 (12.7-16.0)	57.1 (55.7-58.3)	61.1 (59.7-62.6)	12.0 (11.1-12.9)	24.5 (22.9-26.2)
Tumor stage						
Localized	76.4 (75.7-77.1)	63.2 (62.1-64.3)	17.5 (16.9-18.1)	22.7 (21.9-23.6)	6.1 (5.7-6.5)	14.0 (13.2-14.9)
Regional	52.9 (52.1-53.7)	41.7 (40.6-42.8)	42.0 (41.2-42.8)	47.9 (46.9-48.9)	5.1 (4.7-5.5)	10.4 (9.7-11.2)
Distant	23.4 (21.9-25.0)	16.0 (14.3-17.8)	72.4 (70.8-74.0)	77.8 (76.0-79.5)	4.1 (3.4-4.9)	6.2 (5.1-7.4)

Patients diagnosed with head and neck cancer from January 1, 2006, to December 31, 2016, followed up to December 31, 2017. CI, confidence interval; KCCR, Korea Central Cancer Registry. ^{a)}Estimated by the Kaplan-Meier estimator, ^{b)}Estimated by the cumulative incidence function, ^{c)}Include patients with all sex and all tumor stages.

Table 4. Risks of death due to head and neck cancer and other causes under the presence of competing risks^{a)}

Characteristic	Head and neck cancer		Other causes	
	sHR ^{a)} (95% CI)	p-value	sHR ^{a)} (95% CI)	p-value
Sex				
Female	Reference		Reference	
Male	1.19 (1.14-1.25)	< 0.001	1.56 (1.41-1.72)	< 0.001
Age (yr)				
0-44	Reference		Reference	
45-54	1.45 (1.34-1.57)	< 0.001	2.15 (1.67-2.76)	< 0.001
55-64	1.74 (1.61-1.88)	< 0.001	3.38 (2.66-4.28)	< 0.001
65-74	2.64 (2.45-2.84)	< 0.001	6.20 (4.91-7.82)	< 0.001
≥ 75	4.82 (4.46-5.21)	< 0.001	9.81 (7.76-12.39)	< 0.001
Tumor stage				
Localized	Reference		1.86 (1.58-2.21)	< 0.001
Regional	2.96 (2.83-3.09)	< 0.001	1.44 (1.21-1.70)	< 0.001
Distant	6.71 (6.34-7.11)	< 0.001	Reference	
Tumor type				
HPV-unrelated	Reference		Reference	
HPV-related	0.81 (0.77-0.85)	< 0.001	0.96 (0.85-1.08)	0.683
Others	0.89 (0.85-0.92)	< 0.001	1.07 (0.98-1.17)	0.137

Patients diagnosed with head and neck cancer from January 1, 2006, to December 31, 2016, followed up to December 31, 2017. CI, confidence interval; HPV, human papillomavirus; sHR, subdistribution hazard ratio. ^{a)}The Fine-Gray competing risks survival models were used to estimate the subdistribution hazard ratios.

frequent in the elderly (≥ 65), whereas intentional self-harm was predominant in the younger (< 65) male population. Our results demand raising awareness regarding proper survivorship for HNC survivors. Targeting both comorbidities and psychosocial aspects for HNC survivors seems important.

Although the previous study reported that death by competing causes was more frequent than HNC itself [11,37,38], our study showed that the probability of dying from other causes was lower than HNC, even after ≥ 10 years of follow-up, regardless of sex, age, and tumor stage. However, the risk of non-cancer COD increased consistently long after the treatment. In contrast, the probability of HNC death reached a plateau at 5 years. Non-cancer deaths increased in older age and early stage. Comorbidities, age, and intentional self-harm were predominant non-cancer causes. Our results were consistent with the SEER data [2,8], which reported cardiovascular disease and pneumonia as the leading non-cancer deaths. Studies from different countries have shown various patterns of competing mortality [6,8,10,11,26,39,40].

Traditionally, age and comorbidities have been determinants of both HNC- and non-cancer mortality [26,27,39,41,42]. Accordingly, our findings showed that non-cancer deaths sharply increased by age (2.8%, 4.3%, 7.3%, and 12% for age groups 45-54, 55-64, 65-74, and 75 or older, respectively). Additionally, non-cancer deaths by pneumonia, chronic lower respiratory diseases, and heart disease were predominant in the elderly. Cardiovascular disease and stroke were also major causes. Previous studies also showed elevated risks of fatal stroke and heart diseases among HNC patients [6,43,44]. Considering that Asian countries such as South Korea have rapidly aging populations [45,46], our data demand awareness and plans, especially for the frail elderly.

Intentional self-harm was a primary cause of non-cancer death in HNC survivors. Risks of suicide in patients with HNC have generally been reported to be significantly higher than in other sites [47], although this tendency is recently being debated after the emergence of HPV-associated HNC [23]. Meanwhile, our data indicated that HNC survivors had higher mortality from intentional self-harm, 3 times higher than the general population. The risk of suicide among patients with HNC was known to be double that of patients with cancer of other sites and about 4 times that of the general population [47]. Compared to the previously reported risk of suicide in some cancers in South Korea [48], the risk of intentional self-harm in HNC (SMR, 3.1; male, 2.3; female, 2.5) was higher than stomach or colorectal but lower than lung cancer. In particular, risks were higher in the younger (age < 65) males. Higher mortality risk than the general population in South Korea, where the background suicide rates are already high [49,50], seems concerning. HNC survivors

endure unique clinical conditions. HNC has been known to be the most emotionally and psychosocially stressing of all cancers [51]. Sources of distress are persistent effects of treatment, difficulty swallowing and airway care, depression, functional compromise, and esthetic disfigurement [52,53]. Pain and substance abuse are also known to be more prevalent [54]. Considering emotional, esthetic, functional, and eventual psychosocial distress caused by HNC [52,53,55], better psychosocial survivorship strategies and policies are warranted to prevent self-harm.

The pattern of mortality including intentional self-harm in HPV-associated cancers was similar to HPV-unrelated cancers, contrasted to the previous speculation that recent decreasing suicide rate may be secondary to the increasing distribution of HPV-associated HNC, and a decrease in those with tobacco and alcohol [23]. We showed that the risk of HNC and competing deaths tended to be lower in HPV-related than HPV-unrelated cancers, albeit not substantial. Considering occurrence in the healthier and younger population and better survival of HPV-related cancer [55], the risk of death by HPV-associated cancer might continue to remain low, whereas competing death risk is expected to elevate. Yet, differences by HPV association did not appear significantly in this study. Considering the adoption of a de-intensified treatment for HPV-associated cancer may mitigate this pattern in the future, as well as related, debating data [23], follow-up analysis seems in need.

HNC survivors undergo potentially significant effects from cancer and its treatment and deserve comprehensive and coordinated clinical follow-up care. Patients should be provided adequate support to address physical, psychosocial, and practical effects after treatment. In regard, HNC survivorship care guidelines by the American Cancer Society stated that HNC survivors also need to be counseled on health promotion strategies to minimize and mitigate long-term effects and comorbid health conditions to potentially increase survival [56]. In particular, comprehensive assessment and counseling about psychosocial effects, including body and self-image issues, and distress/depression/anxiety, was recommended with a moderate level of evidence. Considering that these aspects have not been addressed enough in Korea, adequate related guidelines or policymaking seems necessary.

This study has several limitations. Although comprehensive, our population-based cancer registry data lacks detailed prognostic factors and clinical information, including p16, HPV test results, treatment information, and TNM stage. Predictive modeling was difficult due to the lack of information. Developing predictive prognosis models that incorporate detailed clinical information in electronic health records regarding significant predictors for survival in pati-

ents with HNC will be followed. While we showed that death from SPM, with the most common being lung, stomach, and liver cancer, similar to the SEER data [2], in-depth mortality analysis focusing on SPM was beyond the scope of this study. Finally, misclassification of the cause of death based on death certificates might exist and bias the survival estimates. However, we used cause of death information from Statistics Korea, where the official cause of death statistics is reported annually in South Korea [30]. Statistics Korea has made ongoing efforts to improve accuracy in the cause of death data collection. We further applied the SEER cause-specific death classification algorithm to enhance the accuracy of cause of death classifications and survival estimates in cancer patients [32]. Nevertheless, our study provided population-level trends in long-term competing mortality and survival, which provides useful insights for proper care for patients with HNC cancer.

In conclusion, competing non-cancer deaths remain frequent in HNC survivors, even long after treatment. Comorbidity-related deaths were distinctively predominant in the elderly, whereas intentional self-harm in the younger population. Population-specific surveillance and survivorship programs seem required. Awareness and a customized provision of care to the psychosocially vulnerable young and the frail elderly HNC survivors are warranted.

Electronic Supplementary Material

Supplementary materials are available at Cancer Research and Treatment website (<https://www.e-crt.org>).

Ethical Statement

The study protocol was approved by the Institutional Review Board of the National Cancer Center (NCC2016-0041) of Korea. This study used secondary de-identified data. Written informed consents were waived.

Author Contributions

Conceived and designed the analysis: Jung YS, Cho H.

Collected the data: Jung KW.

Contributed data or analysis tools: Lee D, Jung KW, Cho H.

Performed the analysis: Jung YS, Lee D, Cho H.

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Conflicts of Interest

Conflict of interest relevant to this article was not reported.

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