Heterogeneous impact of alcohol consumption according to treatment method on survival in head and neck cancer: A prospective study

Michi Sawabe,[1,2] Hidemi Ito,[3,4] Isao Oze,[3] Satoyo Hosono,[3] Daisuke Kawakita,[1,2] Hideo Tanaka,[3,4] Yasuhisa Hasegawa,[5] Shingo Murakami[2] and Keitaro Matsuo[1,4]

[1]Division of Molecular and Clinical Epidemiology, Aichi Cancer Center Research Institute; [2]Department of Otolaryngology, Head and Neck Surgery, Nagoya City University Graduate School of Medicine; [3]Division of Epidemiology and Prevention, Aichi Cancer Center Research Institute; [4]Department of Epidemiology, Nagoya City University Graduate School of Medicine; [5]Department of Head and Neck Surgery, Aichi Cancer Center Hospital, Nagoya, Japan

Alcohol consumption is an established risk factor, and also a potential prognostic factor, for squamous cell carcinoma of the head and neck (HNSCC). However, little is known about whether the prognostic impact of alcohol consumption differs by treatment method. We evaluated the association between alcohol drinking and survival by treatment method to the primary site in 427 patients with HNSCC treated between 2005 and 2013 at Aichi Cancer Center Central Hospital (Nagoya, Japan). The impact of alcohol on prognosis was measured by multivariable Cox regression analysis adjusted for established prognostic factors. Among all HNSCC patients, the overall survival rate was significantly poorer with increased levels of alcohol consumption in multivariable analysis (trend $P = 0.038$). Stratification by treatment method and primary site revealed that the impact of drinking was heterogeneous. Among laryngopharyngeal cancer (laryngeal, oropharyngeal, and hypopharyngeal cancer) patients receiving radiotherapy ($n = 141$), a significant dose–response relationship was observed (trend $P = 0.034$). In contrast, among laryngopharyngeal cancer patients treated with surgery ($n = 80$), no obvious impact of alcohol was observed. This heterogeneity in the impact of alcohol between surgery and radiotherapy was significant (for interaction, $P = 0.048$). Furthermore, among patients with oral cavity cancer treated by surgery, a significant impact of drinking on survival was seen with tongue cancer, but not with non-tongue oral cancer. We observed a significant inverse association between alcohol drinking and prognosis among HNSCC patients, and its impact was heterogeneous by treatment method and primary site.

Squamous cell carcinoma of the head and neck (HNSCC), which includes cancers of the oral cavity, oropharynx, hypopharynx, and larynx, is the sixth most common malignancy worldwide.[1] In 2014, 9600 people died of head and neck cancer in Japan, accounting for 6.7% of all cancer deaths.[2] Like smoking,[3] alcohol drinking is an established risk factor for head and neck cancer.[4,5]

A number of reports have indicated that alcohol consumption is also a prognostic factor for head and neck cancer.[6–10] In their meta-analysis of the association between alcohol consumption and survival in Asia and North America,[7] Li *et al.* reported that heavy drinkers have a significantly worse prognosis than non-drinkers. Leoncini *et al.* reported the potential influence of alcohol consumption on survival by each primary site of HNSCC, with hazard ratios (HRs) of 1.60 for the oral cavity, 1.60 for the oropharynx, and 4.19 for the hypopharynx.[6] We have also reported a similarly poorer prognosis with alcohol drinking among Japanese patients.[10]

However, these studies did not report whether the impact of alcohol consumption on prognosis varied by treatment method. Definitive treatment for head and neck cancer is either surgery or radiotherapy/chemoradiotherapy (RT/CRT), depending on the primary site,[11] and treatment and site are important prognostic factors. Lifestyle factors such as smoking or drinking also influence the therapeutic effect of RT/CRT in cancer of the aerodigestive tract.[12–14] Accordingly, we considered it important to evaluate the heterogeneity of the influence of alcohol consumption on prognosis in combination with treatment method to the primary site. To our knowledge, however, no such study has yet been published.

Using data from the Hospital–based Epidemiologic Research Program at Aichi Cancer Center (HERPACC) in Japan, we evaluated the association between alcohol consumption and HNSCC prognosis by treatment method. All treatments were in accordance with the National Comprehensive Cancer Network (NCCN) clinical practice guideline.

Materials and Methods

Study group. Patients were selected from the database of the HERPACC, which has been described in detail elsewhere.[15,16] Version 3 of HERPACC enrolled first-visit

outpatients at Aichi Cancer Center Hospital (ACCH; Nagoya, Japan) from December 2005 to March 2013, and had a participation rate of 66%. Participants completed the self-administered HERPACC questionnaire on lifestyle factors, which included items on demographic characteristics, family and individual medical history, height, weight, amount of daily exercise, smoking and drinking habits, vitamin use, and consumption of selected foods and beverages before any diagnostic procedure were carried out. Trained interviewers checked the responses. All participants gave written informed consent to participate. This study was approved by the Institutional Ethics Committee of ACCH.

For the present study, we selected subject patients from among HERPACC version 3 participants using the same criteria as our previous study among HERPRACC version 2 participants,[10] as follows: (i) primary and locoregional head and neck cancer in the oral cavity, oropharynx, hypopharynx, or larynx; (ii) histological diagnosis of squamous cell carcinoma; (iii) no previous definitive therapy of the primary site; and (iv) performance status (PS) of 0–2 according to the Eastern Cooperative Oncology Group criteria. Patients with metastatic head and neck cancer were excluded from the analysis, and cases of nasopharyngeal, salivary gland, nasal, and paranasal cancer were also excluded due to their distinct etiology. Finally, 427 cases satisfied the eligibility criteria for analysis and 230 cases were excluded.

Alcohol consumption and other exposure data. Alcohol consumption and other lifestyle factors were evaluated using the self-administered HERPACC questionnaire. All patients were asked about their alcohol consumption, drinking behavior (frequency per week or per month), and intake of various common beverages (Japanese sake, shochu, beer, wine, and whiskey) before the development of their current symptoms. Alcohol consumption was converted to ethanol per day and used to divide subjects into the four categories of non-, light (<23 g ethanol/day), moderate (23–46 g ethanol/day), and heavy drinker (>46 g ethanol/day).

Subjects were categorized by smoking status into the three groups of never, former, and current smokers. Former smokers were defined as those who quit smoking at least 1 year before the survey. Cumulative smoking was evaluated as pack-years (PY), the product of the number of packs of cigarettes smoked per day and the number of years of smoking. In this study, subjects were divided into the four categories of never, PY < 20, PY < 40, and PY ≥ 40.

Therapy. Study patients were generally treated according to the NCCN guideline. Specifically, patients with oral cavity cancer (tongue, and others) at The International Union Against Cancer (UICC) stage T 1–2 and N0 were treated by surgery or RT, while those at other stages were treated by surgery only. In exceptional cases, patients who requested RT received this treatment, subject to physician assessment. Patients with laryngopharyngeal cancer (oropharyngeal, hypopharyngeal, and laryngeal cancer) at any stage were treated by either surgery or RT with or without concomitant chemotherapy. When the surgical margin was positive or extracapsular spread of lymph node metastasis was identified in pathologic tissue, postoperative RT was carried out.

After definitive RT/platinum-based CRT (66–70 Gy), therapeutic effect was evaluated by computed tomography and endoscopy and residual disease was treated by salvage surgery. If platinum-based induction chemotherapy (IC) was undertaken before definitive therapy, the therapeutic effect was evaluated after IC according to Response Evaluation Criteria in Solid Tumors.[17] Patients with complete response or partial response

were treated by RT, and those with stable disease or progressive disease were treated by surgery.

Lesions were considered to be a second primary cancer (SPC) if they were distinct, solid cancers that were histologically proven to be inconsistent with recurrent or metastatic disease. An SPC was classified as synchronous SPC if identified within 6 months of primary HNSCC diagnosis, and metachronous SPC if beyond this 6-month period. In our evaluation, we limited the classification of SPCs as alcohol related-cancers in accordance with the International Agency for Research on Cancer, namely to oral cavity, pharyngeal, laryngeal, esophagus, liver, and colorectal cancers.[18]

Statistical analysis. The primary endpoint of this study was overall survival (OS; interval between the date of first therapy and death from any case, or date of last follow-up) and the secondary endpoints were disease-specific survival (DSS; interval between the date of first therapy and death from head and neck cancer, or date of last follow-up), disease-free survival (DFS; interval between the date of first therapy and the date of locoregional or metastatic relapse, death from any cause, or date of last follow-up), and incidence of metachronous SPC (interval between the date of first therapy and date of onset of metachronous SPC, or date of last follow-up).

Vital status, disease progression, treatment method, and SPC were confirmed by checking medical records. In the case of loss of follow-up, vital status was confirmed by census registration undertaken annually.

Point estimates of OS, DSS, DFS, and incidence of metachronous SPC were estimated by the Kaplan–Meier method.[19] To assess the association between alcohol consumption and prognosis, we estimated multivariable HRs and 95% confidence intervals (CIs) using Cox proportional hazard models. Alcohol consumption was a major exposure of interest. Confounders considered in the multivariate analysis were age, gender, Eastern Corporative Oncology Group PS, smoking status, Union for International Cancer Control stage, definitive therapy and IC, energy, and synchronous SPC. Onset of metachronous SPC was considered in multivariate analysis as a time-varying covariate.

We first analyzed the association between alcohol consumption and the prognosis of all patients with HNSCC. We then classified patients by primary site and definitive therapy according to the NCCN guideline, and analyzed each treatment group. Additionally, we examined the interaction between alcohol consumption and treatment method for laryngopharyngeal cancer using a multivariate Cox regression model.

Distribution of patient characteristics was assessed by the χ^2-test or Fisher's exact test, as appropriate. All analyses were carried out using Stata SE version 13 (StataCorp, College Station, TX, USA). *P*-values <0.05 were considered statistically significant.

Results

Patient characteristics and overall clinical outcomes. Demographic characteristics and selected lifestyle habits of patients are shown in Table 1. Among 427 subjects, 206 patients (48%) had oral cavity cancer, of whom 145 patients (36%) had cancer of the tongue.

The prevalence of the factors of male, hypopharyngeal cancer, synchronous and metachronous SPC, and current or heavy smoker increased with increasing levels of drinking. In contrast, no other significant difference was seen among drinking categories.

Table 1. Characteristics of 427 patients with head and neck squamous cell carcinoma and levels of alcohol consumption

	n = 427 (%)	Drinking categories†				P-value‡
		Non-drinker n = 113 (%)	Light n = 93 (%)	Moderate n = 74 (%)	Heavy n = 147 (%)	
Age, years						
<60	195 (45.7)	53 (47.0)	48 (51.6)	29 (39.2)	65 (44.2)	0.420
≥60	232 (54.3)	60 (53.0)	45 (48.4)	45 (60.8)	82 (55.8)	
Sex						
Male	334 (78.1)	54 (47.8)	72 (77.4)	67 (90.5)	141 (95.9)	<0.001
Female	93 (21.9)	59 (52.2)	21 (22.6)	7 (9.5)	6 (4.1)	
Performance status						
0	305 (71.3)	78 (68.7)	69 (74.2)	50 (67.6)	108 (73.5)	0.419
1	109 (25.6)	30 (27.0)	21 (22.6)	20 (27.0)	38 (25.9)	
2	13 (3.0)	5 (4.3)	3 (3.2)	4 (5.4)	1 (0.7)	
Primary site						
Oral cavity	206 (48.3)	72 (62.6)	51 (54.8)	31 (41.9)	53 (36.1)	<0.001
Tongue	145 (34.0)	45 (40.0)	42 (45.2)	20 (27.0)	38 (25.9)	
Non-tongue§	61 (14.2)	26 (22.6)	9 (9.7)	11 (14.9)	15 (10.2)	
Laryngopharynx	221 (51.5)	42 (45.2)	42 (45.2)	42 (45.2)	94 (63.9)	
Oropharynx	73 (17.0)	14 (12.2)	18 (19.4)	16 (21.6)	25 (17.0)	
Hypopharynx	96 (22.4)	10 (8.7)	12 (12.9)	18 (24.3)	56 (38.1)	
Larynx	52 (12.4)	19 (16.5)	12 (12.9)	9 (12.2)	13 (8.8)	
UICC stage						
1	77 (18.2)	24 (21.7)	18 (19.4)	14 (18.9)	21 (14.3)	0.208
2	94 (21.9)	27 (23.5)	28 (30.1)	12 (16.2)	27 (18.4)	
3	60 (14.0)	18 (15.7)	11 (11.8)	9 (12.2)	22 (15.0)	
4	196 (45.9)	44 (39.1)	36 (38.7)	39 (52.7)	77 (52.4)	
T stage						
1	98 (22.8)	27 (23.9)	26 (28.0)	19 (25.7)	26 (17.7)	0.001
2	177 (41.3)	51 (45.1)	48 (51.6)	28 (37.8)	50 (34.0)	
3	67 (15.6)	11 (9.7)	7 (7.5)	11 (14.9)	38 (25.9)	
4	84 (19.6)	23 (20.4)	12 (12.9)	16 (21.6)	33 (22.4)	
N stage						
0	225 (52.4)	71 (62.8)	52 (55.9)	31 (41.9)	71 (48.3)	0.145
1	51 (11.9)	11 (9.7)	13 (14.0)	10 (13.5)	17 (11.6)	
2	140 (32.6)	30 (26.5)	24 (25.8)	31 (41.9)	55 (37.4)	
3	11 (2.6)	1 (0.9)	4 (4.3)	2 (2.7)	4 (2.7)	
Smoking status						
Never	109 (25.4)	63 (54.8)	30 (32.3)	8 (10.8)	8 (5.4)	<0.001
Former	146 (34.3)	26 (23.5)	36 (38.7)	31 (41.9)	53 (36.1)	
Current	172 (40.1)	24 (20.9)	27 (29.0)	35 (47.3)	86 (58.5)	
Smoking category						
Non–low (0 ≤ and ≤5 PY)	119 (27.7)	65 (56.5)	35 (37.6)	11 (14.9)	8 (5.4)	<0.001
Light (5 ≤ and <20 PY)	60 (14.0)	13 (11.3)	19 (20.4)	10 (13.5)	18 (12.2)	
Moderate (20 ≤ and <40 PY)	95 (22.1)	21 (18.3)	10 (10.8)	28 (37.8)	36 (24.5)	
Heavy (≥40 PY)	140 (32.6)	14 (12.2)	27 (29.0)	21 (28.4)	78 (53.1)	
Unknown	15 (3.5)	2 (1.7)	2 (2.2)	4 (5.4)	7 (4.8)	
Smoking status						
Never	109 (25.4)	63 (54.8)	30 (32.3)	8 (10.8)	8 (5.4)	<0.001
Former	146 (34.3)	26 (23.5)	36 (38.7)	31 (41.9)	53 (36.1)	
Current	172 (40.1)	24 (20.9)	27 (29.0)	35 (47.3)	86 (58.5)	
Therapy						
Induction chemotherapy						
Yes	144 (33.6)	22 (19.1)	28 (30.1)	28 (37.8)	66 (44.9)	<0.001
No	285 (66.4)	93 (80.9)	65 (69.9)	46 (62.2)	81 (55.1)	
Definitive therapy						
Op	269 (62.9)	82 (71.3)	62 (66.7)	45 (60.8)	81 (55.1)	0.041
RT	159 (37.1)	33 (28.7)	31 (33.3)	29 (39.2)	66 (44.9)	
Second primary cancer¶						
Synchronous cancer	40 (0.5)	5 (0.9)	3 (1.1)	6 (0.0)	26 (0.0)	<0.001

†Light, <23 g ethanol/day; moderate, 23–46 g ethanol/day; heavy, >46 g ethanol/day. ‡$\chi2$-test. §Gingiva, oral floor, and buccal mucosa. ¶Alcohol-related cancer (head and neck, esophagus, liver, and colon). Op, surgery; PY, pack-years; RT, radiotherapy; UICC, The International Union Against Cancer.

With regard to treatment, 270 patients (62%) underwent surgery and 62 (14%) received postoperative RT. One hundred and fifty nine patients (38%) underwent RT, of whom 99 (23%) received chemoradiotherapy. After RT, 36 patients (8%) had residual disease and underwent salvage surgery. One hundred and forty four patients (33%) underwent induction chemotherapy, of whom 75 (17%) were responders (complete response or partial response) and received RT, while 69 (16%) were non-responders (stable disease or progressive disease) and received surgery.

Metachronous SPC occurred in 21 patients (7%), 10 of whom had head and neck cancer, 7 had esophageal cancer, and 4 had colorectal cancer.

Median follow-up time was 46 months (range, 0–198 months). Five-year OS, DSS, and DFS of all patients was 0.68 (95% CI, 0.62–0.73), 0.72 (95% CI, 0.67–0.77), and 0.49 (95% CI, 0.43–0.54), respectively.

Impact of alcohol consumption on prognosis. As shown in Figure 1(A), there was a significant difference in OS according to drinking level (log–rank, $P = 0.006$). Five-year OS rates of non-, light, moderate, and heavy drinkers were 0.78 (95% CI, 0.68–0.86), 0.73 (0.60–0.82), 0.64 (0.51–0.76), and 0.58 (0.49.1–0.67), respectively (Fig. 1A).

Table 2 (upper section) shows the results of univariable and multivariable analyses of alcohol consumption and OS. Univariate analysis showed a significantly poorer OS for moderate and heavy drinkers. Even after adjustment for covariates, moderate and heavy drinkers had significantly poorer survival than non-drinkers, with HRs of 2.02 (1.02–3.91) for moderate and 1.91 (1.02–3.59) for heavy drinkers. A dose–response relationship between alcohol consumption and OS was observed with statistical significance (trend $P = 0.038$). As shown in Figure 1(B,C) and Table 2 (middle section), a similar tendency was observed with DSS and DFS.

Regarding the incidence of metachronous SPC, a suggestive association with alcohol consumption was observed in crude analysis (Fig. S1, Table 2, lower section), but this was not statistically significant on multivariable analysis (HR, 2.54; 95% CI, 0.42–15.30 for heavy drinkers).

Stratified analysis by potential confounders. To evaluate the consistency of the association with alcohol consumption, we evaluated Cox proportional hazards models for OS stratified by potential confounders (Fig. S2). Compared with non-drinkers, heavy and moderate drinkers had poor survival in all subgroups, except in those aged <60 years. Survival was suggested to be poorer in the non-smoker than in the smoker group (P for interaction = 0.103; Table S1).

Distribution of primary site and definitive therapy. Table 3 shows the distribution of primary site and definitive therapy according to alcohol consumption. Among patients with oral cavity cancer, 189 patients received surgery and the remaining 17 received RT. Among those with laryngopharyngeal cancer (oropharyngeal, hypopharyngeal, and laryngeal cancer), 80 patients were treated by surgery and 142 by RT.

As the NCCN guideline recommends RT as an optional treatment for primary oral cancer and only 17 of our patients were under this category, we decided that further evaluation of the interaction of therapy and alcohol consumption on prognosis should focus on patients with oral cavity cancer treated by surgery and laryngopharyngeal cancer treated by either surgery or RT. We further divided patients with oral cavity cancer by subsite (tongue and non-tongue oral cancer, consisting of the buccal mucosa, floor of mouth, and gingiva).
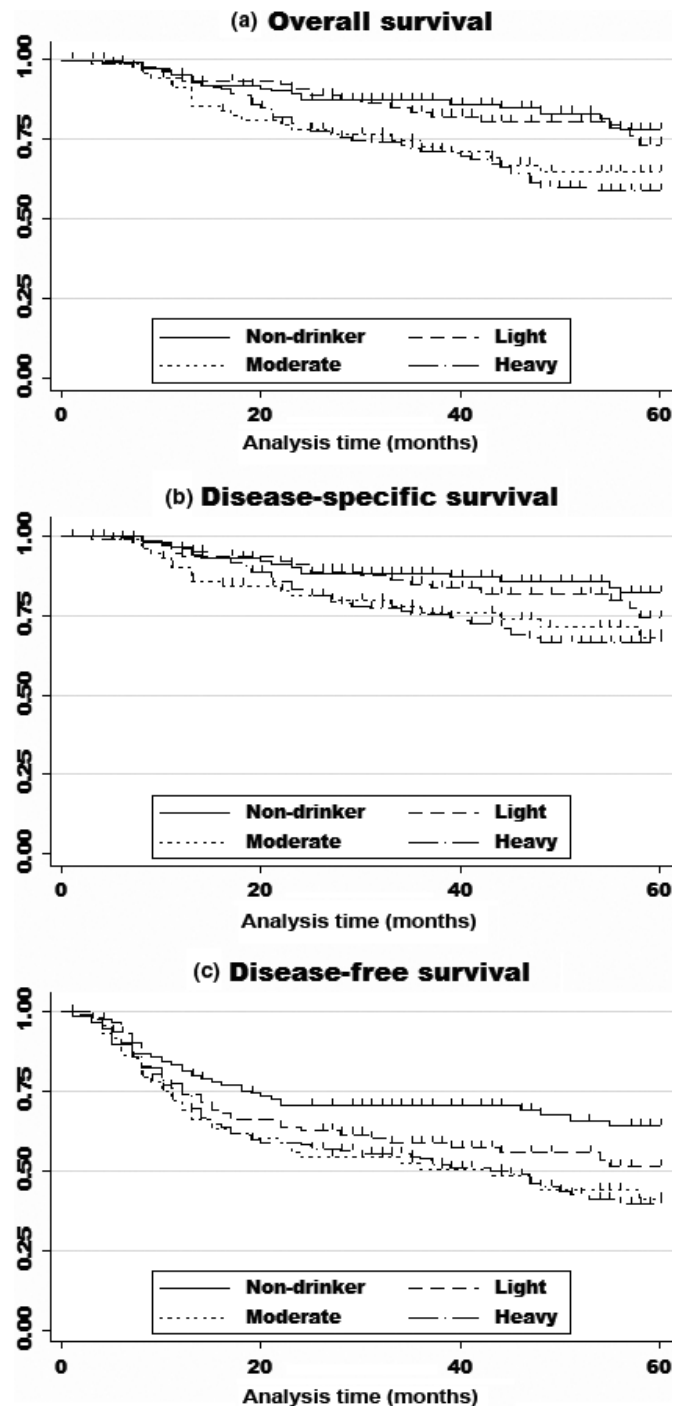

Fig. 1. Kaplan–Meier survival curves of overall survival (A), disease-specific survival (B), and disease-free survival (C) for all 429 patients with head and neck squamous cell carcinoma. (A) Kaplan–Meier survival curve of overall survival. Heavy (>46 g ethanol/day; $n = 147$) and moderate (23–46 g ethanol/day; $n = 89$) alcohol consumption were significantly associated with poorer survival compared with non-drinking (hazard ratio [HR], 1.92; 95% confidence interval [CI], 1.02–3.91, $P = 0.044$; and HR, 2.00; 95% CI, 1.02–3.59, $P = 0.042$, respectively). (B) Kaplan–Meier survival curve of disease-specific survival. Heavy and moderate alcohol consumption were significantly associated with poorer survival than non-drinking (HR, 2.12; 95% CI, 1.02–4.40, $P = 0.043$; and HR, 1.96; 95% CI, 0.99–3.86, $P = 0.053$, respectively). (C) Kaplan–Meier survival curve of disease-free survival. Heavy and moderate alcohol consumption were significantly associated with poorer survival than non-drinking (HR, 1.87; 95% CI, 1.16–2.91, $P = 0.010$; and HR, 1.87; 95% CI, 1.14–3.08, $P = 0.014$, respectively).

Table 2. Impact of alcohol consumption on overall, disease-specific, and disease-free survival, and incidence of metachronous second primary cancer (SPC) by multivariable proportional hazard models

	n (%)	5-year values (95% CI)	Crude		Adjusted†	
			HR (95% CI)†	*P*-value	HR (95% CI)†	*P*-value
Overall survival						
Non-drinker	113 (26)	0.78 (0.68–0.86)	1.00 (Reference)		1.00 (Reference)	
Light	93 (21)	0.73 (0.60–0.82)	1.26 (0.68–2.30)	0.454	1.34 (0.71–2.60)	0.367
Moderate	74 (17)	0.64 (0.51–0.76)	2.05 (1.14–3.69)	0.016	2.00 (1.02–3.91)	0.044
Heavy	147 (34)	0.59 (0.49–0.67)	2.17 (1.31–3.61)	0.003	1.91 (1.02–3.59)	0.042
				Trend *P* = 0.001		Trend *P* = 0.038
Disease-specific survival						
Non-drinker	113 (26)	0.82 (0.72–0.89)	1.00 (Reference)		1.00 (Reference)	
Light	93 (21)	0.74 (0.61–0.84)	1.39 (0.73–2.63)	0.306	1.55 (0.78–3.05)	0.210
Moderate	74 (17)	0.68 (0.54–0.79)	1.99 (1.05–3.78)	0.033	2.12 (1.02–4.40)	0.043
Heavy	147 (34)	0.66 (0.57–0.74)	2.04 (1.18–3.55)	0.011	1.96 (0.99–3.86)	0.053
				Trend *P* = 0.006		Trend *P* = 0.066
Disease-free survival						
Non-drinker	113 (26)	0.64 (0.53–0.73)	1.00 (Reference)		1.00 (Reference)	
Light	93 (21)	0.51 (0.39–0.62)	1.55 (1.01–2.39)	0.046	1.65 (1.04–2.60)	0.033
Moderate	74 (17)	0.41 (0.27–0.53)	1.94 (1.22–3.03)	0.003	1.87 (1.13–3.08)	0.014
Heavy	147 (34)	0.40 (0.31–0.49)	1.91 (1.30–2.80)	0.001	1.84 (1.16–2.91)	0.010
				Trend *P* = 0.001		Trend *P* = 0.020
Incidence of metachronous SPC						
Non-drinker	113 (26)	0.03 (0.01–0.09)	1.00 (Reference)		1.00 (Reference)	
Light	93 (21)	0.04 (0.01–0.15)	1.10 (0.22–5.53)	0.887	1.94 (0.33–11.96)	0.471
Moderate	74 (17)	0.03 (0.01–0.22)	1.70 (0.34–8.44)	0.515	1.75 (0.22–13.54)	0.594
Heavy	147 (34)	0.07 (0.03–0.15)	2.98 (0.82–10.70)	0.095	2.54 (0.42–15.30)	0.309
				Trend *P* = 0.049		Trend *P* = 0.331

Alcohol consumption graded as: light, <23 g ethanol/day; moderate, 23–46 g ethanol/day; and heavy, >46 g ethanol/day. †Adjusted by sex, age, Union for International Cancer Control performance status, stage, primary site, smoker, energy, synchoronous and metachronous, SPC, definitive therapy, and induction chemotherapy. CI, confidence interval; HR, hazard ratio.

Table 3. Distribution of primary site, definitive therapy, and alcohol consumption in 427 patients with head and neck squamous cell carcinoma

Primary site	Definitive therapy	n = 427 (%)	Drinking categories				*P*-value†
			Non-drinker n = 115 (%)	Light n = 93 (%)	Moderate n = 74 (%)	Heavy n = 147 (%)	
Oral cavity	Op	189 (44.3)	67 (59.1)	48 (51.6)	28 (37.8)	46 (31.3)	0.420
	RT	17 (4.0)	4 (3.5)	3 (3.2)	3 (4.1)	7 (4.8)	
Tongue	Op	132 (31.0)	41 (36.5)	39 (41.9)	18 (24.3)	34 (23.1)	0.958
	RT	13 (3.0)	4 (3.5)	3 (3.2)	2 (2.7)	4 (2.7)	
Non-tongue‡	Op	57 (13.3)	26 (22.6)	9 (9.7)	10 (13.5)	12 (8.2)	0.072
	RT	4 (0.9)	0 (0.0)	0 (0.0)	1 (1.4)	3 (2.0)	
Laryngopharynx (oropharynx, hypopharynx, larynx)	Op	80 (18.6)	14 (12.2)	14 (15.1)	17 (23.0)	35 (23.8)	0.908
	RT	141 (33.1)	28 (25.2)	28 (30.1)	26 (305.4)	59 (40.1)	
Oropharynx	Op	29 (6.8)	3 (2.6)	7 (7.5)	9 (12.2)	10 (6.8)	0.285
	RT	44 (10.3)	11 (9.6)	11 (11.8)	7 (9.5)	15 (10.2)	
Hypopharynx	Op	40 (9.3)	6 (5.2)	5 (5.4)	6 (8.1)	23 (15.6)	0.592
	RT	56 (13.1)	4 (3.5)	7 (7.5)	12 (16.2)	33 (22.4)	
Larynx	Op	11 (2.6)	5 (4.3)	2 (2.2)	2 (2.7)	2 (1.4)	0.829
	RT	42 (9.8)	13 (12.2)	10 (10.8)	7 (9.5)	11 (7.5)	

Alcohol consumption graded as: light, <23 g ethanol/day; moderate, 23–46 g ethanol/day; and heavy, >46 g ethanol/day. †χ2-test. ‡Oral cancer and not tougue consist of gingiva, oral floor, and buccal mucosa. Op, surgery; RT, radiotherapy.

Impact of alcohol consumption on prognosis by primary site and definitive therapy. *Oral cavity.* In all patients with oral cavity cancer who received surgery (*n* = 189), light, moderate, and heavy drinkers had poorer survival than non-drinkers, although the trend was not significant. Among these patients, this trend was significant in moderate drinkers after adjustment for covariates (HR, 3.61; 95% CI, 1.27–10.22; Table 4, upper left). Furthermore, when we stratified these patients by subsite

Table 4. Impact of alcohol consumption on survival in 429 patients with head and neck squamous cell carcinoma according to treatment method to primary site

	n (%)	Overall survival			Disease-specific survival			Disease-free survival		
		5-year values (95% CI)	HR (95% CI)†	P-value	5-year values (95% CI)	HR (95%CI)†	P-value	5-year values (95% CI)	HR (95% CI)†	P-value
Oral cavity (Op)										
Non-drinker	68 (35)	0.79 (0.65–0.87)	1.00 (Reference)		0.79 (0.65–0.88)	1.00 (Reference)		0.67 (0.54–0.78)	1.00 (Reference)	
Light	48 (25)	0.72 (0.54–0.85)	1.92 (0.77–4.76)	0.157	0.73 (0.54–0.85)	1.89 (0.76–4.68)	0.171	0.61 (0.43–0.74)	1.99 (1.02–3.90)	0.043
Moderate	28 (14)	0.57 (0.32–0.76)	3.61 (1.27–10.22)	0.016	0.48 (0.24–0.69)	4.15 (1.55–11.17)	0.005	0.33 (0.14–0.54)	3.17 (1.45–6.94)	0.004
Heavy	46 (24)	0.68 (0.49–0.81)	2.02 (0.72–5.70)	0.184	0.76 (0.58–0.87)	1.36 (0.47–3.96)	0.572	0.53 (0.36–0.68)	1.94 (0.90–4.18)	0.090
				Trend P = 0.173			Trend P = 0.429			Trend P = 0.077
Tongue (Op)										
Non-drinker	42 (31)	0.83 (0.62–0.93)	1.00 (Reference)		0.83 (0.63–0.92)	1.00 (Reference)		0.68 (0.50–0.81)	1.00 (Reference)	
Light	39 (29)	0.66 (0.43–0.81)	3.20 (0.96–10.60)	0.057	0.66 (0.43–0.81)	3.19 (0.93–10.92)	0.064	0.54 (0.35–0.70)	2.19 (0.99–4.88)	0.054
Moderate	18 (13)	0.43 (0.13–0.70)	11.70 (2.99–45.74)	<0.001	0.40 (0.13–0.67)	11.63 (3.04–44.53)	<0.001	0.15 (0.01–0.43)	6.36 (2.43–16.65)	<0.001
Heavy	34 (25)	0.67 (0.44–0.82)	3.07 (0.76–12.42)	0.117	0.75 (0.54–0.88)	2.04 (0.48–8.58)	0.332	0.51 (0.31–0.68)	2.44 (0.93–6.40)	0.071
				Trend P = 0.126			Trend P = 0.345			Trend P = 0.055
Non-tongue‡ (Op)										
Non-drinker	26 (42)	0.72 (0.50–0.85)	1.00 (Reference)		0.72 (0.49–0.85)	1.00 (Reference)		0.65 (0.43–0.80)	1.00 (Reference)	
Light	9 (14)	1.00			1.00			0.88 (0.39–0.98)	0.21 (1.03–1.88)	0.166
Moderate	10 (17)	0.74 (0.29–0.93)	0.09 (0.08–1.07)	0.057	0.59 (0.19–0.85)	0.26 (0.39–2.17)	0.213	0.61 (0.20–0.86)	0.56 (0.94–3.31)	0.522
Heavy	12 (21)	0.71 (0.34–0.90)	0.31 (0.05–1.94)	0.209	0.77 (0.35–0.94)	0.21 (0.03–1.51)	0.123	0.60 (0.22–0.84)	0.58 (0.13–2.54)	0.467
				Trend P = 0.322			Trend P = 0.222			Trend P = 0.468
Laryngopharyngeal cancer (oropharyngeal, hypopharyngeal, laryngeal)										
Non-drinker	43 (19)	0.82 (0.60–0.93)	1.00 (Reference)		0.95 (0.81–0.98)	1.00 (Reference)		0.63 (0.42–0.78)	1.00 (Reference)	
Light	43 (18)	0.71 (0.49–0.85)	1.43 (0.49–4.19)	0.513	0.73 (0.51–0.86)	2.67 (0.67–10.64)	0.164	0.39 (0.22–0.55)	2.27 (1.08–4.79)	0.030
Moderate	43 (19)	0.69 (0.51–0.81)	1.89 (0.66–5.40)	0.233	0.80 (062–0.90)	2.38 (0.57–9.86)	0.232	0.43 (0.25–0.59)	2.05 (0.96–4.35)	0.062
Heavy	94 (42)	0.54 (0.42–0.65)	2.35 (0.88–6.25)	0.086	0.62 (0.50–0.72)	4.09 (1.11–15.08)	0.034	0.33 (0.23–0.44)	2.35 (1.17–4.69)	0.016
				Trend P = 0.054			Trend P = 0.025			Trend P = 0.047
Op										
Non-drinker	14 (17)	0.84 (0.50–0.96)	1.00 (Reference)		0.84 (0.49–0.96)	1.00 (Reference)		0.31 (0.05–0.62)	1.00 (Reference)	
Light	14 (17)	0.36 (0.07–0.68)	1.35 (0.23–8.13)	0.737	0.41 (0.07–0.73)	1.05 (0.15–7.32)	0.958	0.21 (0.04–0.46)	1.67 (0.54–5.20)	0.377
Moderate	17 (21)	0.88 (0.59–0.97)	0.60 (0.08–4.33)	0.615	0.93 (0.63–0.99)	0.50 (0.06–4.31)	0.531	0.44 (0.17–0.69)	0.67 (0.20–2.20)	0.507
Heavy	35 (43)	0.48 (0.25–0.68)	1.45 (0.28–7.43)	0.653	0.62 (0.39–0.79)	1.46 (0.28–7.61)	0.648	0.36 (0.16–0.56)	0.98 (0.34–2.82)	0.967
				Trend P = 0.592			Trend P = 0.511			Trend P = 0.666
RT										
Non-drinker	29 (20)	0.81 (0.50–0.94)	1.00 (Reference)		1.00	Cannot be estimated§		0.78 (0.52–0.91)	1.00 (Reference)	
Light	28 (19)	0.89 (0.69–0.96)	0.86 (0.16–4.69)	0.862	0.88 (0.69–0.96)			0.46 (0.23–0.66)	3.02 (0.94–10.01)	0.067
Moderate	26 (18)	0.59 (0.36–0.76)	2.94 (0.69–12.51)	0.145	0.74 (0.50–0.87)			0.42 (0.21–0.61)	4.37 (1.37–13.93)	0.013
Heavy	59 (41)	0.56 (0.41–0.68)	3.11 (0.76–12.69)	0.113	0.62 (0.48–0.74)			0.31 (0.19–0.44)	5.03 (1.64–15.40)	0.005
				Trend P = 0.034			Trend P = 0.009			Trend P = 0.004

Alcohol consumption graded as: light, <23 g ethanol/day; moderate, 23–46 g ethanol/day; and heavy, >46 g ethanol/day. †Adjusted by sex, age, Union for International Cancer Control performance status, stage, primary site, smoker, energy, synchronous and metachronous, second primary cancer, definitive therapy, and induction chemotherapy. ‡Oral cancer and non-tongue consist of gingiva, oral floor, and buccal mucosa. §Non-drinker was no event and hazard ratio (HR) cannot be estimated. CI, confidence interval; Op, surgery; RT, radiotherapy.

(tongue and non-tongue), those with tongue cancer ($n = 132$) showed increased HRs for OS compared to non-drinkers, with HRs of 3.20 (95% CI, 0.96–10.6) for light, 11.70 (95% CI, 2.99–45.74) for moderate, and 3.07 (95% CI, 0.75–12.15) for heavy drinkers (Fig. S3). In patients with non-tongue oral cancer ($n = 57$), in contrast, the contribution of alcohol consumption was not clear. These results in OS were also consistently observed for DSS and DFS.

Laryngopharyngeal. Among all subjects with laryngopharyngeal cancer, the survival rate decreased as drinking levels increased with marginal statistical significance (trend $P = 0.054$; Table 4, lower left).

On stratification by treatment method, a significant dose–response relationship was observed among patients receiving RT ($n = 143$; *trend P = 0.034*), with moderate and heavy alcohol consumption associated with poorer survival (HR, 2.94 and 95% CI, 0.69–12.51 for moderate drinkers; HR, 3.11 and 95% CI, 0.76–12.69 for heavy drinkers; Fig. S4A). In contrast, among patients treated by surgery ($n = 80$), no association between alcohol consumption and OS was observed (Fig. S3B).

To clearly assess the interaction between treatment method and alcohol consumption on prognosis, we undertook an analysis with dichotomization by non–light *versus* moderate–heavy alcohol consumption. Among patients receiving RT, survival of moderate–heavy drinkers was significantly poorer than that of non–light drinkers (5-year OS, 0.56 and 0.85, respectively; HR relative to non–light drinkers, 3.32 [95% CI, 1.22–8.98]) (Table 5, upper). In contrast, among patients receiving surgery, there was no obvious difference in survival between non–light and moderate–heavy drinkers (5-year OS, 0.60 and 0.62, respectively; HR relative to non–light drinkers, 0.94 [95% CI, 0.34–2.63]) (Fig. 2). A significant interaction between alcohol consumption and therapy on prognosis were observed (P for

interaction = 0.048 for OS [Table 5, upper]). A similar tendency was observed with DSS and DFS.

Discussion

In this study, we found significantly poor survival, in terms of OS, DSS, and DFS, among HNSCC patients with higher alcohol consumption after adjustment for clinical covariates. This association was consistently observed in strata of age, sex, smoking status, and stage. More importantly, the association between alcohol consumption and prognosis differed by definitive treatment in each primary site. Among patients with laryngopharyngeal cancer, alcohol consumption had a more significant impact on prognosis in patients treated by RT than surgery; among patients with oral cavity cancer treated by surgery, a standard therapy for oral cavity cancer, alcohol consumption had a more significant impact in patients with tongue cancer than non-tongue cancer. To our knowledge, this is the first study to indicate a heterogeneous impact of alcohol consumption on the prognosis of HNSCC by treatment method.

Several reports have noted an association between alcohol consumption and survival of HNSCC. In their meta-analysis, Li *et al.* reported that heavy drinking was a poor prognostic factor, with an HR of 4.19 (95% CI, 2.32–7.55) compared to non-drinkers with HNSCC, whereas moderate drinkers had an HR of 1.51 (95% CI, 0.77–2.96).[7] Another study reported an association between alcohol drinking and prognosis in patients with head and neck cancer who received RT:[14] Fortin *et al.* evaluated the prognostic value of smoking and drinking in 1871 patients with head and neck cancer who received RT, and reported that active drinkers had a poorer prognosis compared to non-drinkers on multivariate analysis (HR, 1.3; 95% CI, 1.13–1.54).[14] In our previous study, a positive dose relationship was evident in the prognosis of Aldehyde

Table 5. Interaction between alcohol consumption and treatment method of laryngopharyngeal cancer

	n (%)	5-year values (95% CI)	HR (95% CI)†	*P*-value	*P* for interaction
Overall survival					
Op‡					
Non–light	28 (35)	0.60 (0.34–0.79)	1.00 (Reference)		0.048
Moderate–heavy	52 (65)	0.62 (0.44–0.76)	0.94 (0.34–2.64)	0.875	
RT‡					
Non–light	56 (40)	0.85 (0.69–0.93)	1.00 (Reference)		
Moderate–heavy	85 (60)	0.56 (0.44–0.66)	3.32 (1.22–8.98)	0.018	
Disease-specific survival					
Op‡					
Non–light	28 (35)	0.63 (0.36–0.82)	1.00 (Reference)		0.036
Moderate–heavy	52 (65)	0.78 (0.55–0.84)	1.08 (0.35–3.33)	0.890	
RT‡					
Non–light	56 (40)	0.94 (0.083–0.98)	1.00 (Reference)		
Moderate–heavy	85 (60)	0.65 (0.53–0.75)	4.56 (1.27–16.44)	0.020	
Disease-free survival					
Op‡					
Non–light	28 (35)	0.27 (0.10–0.48)	1.00 (Reference)		0.022
Moderate–heavy	52 (65)	0.39 (0.23–0.55)	0.64 (0.30–1.35)	0.241	
RT‡					
Non–light	56 (40)	0.79 (0.54–0.91)	1.00 (Reference)		
Moderate–heavy	85 (60)	0.31 (0.19–0.43)	2.25 (1.21–4.16)	0.010	

Alcohol consumption classified as: non–light, non-drinker and <23 g ethanol/day; and moderate–heavy, ≥23 g ethanol/day. †Adjusted by sex, age, Union for International Cancer Control performance status, stage, primary site, smoker, energy, second primary cancer, and induction chemotherapy. ‡Laryngopharyngeal cancer (oropharyngeal, hypopharyngeal, and laryngeal). CI, confidence interval; HR, hazard ratio; Op, surgery; RT, radiotherapy.
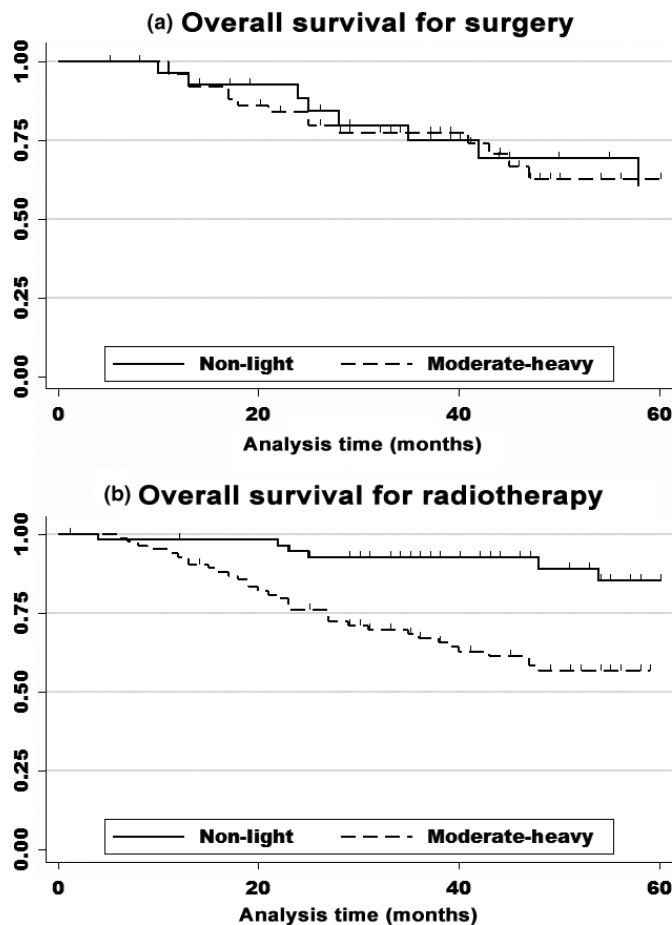
(a) Overall survival for surgery

(b) Overall survival for radiotherapy

Fig. 2. Kaplan–Meier survival curves for patients with laryngopharyngeal cancer by treatment method. (A) Surgery: no obvious difference was observed between non–light drinkers (0 and <23 g ethanol/day; n = 28) and moderate–heavy drinkers (23–46 and >46 g ethanol/day; n = 52) (5-year overall survival: 0.60 and 0.62, respectively; hazard ratio relative to non–light drinkers, 0.94 [95% confidence interval, 0.34–2.63], P = 0.875). (B) Radiotherapy: a significant association was observed between non–light drinkers (n = 56) and moderate–heavy drinkers (n = 85) (5-year overall survival, 0.56 and 0.85, respectively; hazard ratio relative to non–light drinkers, 3.26 [95% confidence interval, 1.19–8.98], P = 0.018).

dehydrogenase-2 (ALDH2) Glu/Glu patients with HNSCC.[10] These findings consistently show an association between poor prognosis and heavy drinking. Our present results are consistent with these earlier findings.

The background mechanisms behind the association behind alcohol drinking and survival of all HNSCC patients remain unclear, however, several mechanisms appear plausible for alcohol drinking and prognosis. First, several molecular effects of ethanol are proposed, including enhanced cell proliferation and altered expression of cytokeratin suggesting inhibition of squamous cell differentiation,[20,21] interference with DNA repair machinery and DNA synthesis,[12,22,23] and impaired antioxidant defense and enhanced production of reactive oxygen species.[24] A second possible explanation is that alcohol consumption impairs patients' nutrient status and immune system, leading to the inability to destroy cancer cells.[25] Among head and neck cancer, it has been reported that alcohol has significant immunomodulatory effects, by impairing cellular immunity,[26] particularly antigen-specific immune responses.[27]

As previous studies did not evaluate potential heterogeneity in the association between alcohol consumption and prognosis by treatment method, we evaluated this association by treatment method as indicated in the NCCN guideline. We found that alcohol consumption had a considerable impact on prognosis in subjects with laryngopharyngeal cancer who received RT, but no impact among patients who were treated with surgery. Although the cause of this heterogeneous association is unclear, several possibilities can be considered. First, the prevalence of human papilloma virus (HPV)-related oropharyngeal cancer among laryngopharyngeal cancer patients treated by RT might be high. Clinically, it is known that HPV-related oropharyngeal cancers are sensitive to RT,[28–30] and prevalence is high among non-smokers and non-drinkers.[31,32] In our study, although we did not evaluate HPV status, it is likely that non-drinkers receiving RT accounted for a substantial portion of HPV-related oropharyngeal cancer cases. An association between alcohol and HPV status on survival has been reported.[33,34] Broglie et al. evaluated patients with oropharyngeal cancer who were treated with RT and found that p16, a potential surrogate marker of HPV infection, and lifestyle factors (smoking and drinking) were associated with survival.[34] After multivariate analysis, including p16 status, alcohol dinking was a poor prognostic factor, as was N classification.[34] These results are congruent with our study. Further studies to examine the association between HPV infection and alcohol on prognosis are warranted.

A second possibility is genetic alteration induced by ethanol and an acetaldehyde-introduced heterogeneous impact of alcohol drinking between radiation therapy and surgery. A previous study of 136 patients with head and neck cancer reported that acetaldehyde induced upregulation of miRNA30 and miRNA934, which are related with proliferation, cisplatin sensitivity, and tumor suppressor genes.[35] The association of cisplatin sensitivity with radiation sensitivity among head and neck cancer patients is well known.[36,37] Taken together, these reports lead us to hypothesize that these genomic alterations induced by heavier acetaldehyde exposure might lead to radiation resistance.

We also found that the impact of alcohol drinking between tongue and non-tongue oral cavity cancer patients treated by surgery was heterogeneous. Patients with tongue cancer showed a significant association between alcohol consumption and prognosis, whereas those with non-tongue cancer showed no clear association. The reason for this difference of impact by subsite is unclear. To our knowledge, this is the first study to report this heterogeneity, and further investigations to replicate and explain it are warranted.

Several methodological strengths of our study should be mentioned. First, potential confounding by age, sex, PS, smoking, energy, and SPC were adjusted in the analysis. In particular, SPC was a major alcohol-related comorbidity,[38] so we treated the onset of synchronous SPC as a usual covariate and the onset of metachronous SPC as a time-varying covariate in multivariable analysis. Second, to exclude the effect of other alcohol-related comorbidities such as coronary disease, cerebral vessel disease, and pulmonary disease, we also evaluated DSS and DFS, and found a similar tendency. Third, alcohol consumption, the exposure of interest, was measured before treatment, ensuring the chronological relationship between exposure and outcome. Moreover, clinicians associated with the study cases were blinded to exposure status, limiting the possibility of information bias among researchers.

Two potential limitations of this study also warrant mention. First, as previously mentioned, we did not evaluate HPV status, which is potentially related to alcohol consumption in oropharyngeal cancer. Second, our information about drinking was limited to pretreatment behavior and we did not evaluate behavioral change after diagnosis. Evidence is limited about the impact of drinking after diagnosis on prognosis. However, most of the previous studies reported that patients did not change their drinking behavior even after diagnosis of HNSCC.[39,40] For example, López-Pelayo *et al.* reported that more than 80% of drinkers continued drinking even after HNSCC was diagnosed.[40] In other reports, older patients and those with a longer and heavier drinking habit prior to diagnosis were more likely to continue drinking after diagnosis.[39,41,42] Therefore, it may be likely that a substantial number of heavy drinkers before diagnosis continued drinking after diagnosis in our study. There have been several reports on the prognostic impact of continued drinking. Continued drinking after diagnosis of HNSCC increases treatment complications, the likelihood of recurrent cancer,[43,44] second primary cancer,[45] and the risk of mortality with relative risk 2.7 compared to non-drinkers.[46] By all means, worse prognosis observed in our study might be explained by the potential number of heavy drinkers who continued drinking after diagnosis. Moreover, if the negative association between drinking behavior after diagnosis and prognosis is true and HNSCC patients have the potential to quit drinking after diagnosis, one may say that our evaluation by using drinking behavior before diagnosis might give bias to a null association. Prospective evaluations of alcohol drinking after diagnosis on prognosis are needed.

In conclusion, we found that alcohol consumption was strongly associated with prognosis of HNSCC overall, and that its impact was heterogeneous by treatment method and primary site. Further study to validate these results and clarify the mechanisms behind these observed heterogeneous impacts of alcohol on prognosis by treatment method and primary site is warranted. In particular, we emphasize the importance of evaluation of HPV status in this context to depict the differential sensitivity to RT by alcohol consumption.

Acknowledgments

Disclosure Statement

The authors have no conflict of interest.

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Supporting Information

Additional Supporting Information may be found online in the supporting information tab for this article:

Fig. S1. Kaplan–Meier survival curve of onset of metachronous cancer in patients with head and neck squamous cell carcinoma.

Fig. S2. Subgroup analysis of impact of drinking categories on overall survival in patients with head and neck squamous cell carcinoma.

Fig. S3. Impact of drinking categories on survival according to treatment method at the primary site in patients with head and neck squamous cell carcinoma.

Fig. S4. Kaplan–Meier survival curves of overall survival (A), disease-specific survival (B), and disease-free survival (C) for laryngopharyngeal cancer patients.

Table S1. Interaction between alcohol consumption and potential confounders on overall survival of patients with head and neck squamous cell carcinoma