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RESEARCH ARTICLE

Postdiagnostic use of β-blockers and other antihypertensive drugs and the risk of recurrence and mortality in head and neck cancer patients: an observational study of 10,414 person–years of follow-up

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Abstract
Introduction Growing evidence indicates that norepinephrine promotes cancer growth and metastasis whereas β-blockers decrease these risks. This study aimed to examine the clinical impact of β-blockers and other hypertensive drugs on disease recurrence and survival in patients with head and neck squamous cell carcinoma (HNSCC).
Materials and methods This study analyzed a cohort of 1274 consecutive patients who received definitive treatments for previously untreated HNSCC at our tertiary referral center between January 2001 and December 2012. Antihypertensive use was considered positive if patients were on medication from HNSCC diagnosis to at least 1 year after treatment initiation. Cox proportional hazard models were utilized to determine associations between antihypertensive drugs and recurrence, survival, and second primary cancer (SPC) occurrence.
Results Hypertension itself was not a significant variable of recurrence and survival and no antihypertensive drug use affected SPC occurrence (all $P > 0.1$). After controlling for clinical factors, calcium-channel blocker use remained an independent variable for index cancer recurrence, and β-blocker use was significantly associated with poor cancer-specific mortality, competing mortality, and all-cause mortality (all $P < 0.05$). β-blocker use significantly affected competing and all-cause mortalities in normotensive patients, and calcium-channel blocker use affected index cancer recurrence in normotensive patients (all $P < 0.05$).
Conclusions Our data show that β-blocker use is associated with decreased survival and calcium-channel blockers is associated with increased cancer recurrence in patients of HNSCC.

Keywords Head and neck squamous cell carcinoma · Hypertension · β-Blockers · Recurrence · Survival

Introduction

Antihypertensive agents are typically prescribed for hypertension and heart disease worldwide. The antitumor activity of these drugs has been actively examined by preclinical and epidemiological studies, which showed the association between neuroendocrine hormones with cancer progression. Neurotransmitters such as epinephrine and norepinephrine induce tumor progression and metastasis by increasing the migratory activity of cancer cells [1]. Preclinical studies of stress-induced neuroendocrine activation or pharmacological activation of β-adrenergic signaling show significant increases in metastasis to lymph nodes and distant sites [2, 3]. The use of the β-antagonist propranolol reversed the stress-induced tumor spread to distant sites in animal models [2, 3]. Several studies have also investigated the clinical impact of β-blocker use in cancer patients, with results indicating that it was associated with improved

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survival outcomes [4–6]. However, the results of some population-based cohort studies do not support these findings [7–9]. The contradicting results may be caused by selective β1-blocker using, varying periods of use (incidental, prediagnostic, and postdiagnostic, etc.), and varying patient demographics. In fact, because antitumor effects are expected with β2-receptor antagonists (e.g., propranolol) but not β1-selective antagonists (e.g., atenolol) [1, 10, 11], using β2-receptor antagonists might result in decreased risks of cancer development and progression [12, 13].

In head and neck cancer (HNC), β-adrenergic receptors are highly expressed in tumor tissues compared with normal mucosa, and norepinephrine induces the migratory activity of tumor cells [14]. Use of propranolol also decreases HNC viability and induces apoptosis [15]. However, the clinical impact of β-blockers has not yet been examined in detail an HNC-specific cohort. In the only population-based cohort study with a 12-year follow-up, propranolol was shown to decrease the risk of human cancers, including HNC [12]. β-blockers have been actively used for patients with severe vascular lesions of the head and neck but not in treatment for HNC [16]. HNC is the eighth most common cancer worldwide and >90% of these cancers are head and neck squamous cell carcinomas (HNSCC) [17]. At presentation, approximately half of HNSCC patients are found to have advanced stage disease and regional metastasis is frequently seen [18, 19]. Therefore, the clinical impact of β-blockers needs to be examined in a large HNC cohort. It could be hypothesized that using β-blockers improves recurrence and survival outcomes in patients who are diagnosed with HNSCC. We reviewed antihypertensive medication use and clinical outcomes in a large cohort of 1274 patients with a median follow-up of 98 months. The purpose of this study was to evaluate the clinical impact of the use of β-blockers and other hypertensive drugs on recurrence and survival outcomes of patients with HNSCC.

Materials and methods

The medical records of all patients who were diagnosed and treated for previously untreated HNSCC at our tertiary referral hospital between January 2001 and December 2012 were reviewed. The primary objective was to find the relationship between the use of β-blockers and other hypertensive drugs and the survival of patients who received definitive treatments for HNSCC. The secondary objectives were to examine the association of hypertension with patient survival and disease recurrence as well as the potential clinical impacts of β-blockers and other hypertensive drugs on survival and recurrence in patients with or without hypertension. The samples size of 978–1489 HNSCC patients might be calculated to meet the power 0.9, alpha error 0.05, hazard ratio (HR, of survival between β-blocker users and nonusers) 1.3–1.8, and known accrual and follow-up periods. This study was reviewed and approved by the institutional review board, and the requirement for informed consent from each patient was waived. All 1274 patients met all of the following inclusion criteria: age ≥18 years; pathologically proven HNSCC in the oral cavity, oropharynx, larynx or hypopharynx; no distant metastasis at initial presentation; treated with curative intent; and followed for ≥2 year after treatment.

We reviewed the medical records of all the patients. These patients were queried about past medical histories, including medication at the time of diagnosis of HNSCC. Records of all medications used at initial staging and for treatment and post-treatment follow-up were also carefully reviewed. We defined β-blocker or other antihypertensive drug users as patients who were taking the drug at the time of diagnosis of HNSCC and continued to do so for ≥1 year after cancer treatment.

The treatment modality of each patient was determined by the consensus of our head and neck tumor board. Tumors were initially treated with primary curative surgery, radiotherapy (RT), concurrent chemoradiotherapy (CRT) with or without induction chemotherapy (IC), or a combinations of these treatments. Primary surgery was performed for wide excision of the primary lesion with or without neck dissection of regional metastases. Elective neck dissection was performed in some patients, particularly those with oral cavity cancer (of any T stage) or locally advanced tumors. High-risk patients received postoperative RT or CRT. RT consisted of intensity-modulated or three-dimensional conformal RT. RT was administered in daily fractions of 1.8 or 2.0 Gy 5 days each week for 6–8 weeks. The total radiation dose for each patient was 57–80 Gy. Concurrent chemotherapy consisted of high-dose cisplatin (75–100 mg/m^2) infused on days 1, 22, and 43 of the CRT. Salvage surgery was indicated for patients with progression of primary tumors after IC or residual disease at the primary site or neck after RT or CRT.

All patients underwent physical and endoscopic examinations at every clinic visit after the completion of initial treatments. The patients were evaluated every 1–3 months in the first year, every 2–4 months in the second and third years, every 6 months in the fourth and fifth years, and annually thereafter. Any lesions suggestive of recurrence or second primary cancer (SPC) were confirmed by biopsy and additional diagnostic tests. Patients with confirmed recurrence or SPC were scheduled for salvage or palliative treatment.

The data obtained included patient age and sex, underlying diseases, the site and tumor–node–metastasis (TNM) category of the primary tumor, smoking status, alcohol consumption, body mass index (BMI), Charlson comorbidity index (CCI) score, initial treatment modalities and usage of specific and

nonspecific β-blockers, and usage of angiotensin-converting enzyme inhibitors (ACEi), angiotensin-receptor blockers (ARB) and/or calcium-channel blockers (CCB). Heavy smokers were defined as those having smoked ≥30 pack–years, and heavy alcohol usage was defined as >1 drink (defined as 15.6 mL of 100% ethanol) per day. Patients who were assigned to undergo surgery with or without IC as the initial definitive treatment were classified as the surgery group. Patients who were initially assigned to undergo nonsurgical treatments were classified as the nonsurgical group.

Comparisons among groups were performed using Pearson's Chi-square test or Fisher's exact test for categorical data. The effects of hypertensive medication exposure on disease-free survival (DFS), cancer-specific survival (CSS), non-cancer-related survival (NCS), and overall survival (OS) were assessed with univariate and multivariate analyses using a Cox proportional hazards model. Estimated HR and 95% confidence intervals (CI) were calculated. Survival curves were estimated and compared using the Kaplan–Meier method and the log-rank test. A two-sided P value of <0.05 was considered statistically significant. All statistical analyses were performed using SPSS version 21.0 (IBM, Armonk, NY, USA).

Results

The study population of 1274 patients consisted of 1087 men (85.3%) and 187 women (14.7%) with a median age at diagnosis of 61 years (range: 20–87 years). Patient

Table 1 Patient characteristics ($n = 1274$)

Characteristics	β-Blocker users	Nonusers	P
Total no.	114	1160	
Age ≥65, *n* (%)	44 (37.9)	362 (31.3)	0.145
Sex, *n* (%)			0.839
Male	98 (85.3)	989 (86.0)	
Female	16 (14.7)	171 (14.0)	
Site of primary tumor, *n* (%)			0.108
Oropharynx	16 (14.0)	233 (20.1)	
Oral cavity	33 (28.9)	240 (20.7)	
Larynx	54 (47.4)	539 (46.5)	
Hypopharynx	11 (9.6)	148 (12.8)	
Smoking ≥30 pack–years, *n* (%)	58 (50.0)	619 (53.5)	0.496
Alcohol current heavy, *n* (%)	19 (16.4)	199 (17.2)	0.898
BMI <20, *n* (%)	12 (10.3)	194 (16.8)	0.085
CCI ≥3, *n* (%)	19 (16.7)	48 (4.1)	**<0.001**
Hypertension, *n* (%)	86 (75.4)	277 (23.9)	**<0.001**
Diabetes mellitus, *n* (%)	23 (20.2%)	162 (14.0%)	0.073
Second primary cancer, *n* (%)	16 (14.0)	173 (14.9)	0.891
Clinical TNM stage, *n* (%)			
T1–2/T3–4	80/34 (70.2/29.8)	750/410 (64.7/35.3)	0.258
N0/N1–3	83/31 (72.8/27.2)	787/373 (67.8/32.2)	0.293
Overall I–II/III–IV	50/64 (43.9/56.1)	478/682 (41.2/58.8)	0.619
Treatment, *n* (%)			0.526
Surgery	82 (71.9)	799 (68.9)	
Non-surgery	32 (28.1)	361 (31.1)	
Antihypertensive drug, *n* (%)			
CCB	71 (62.8)	191 (16.5)	**<0.001**
ACEi/ARB	20 (17.7)	51 (4.4)	**<0.001**
Median follow-up of survivors, months (range)	97 (24–168)	98 (24–192)	
Last status, alive/ICD/SCD/NCD	59/27/5/23 (51.8/23.7/4.4/20.2)	789/193/47/131 (68.0/16.6/4.1/11.3)	**0.003**

Bold numbers indicate $P < 0.05$

ACEi angiotensin-converting enzyme inhibitor, *ARB* angiotensin-receptor blocker, *BMI* body mass index, *CCB* calcium-channel blocker, *CCI* Charlson comorbidity index, *ICD* index cancer death, *NCD* non-cancer death, *SCD* second cancer death

[a] Calculated by using the χ^2 test

characteristics are summarized in Table 1. The most common tumor site was the larynx (593 cases, 46.5%), followed by the oral cavity (273 cases, 21.4%), oropharynx (249 cases, 19.5%), and hypopharynx (159 cases, 12.5%). A CCI score of ≥3 and SPCs were found in 67 (5.3%) and 189 (14.8%) patients, respectively. T3–4, N1–3, and overall III–IV stage tumors were found in 444 (34.9%), 404 (31.7%), and 746 (58.6%) patients, respectively. The median follow-up period was 98 months (range 24–192 months). The overall death was found in 426 patients (33.4%); index cancer death in 220 patients (17.3%); SPC death in 52 patients (4.1%); and the non-cancer death (competing mortality) in 154 patients (12.1%). The 5-year DFS, CSS, and OS rates of all study patients were 77.2, 82.7, and 73.8%, respectively. The 5-year and 10-year cumulative probabilities of second cancer were 14.8 and 23.1%, respectively. The cumulative probabilities of index cancer, second cancer, and non-cancer mortalities at 5 years were 17.3, 3.0, and 8.1%, respectively, and those at 10 years were 20.9, 8.1, and 21.0%, respectively.

Of all study patients, 114 (8.9%) were β-blocker users. Reasons for β-blocker usage were hypertension (71.9%), coronary artery disease (14.0%), arrhythmia (5.3%), heart failure (1.8%), and other noncardiac diseases (7.0%) such as peptic ulcer bleeding, psychiatric disease, liver cirrhosis, and Grave's disease. Of the β-blocker users, 18 (15.8%) were using nonselective β-blockers and 96 (84.2%) were using β1-selective blockers. Other antihypertensives were also reviewed: 71 patients (5.6%) were using an ACEi/ARB and 262 patients (20.6%) were taking a CCB. β-blocker, ACEi/ARB, and CCB usage was partially overlapping among the patients. Supplementary Table S1 shows the number of patients taking antihypertensive drugs. The patients were divided into two groups: β-blocker users and nonusers. The characteristics of the two groups are compared in Table 1. A CCI score of ≥3, hypertension, and the use of antihypertensive drugs were

Table 2 Univariate analysis of factors affecting disease-free survival, cancer-specific survival, overall survival, and non-cancer survival in study patients

Variable	Disease-free survival			Cancer-specific survival			Overall survival			Non-cancer survival		
	HR	95% CI	*P*	HR	95% CI	*P*	HR	95% CI	*P*	HR	95% CI	*P*
Age >65 years	1.08	0.85–1.38	0.516	1.10	0.83–1.47	0.491	1.75	1.44–2.12	**<0.001**	3.25	2.36–4.47	**<0.001**
Sex, female	1.20	0.89–1.63	0.240	1.05	0.73–1.52	0.781	0.86	0.64–1.15	0.305	0.63	0.36–1.09	0.097
BMI <20 kg/m^2	1.58	1.19–2.09	**0.001**	1.73	1.25–2.38	**0.001**	1.82	1.45–2.29	**<0.001**	1.88	1.29–2.74	**0.001**
CCI ≥3	1.64	1.07–2.51	**0.023**	1.46	0.86–2.48	0.157	2.21	1.60–3.05	**<0.001**	3.32	2.09–5.26	**<0.001**
Smoking ≥30 pack–years	1.10	0.83–1.33	0.683	1.24	0.95–1.62	0.113	1.41	1.16–1.71	**0.001**	1.38	1.00–1.90	0.053
Alcohol, heavy	1.27	0.95–1.69	0.114	1.11	0.79–1.57	0.539	1.07	0.83–1.34	0.621	0.96	0.61–1.49	0.841
Tumor site												
Oropharynx	1.00		**<0.001**	1.00		**<0.001**	1.00		**<0.001**	1.00		0.146
Oral cavity	1.99	1.37–2.90	**<0.001**	1.55	1.03–2.35	**0.037**	1.33	0.96–1.85	0.085	0.98	0.56–1.73	0.953
Larynx	1.26	0.88–1.79	0.207	0.80	0.54–1.19	0.261	1.14	0.85–1.52	0.386	1.22	0.76–1.94	0.409
Hypopharynx	2.26	1.50–3.40	**<0.001**	2.66	1.75–4.04	**<0.001**	2.63	1.91–3.64	**<0.001**	1.79	1.00–3.19	0.050
Tumor classification, T3–4	1.61	1.13–2.15	**0.005**	3.09	2.36–4.04	**<0.001**	2.37	1.96–2.87	**<0.001**	1.83	1.33–2.53	**<0.001**
Nodal classification, N1–3	1.42	1.09–1.91	**0.036**	2.36	1.81–3.08	**<0.001**	2.00	1.65–2.42	**<0.001**	1.77	1.27–2.46	**0.001**
Overall TNM stage, III–IV	1.58	1.11–2.19	**0.011**	3.79	2.70–5.32	**<0.001**	3.17	2.53–3.97	**<0.001**	3.24	2.24–4.67	**<0.001**
Primary treatment, non-surgery	1.22	0.93–1.55	0.115	1.24	0.94–1.63	0.128	1.08	0.88–1.32	0.470	0.81	0.57–1.16	0.246
Second primary cancer	0.73	0.51–1.05	0.086	0.43	0.26–0.72	**0.001**	1.54	1.23–1.94	**<0.001**	1.15	0.76–1.75	0.503
Hypertension	1.12	0.87–1.43	0.383	1.05	0.78–1.41	0.746	1.00	0.81–1.24	0.970	1.11	0.79–1.57	0.554
Antihypertensive drugs												
β-blocker	1.33	0.93–1.91	0.122	1.49	0.99–2.22	0.054	1.54	1.17–2.05	**0.002**	1.80	1.17–2.79	**0.008**
CCB	1.35	1.04–1.76	**0.026**	1.14	0.83–1.56	0.428	1.20	0.96–1.50	0.109	1.31	0.91–1.88	0.146
ACEi/ARB	1.36	0.86–2.14	0.185	1.07	0.60–1.91	0.822	1.25	0.83–1.87	0.282	1.52	0.80–2.88	0.203
Nonselective β-blocker[a]	1.47	0.66–3.31	0.347	1.38	0.51–3.70	0.528	1.79	0.95–3.35	0.071	1.98	0.73–5.36	0.178

Bold values indicate $P < 0.05$

ACEi angiotensin-converting enzyme inhibitor, *ARB* angiotensin-receptor blocker, *BMI* body–mass index, *CCB* calcium-channel blocker, *CI* confidence interval, *CCI* Charlson comorbidity index, *HR* hazard ratio

[a] Compared with the nonusers of β-blockers

more frequently found in the β-blocker users ($P < 0.001$). No significant differences in patient age, sex, primary tumor location, alcohol consumption, smoking, BMI, SPC development, or initial TNM stage were observed among the groups (Table 1).

The results of the univariate and multivariate analyses of factors affecting DFS, CSS, OS, and NCS are shown in Tables 2 and 3, respectively. Locoregional failure and distant metastasis were identified in 294 (23.1%) and 123 (9.7%) patients, respectively. For DFS, multivariate analysis showed that a BMI of <20 kg/m^2, a CCI score of ≥3, tumor site, T and N classifications, N stage, and CCB use were significantly related to a higher risk of recurrence (all $P < 0.05$, Table 3). Index cancer death occurred in 123 (9.7%) patients. For CSS, multivariate analysis showed that tumor site, T and N classifications, SPC, and β-blocker use were significantly correlated with index cancer survival (all $P < 0.05$). All-cause death occurred in 426 (33.4%) patients. For OS, multivariate analysis showed that being aged >65 years, having a BMI of <20 kg/m^2, a CCI score of ≥3, smoking ≥30 pack–years, tumor site, T and N classifications, SPC, and β-blocker use were related to a high risk of all-cause death (all $P < 0.05$). Non-cancer-related death occurred in 154 cases. Multivariate analyses showed that patients aged >65 years, those with a BMI of <20 kg/m^2, those with a CCI score of ≥3, T and N classifications, and β-blocker use were significantly correlated with competing mortality. Of the 1274 patients, 189 (14.8%) developed synchronous or metachronous SPCs. In univariate analyses, an age of >65 years, male gender, smoking ≥30 pack–years, tumor site, and primary treatment modality were significantly correlated with a higher risk of SPC occurrence (all $P < 0.05$) (Supplementary Table S2). Multivariate analyses showed that age, smoking, and hypopharyngeal tumor site remained independent variables for SPC occurrence (all $P < 0.05$).

Patients were divided into two groups: β-blocker users and nonusers, or CCB users or nonusers. Kaplan–Meier survival curves are depicted in Fig. 1. β-blocker users showed significantly higher overall, index cancer, and competing mortality rates than the other groups (all $P < 0.05$) (Fig. 1). Figure 2 shows the cumulative incidence probabilities for all-cause death, cancer-specific death, and non-cancer death in the β-blocker users according to hypertension status. Index cancer recurrence in CCB users is also shown. β-blocker use more significantly affected competing and all-cause mortalities in normotensive patients (all $P < 0.05$), whereas CCB use more affected index cancer recurrence in normotensive patients ($P = 0.026$).

Table 3 Multivariate analysis of factors affecting disease-free survival, cancer-specific survival, overall survival, and non-cancer survival in study patients

Variable	Disease-free survival			Cancer-specific survival			Overall survival			Non-cancer survival		
	HR	95% CI	*P*	HR	95% CI	*P*[a]	HR	95% CI	*P*	HR	95% CI	*P*
Age >65years							1.59	1.13–1.80	**<0.001**	3.09	2.22–4.31	**<0.001**
BMI <20 kg/m^2	1.41	1.06–1.88	**0.020**	1.23	0.88–1.70	0.223	1.42	1.13–1.80	**0.003**	1.51	1.02–2.24	**0.040**
CCI ≥3	1.67	1.08–2.58	**0.021**				2.20	1.57–3.08	**<0.001**	2.79	1.73–4.52	**<0.001**
Smoking ≥30 pack–years							1.33	1.08–1.64	**0.008**	1.27	0.89–1.81	0.189
Tumor site												
Oropharynx			**<0.001**			**<0.001**			**<0.001**			0.851
Oral cavity	2.95	1.91–4.55	**<0.001**	2.44	1.55–3.86	**<0.001**	1.82	1.29–2.57	**0.001**	1.32	0.71–2.44	0.387
Larynx	1.45	0.97–2.16	0.069	1.10	0.72–1.70	0.656	1.18	1.85–1.64	0.334	1.18	0.67–2.05	0.568
Hypopharynx	1.93	1.26–2.95	**0.002**	2.31	1.50–3.56	**<0.001**	1.89	1.35–2.65	**<0.001**	1.19	0.65–2.18	0.568
Tumor classification, T3–4	1.58	1.08–2.10	**0.037**	2.70	2.04–3.59	**<0.001**	2.02	1.65–2.47	**<0.001**	1.50	1.06–2.12	**0.023**
Nodal classification, N1–3	1.43	1.05–1.91	**0.046**	1.97	1.45–2.66	**<0.001**	1.91	1.52–2.41	**<0.001**	1.12	1.41–3.20	**<0.001**
Second primary cancer	0.69	0.48–1.00	**0.048**	0.42	0.25–0.69	**0.001**	1.38	1.09–1.75	**0.008**			
Antihypertensive drugs												
β-Blocker				1.81	1.20–2.72	**0.004**	1.65	1.23–2.20	**0.001**	1.85	1.17–2.93	**0.009**
CCB	1.34	1.02–1.75	**0.035**									

Bold values indicate $P < 0.05$

ACEi angiotensin-converting enzyme inhibitor, *ARB* angiotensin-receptor blocker, *BMI* body–mass index, *CCB* calcium-channel blocker, *CI* confidence interval, *CCI* Charlson comorbidity index, *HR* hazard ratio

[a] Cox proportional hazard regression analyses were performed with backward elimination using variables with *P* values <0.1 from univariate analyses

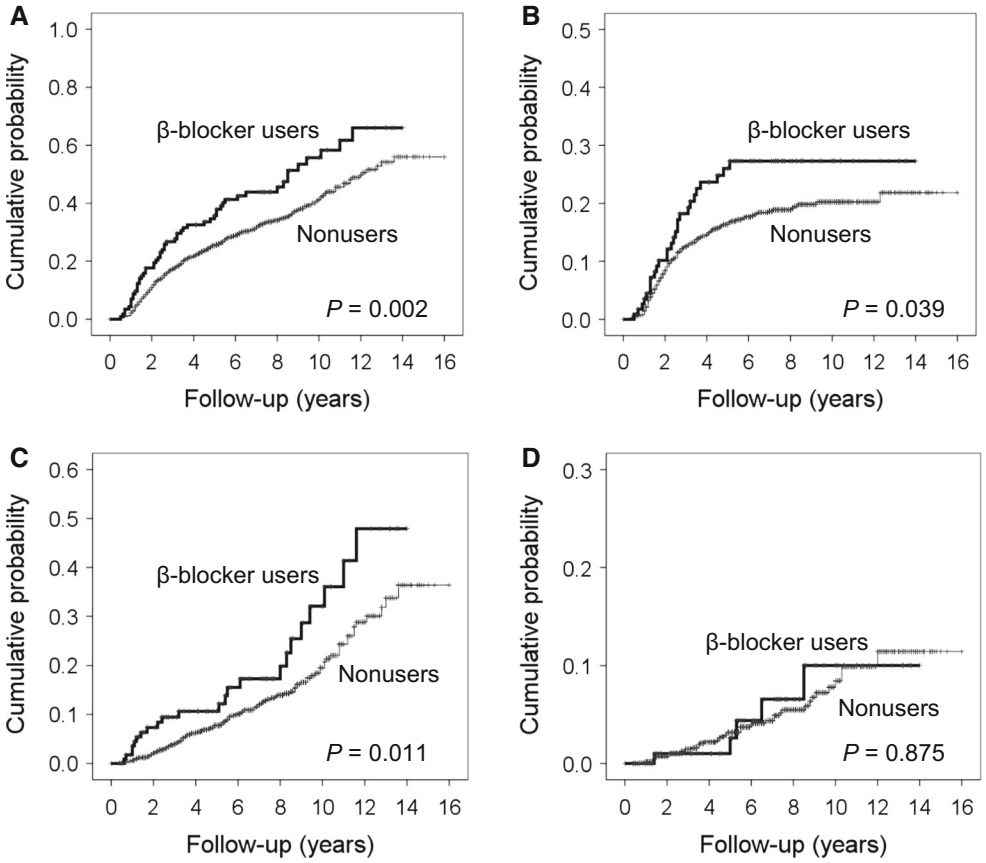

Fig. 1 Cumulative incidence probabilities for **a** all-cause mortality, **b** cancer-specific mortality, **c** competing mortality, and **d** second cancer mortality according to the use of β-blockers. For log-rank tests, $P < 0.05$

Discussion

In this study, hypertension itself did not affect disease recurrence, survival, or second cancer occurrence in patients with HNSCC. It has been reported that, regardless of the use of antihypertensive treatment, high blood pressure is associated with a modestly increased risk of cancer and mortality from cancer [20, 21]. A recent study showed that, compared with normotensive patients, patients with both treated and untreated hypertension had a 1.06 (95% CI 1.02–1.12) increased risk of cancer and a 1.10 (1.01–1.20) increased risk of cancer mortality [20]. There are, however, inconsistencies in the reports on the association between hypertension and cancer. Another study reported a 7% (4–9%) increase in incidental cancer risk per 10 mmHg increase in mid-blood pressure, but the relation of mid-blood pressure to total incidental cancer was observed only in men [22]. A Swedish cohort also showed a 41% increased risk of cancer in hypertensive men [23]. A case–control study reported that hypertension was associated with a 1.75 (1.61–1.90) increased risk of mortality from cancer, particularly renal cell carcinoma [21]. In addition, a population-based study showed no association between hypertension and lung-cancer related deaths [24]. However, the relationship between hypertension and HNC risk has rarely been studied. No close relationship between hypertension and HNC outcomes was observed in our cohort.

This study showed that β-blocker use was associated with increased cancer-specific mortality, competing mortality, and all-cause mortality in HNSCC patients. A prior study demonstrated the association of the incidental use of β-blockers with improved distant metastasis-free survival, DFS, and OS in a retrospective cohort of 722 patients with non-small cell lung cancer treated with definitive RT [5]. Of 155 β-blocker users, most patients (86.5%) received a selective β1-blocker such as metoprolol (57.4%), atenolol (27.7%), and bisoprolol (1.3%), and 13.5% patients received nonselective β-blockers [5]. A recent study showed that the use of any β-blocker increased median OS compared with not using a β-blocker in 1425 patients with ovarian cancer (47.8 vs 42.0 months, $P = 0.04$). Furthermore, the median OS of women using nonselective β-blockers was 94.9 months, which was much higher than the 38 months of β1-selective blocker users ($P < 0.01$). A population-based study reported that the cumulative probability of breast cancer-specific mortality was significantly lower for nonselective β-blocker

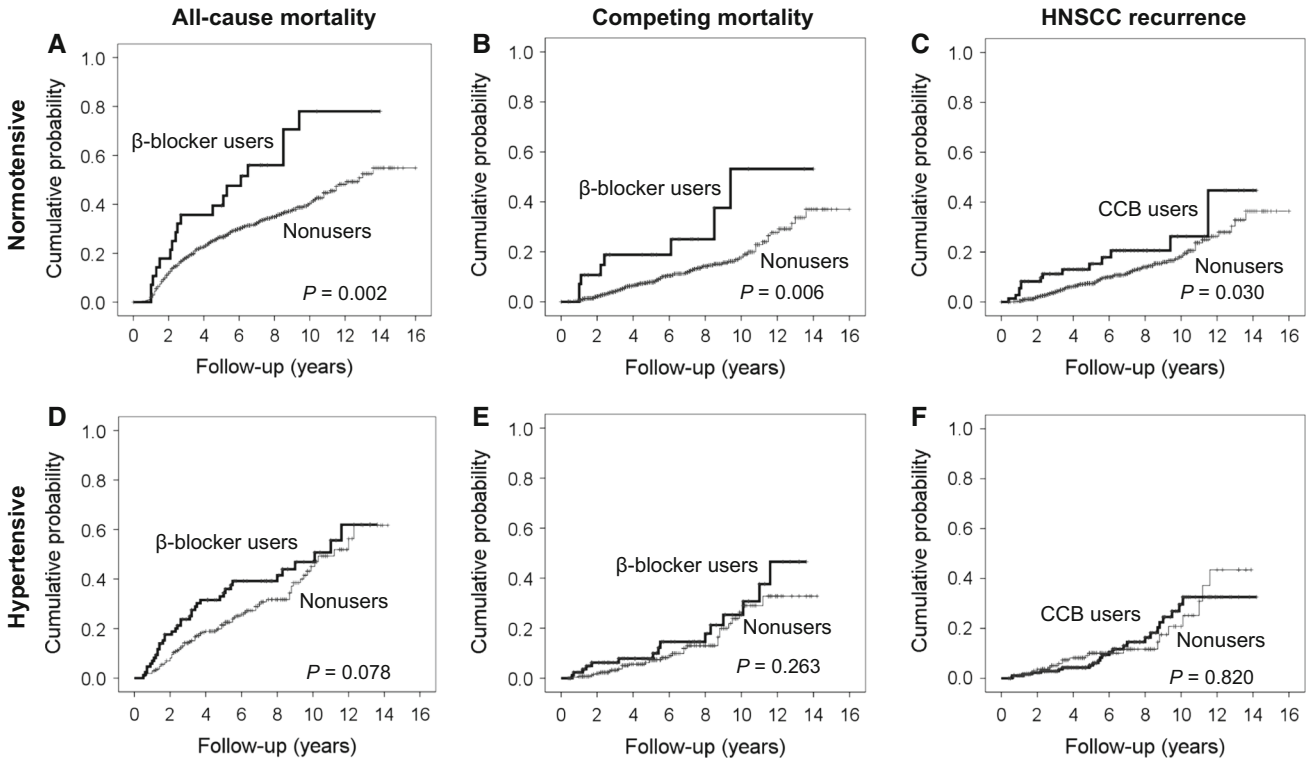

Fig. 2 Cumulative incidence probabilities for **a**, **d** all-cause mortality and **b**, **e** competing mortality in the patients with β-blocker use, and **c**, **f** index cancer recurrence in patients with calcium-channel blocker (CCB) use, according to the presence (**a–c**) or absence **d–f** of hypertension. For log-rank tests, $P < 0.05$ for **a–c** and $P > 0.1$ for (**d–f**)

propranolol users than matched nonusers (HR = 0.19, 95% CI 0.06–0.60), but did not differ between selective β1-blocker atenolol users and matched nonusers [4].

There was also no evidence of association between β-blocker usage and cancer mortality. A large UK population-based cohort study of colorectal cancer patients identified that postdiagnostic use of β-blockers, such as propranolol, was associated with only a weak reduction in all-cause mortality (adjusted odds ratio [OR] = 0.88, 95% CI 0.77–1.00, $P = 0.04$) [10]. Postdiagnostic use of β-blockers was not associated with a decreased risk of cancer-specific or all-cause mortality in prostate cancer patients [9]. Furthermore, in our study, postdiagnostic use of β-blockers was associated with increased cumulative probabilities of all cancer-specific, all-cause, and non-cancer mortalities rather than improving survival outcomes in HNSCC. β-blocker use in patients without hypertension significantly decreased survival compared with β-blocker use in hypertensive patients. This might in part result from the fact that most (84.2%) of the β-blockers used were selective β1-antagonists such as atenolol. A recent report suggested that the use of atenolol was related to a 1.91 (95% CI 1.04–4.31) increased long-term mortality in community-dwelling hypertensive older adults [25]. However, this might be rebutted by a report that cancer mortality did not rise in the clinic after a large increase in atenolol prescription [26].

In this study, the use of CCB was associated with increased index cancer recurrence, but not cancer or non-cancer mortality. CCB use in normotensive patients affected index cancer recurrence more than in hypertensive patients. The survival disadvantage of CCBs in cancer patients has been well reported. The use of CCBs for 10 or more years was associated with a 2.4 (95% CI 1.2–4.9) increased risk of breast cancer in a population-based case–control study [27]. The biological mechanisms of increased cancer risk from CCBs are unknown. It has been hypothesized that CCB may inhibit apoptosis via increasing intracellular calcium levels [28]. This might in part explain our results. However, a meta-analyses of 324,168 patients from randomized trials refuted a 5–10% relative increase of cancer and cancer-related death associated with the use of β-blockers, diuretics, ARBs, ACEis, and CCBs [29]. The combination of ARBs and ACEis may cause at least a 10% increase in cancer relative risk. However, the combination effect was not observed in our study.

Our study showed no association between the use of β-blockers or other hypertensive drugs and second cancer occurrence. The risk factors for the development of second cancer were in agreement with those previously reported in

the HNSCC patients [30]. Furthermore, our study suggests that postdiagnostic use of antihypertensive drugs in the HNSCC patients is not associated with a significant increase in second cancer occurrence. Thus, ours is the first study to show a negative clinical impact of the postdiagnostic use of β-blockers and CCBs in a large cohort of HNSCC patients who received definitive treatment. Nonetheless, our study has several limitations, including the retrospective design and the varieties of tumor sites and treatment modalities. These factors may all weaken its statistical power. However, our institution used a multidisciplinary team approach with proper planning, multimodal treatment, and post-treatment surveillance for each HNSCC patient. Data on p16 and human papilloma virus status were only obtained for some patients, so we could not analyze the effect of these biomarkers on survival.

In conclusion, our study showed that postdiagnostic β-blocker use was associated with decreased survival and that CCBs were associated with increased cancer recurrence in a large cohort of HNSCC patients. This may provide valuable information on quantification of the potential relationship between antihypertensive drugs and HNC progression. Future prospective trials are needed to validate our findings, which contradict the previous clinical results concerning β-blocker use in other cancer types. Our results have the potential to aid oncologists in selecting antihypertensive drugs for HNSCC patients, when weighing the risks and benefits of antihypertensive medications.

Compliance with ethical standards

Conflict of interest The authors have no conflict of interest to declare.

Research involving human participants and/or animals This article does not contain any studies with human participants or animals performed by any of the authors.

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