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Effect of polypharmacy and potentially inappropriate medications on treatment and posttreatment courses in elderly patients with head and neck cancer

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Abstract
Purpose The use of excessive and inappropriate medications is a common problem in elderly populations. The use of polypharmacy (PP) and potentially inappropriate medication (PIM) may affect treatment-related morbidities in elderly cancer patients, which has rarely been studied in patients with head and neck cancer (HNC). Here, we evaluate the effects of PP and PIM on treatment and posttreatment courses in elderly HNC patients.
Methods This study included 229 elderly HNC patients who underwent definitive treatment. Medications were carefully recorded, and the prevalences of PP and PIM are reported. We evaluated the associations between PP, PIM, treatment, and posttreatment course in terms of comorbidities, treatment-related toxicity, prolonged hospitalization, and posttreatment noncancer health events.
Results The prevalences of PP and PIM in our elderly HNC patients were 29.3 and 24.0 %, respectively, and frequently described PIMs include aspirin (12.2 %), calcium channel blockers (4.8 %), benzodiazepines (4.3 %), and nonsteroidal anti-inflammatory drugs (3.9 %). PP and PIM were not significantly associated with treatment-related toxicity, but were associated with modestly increased prolonged hospitalization [odds ratio [OR] 2.30 (95 % confidence interval 0.89–5.95); $P = 0.080$] and noncancer health events [OR 1.81 (0.99–3.31); $P = 0.052$], respectively. Among high-risk medications, benzodiazepine [OR 5.09 (1.21–21.5); $P = 0.015$] and calcium channel blockers [OR 5.69 (1.07–33.25); $P = 0.031$) were significantly associated with prolonged hospitalization.
Conclusions Neither PP nor PIM are significantly associated with treatment-related toxicity in elderly HNC patients, but these are associated with modest increases in prolonged hospitalization and noncancer health events.

Keywords Head and neck cancer · Elderly patients · Polypharmacy · Potentially inappropriate medication · Treatment

Introduction

The population of seniors is increasing in developed countries, and the health-related problems of this population are thus becoming more prominent. The use of polypharmacy (PP) and potentially inappropriate medication (PIM) is an increasing concern among oncologists and health care providers because the geriatric population is generally considered vulnerable in terms of physical, cognitive, and psychosocial impairments, all of which hinder proper cancer-related therapy. PP is a common problem in older adults, with a high prevalence of up to 37–92 % (Hajjar et al. 2005; Steinman et al. 2006; Rothberg et al. 2008; Buck et al. 2009). Moreover, the prevalences of PP and

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PIM among elderly cancer patients are reportedly as high as 48–80 and 8–41 %, respectively (Prithviraj et al. 2012; Nightingale et al. 2015). PP can increase clinically significant drug–drug interactions and ultimately lead to increases in drug-related adverse events, poor health resource utilization, poor quality of life, and morbidity (e.g., falls, fractures, prolonged hospitalization) (Leipzig et al. 1999a, b; Hanlon et al. 2006; Maggiore et al. 2014).

The use of PP and PIM is an important issue in cancer patients >65 years, who comprise the major populations of all newly diagnosed cancers in the USA and other developed countries (Smith et al. 2009; Torre et al. 2015). The occurrence of cancer is increasing along with the aging of the population and increasing the prevalence of known risk factors (Torre et al. 2015). Elderly cancer patients are more vulnerable to the adverse effects of PP and PIM than older adults without cancer because they have a higher chance of exposure to chemotherapeutic agents and other related medications. The use of PP and PIM in elderly patients may also affect cancer therapy-related toxicity and morbidity (Maggiore et al. 2014).

Head and neck cancer (HNC) arises from the vital anatomical region that is associated with critical functions required for maintaining daily life (e.g., respiration, speaking, swallowing). Because more than half of HNC patients are diagnosed at an advanced stage, they commonly undergo multidisciplinary multimodal treatments, including surgery, radiotherapy, and chemotherapy (Haddad and Shin 2008). Accordingly, the role of systemic chemotherapy in the management of HNC has increased, as well as its active use in definitive chemoradiotherapy and induction chemotherapy (Gibson and Forastiere 2006; Busch et al. 2015). Cancer therapy-related toxicity and health-related events in older adults with cancer might be affected by the inappropriate use of other multiple drugs (Maggiore et al. 2010; Balducci et al. 2013). The use of PP and PIM may increase the risk of chemotherapy-related toxicity by affecting drug–drug interactions, surgery-related complications, and prolonging hospitalization. Although several studies have evaluated some of the effects of PP and PIM in older adults with cancer, their associations with clinical importance remain undefined (Flood et al. 2009). In addition, the use of PP and PIM has rarely been examined in elderly HNC patients.

We hypothesized that the use of PP and PIM may affect treatment-related toxicity, hospitalization, and noncancer health events in elderly HNC patients. In our present study, we assessed the prevalence of PP and PIM use in elderly HNC patients and their effects on treatment and posttreatment courses.

Materials and methods

Study patients

A total of 805 patients with head and neck squamous cell carcinoma that arose in the oral cavity, oropharynx, nasopharynx, larynx, or hypopharynx were treated at our tertiary referral hospital between 2008 and 2013. Of these, 576 patients were excluded from our current analyses because they were <65 years of age ($n = 415$), underwent previous treatment for HNC ($n = 74$), had initial distant metastasis ($n = 30$), had a history of second primary cancer within 5 years prior to index cancer diagnosis ($n = 47$), or were lost on follow-up within 1 year after treatment ($n = 10$). The remaining 229 patients were eligible for this study. The records describing their comorbidities and medications at the time of diagnosis were obtained. This study was reviewed and approved by the institutional review board of our institution, and the requirement for informed consent from each patient was waived.

Definition of PP and PIM

All medications administered to each patient were carefully reviewed at the initial diagnosis and during primary treatments. PP was defined as ≥5 medications, including prescription, nonprescription, and herbal medications (Hajjar et al. 2007; Nightingale et al. 2015). The use of PIM was measured using the 2012 Beers criteria (Blanco-Reina et al. 2014). The Beers criteria identify medications that can be inappropriately used according to a risk–benefit ratio. These criteria are based on two components: (1) drugs and drug classes considered inappropriate for any older adult, and (2) drugs and drug classes that may be inappropriate based on a specific coexisting illness.

Treatment and follow-up

All patients were primarily treated with curative intent following consensus among the members of the tumor board at our hospital. All study patients received the primary modalities for surgery- or radiotherapy-based treatments. Of the 132 surgical patients, 53 patients (40.2 %) underwent postoperative adjuvant radiotherapy or cisplatin-based chemoradiotherapy, as these patients were diagnosed with advanced-stage cancer or adverse features. The nonsurgical patients underwent definitive radiotherapy ($n = 44$; 19.2 %) or chemoradiotherapy ($n = 53$; 23.1 %). Induction chemotherapy followed by surgery or radiotherapy/chemoradiotherapy was also introduced to 29 patients (12.7 %) following tumor board consensus.

After treatment completion, each patient was regularly followed with physical and endoscopic examinations at the outpatient clinic, and imaging tests were performed according to the appropriate follow-up schedules. If recurrence was suspected, those patients received curative or palliative treatments according to status of the disease or host. All surviving patients were followed >1 year.

Variables

At the time of initial staging workup, patients were evaluated to determine age, sex, body mass index, residence, education level, smoking history, alcohol consumption, marital status, Charlson comorbidity index (Charlson et al. 1987), Eastern Cooperative Oncology Croup performance status scale, functional status, treatment modality, time between diagnosis and treatment, and general laboratory data. During and after the initial treatments, we carefully recorded the treatment toxicities, duration of hospitalization, and noncancer health events. Adverse events and complications were identified, and the causes and severities were graded according to the Common Terminology Criteria for Adverse Effects (CTCAE; version 4.0) (Liu et al. 2012). An noncancer health event was defined as readmission to the hospital within 2 years after the initial treatment for any cause that was not directly related to the index cancer or newly developed second primary cancer (Ryu et al. 2013; Kwon et al. 2014).

Statistical analysis

Commonly prescribed medications and PIMs were reviewed, and the prevalences of PP and PIM were reported. The χ^2 or Fisher's exact test for categorical data and the Student's t test or Mann–Whitney U test for continuous data were used to compare the differences between variables in patients with and without PP or PIM. Logistic regression analysis was used to determine the associations between medication measures and treatment-related toxicity, hospitalization, and noncancer health event. The odds ratios (ORs) and 95 % confidential intervals (CIs) were calculated. Statistical significance was defined as a two-sided P value <0.05. All statistical analyses were performed using SPSS version 21.0 (IBM, Armonk, NY, USA).

Results

Patient characteristics

The study patients included 192 men and 37 women with a median age of 73 years (range 65–87 years) (Table 1). The most common site for the primary tumor was the larynx (41.9 %), followed by the oral cavity (21.8 %), oropharynx (17.5 %), hypopharynx (12.2 %), and nasopharynx (6.6 %). Ninety-two patients (40.2 %) were diagnosed as advanced T3–T4 stages, 97 patients (42.3 %) were N1–N3 stages, and 133 patients (58.1 %) were overall stages III–IV. One hundred and thirty-two patients (57.6 %) received surgical treatment, and 97 patients (42.3 %) underwent radiotherapy/chemoradiotherapy. During the follow-up period (median 35 months; range 12–86 months), instances of local, regional, and distant recurrence were found as 24 (10.5 %), 10 (4.4 %), and 13 (5.7 %) patients, respectively. At the last follow-up examination, 172 patients (75.1 %) were alive without disease, seven patients (3.1 %) were alive with disease, 37 (16.2 %) patients had died of the index cancer, and 13 (5.7 %) patients had died of other causes.

Prevalence and factors associated with PP and PIM

Of the 229 study patients, 67 patients (29.3 %) were receiving PP at the time of diagnosis and four patients (1.7 %) were receiving excessive PP (defined as ≥10 medications). The mean number of medications was 2.8 ± 2.7 (range 0–10) among all study patients and was 6.6 ± 1.5 (range 5–10) in the PP group. The most common medication category was cardiovascular drugs (50.7 %) (e.g., alpha-adrenergic agonists/antagonists, antiarrhythmics, beta-adrenergic antagonists, calcium channel antagonists, digoxin, renin–angiotensin aldosterone antagonists, vasodilators), followed by gastrointestinal (22.3 %), endocrinological (18.3 %), and antiplatelet drugs (16.6 %) (Table 2). Table 2 presents the prevalence of PP according to comorbidity: hypertension (41.5 %), diabetes (17.9 %), and dyslipidemia (10.9 %) were the most common comorbidities by disease status (Table 3). Of those patients with comorbidities, PP was most commonly noted in patients with coronary artery disease (6 of 6 patients; 100 %), epilepsy (1 of 1 patients; 100 %), or stroke history (9 of 11 patients; 81.8 %).

At the time of diagnosis, PIM was noted in 55 of all study patients (24.0 %) and 36 of 67 PP patients (53.7 %). The mean number of inappropriate medications was 0.31 ± 0.62 (range 0–4) among all study patients and 1.06 ± 0.74 (range 1–4) among all PP patients. The most common PIM was aspirin (28 of 229 patients; 12.2 %), which may increase the risk of gastrointestinal bleeding or peptic ulcer disease in elderly patients (Supplementary Table S1). The next most common PIM was calcium channel blockers (4.8 %) (e.g., nifedipine), which can cause hypotension and carries the risk of precipitating myocardial ischemia. The third most common PIM was benzodiazepine (4.3 %), which demonstrates increased sensitivity in the older adults and an increased risk of cognitive impairment, delirium, falls, fractures, and motor vehicle accident.

Table 1 Patient characteristics ($n = 229$)

Variable	*N*	%
Age, median (range) in years	73 (65–87)	
Sex		
Male/female	192/37	83.8/16.2
BMI, median (range) in kg/m^2	23.0 (14.8–36.8)	
Residence		
Urban/rural	129/100	56.3/43.7
Education level		
<High school/≥high school	121/108	52.8/47.2
Smoking, pack-years		
Nonsmoker/<30/≥30	63/50/116	27.5/21.8/50.7
Alcohol use, drinks per day		
<1/≥1	104/125	45.4/54.6
Status of spouse		
Alive/dead or none	111/118	48.5/51.5
CCI		
0/≥1	167/62	72.9/27.1
ECOG performance status		
0/1/2/3	200/6/3/20	87.3/2.6/1.3/8.7
Functional status		
Fit/vulnerable/frail	187/39/3	81.7/17.0/1.3
Prevalence of PP or PIM		
PP	67	29.3
PIM	55	24.0
Primary tumor site		
Larynx	96	41.9
Oral cavity	50	21.8
Oropharynx	40	17.5
Hypopharynx	28	12.2
Nasopharynx	15	6.6
Clinical TNM stage		
T1/T2/T3/T4	96/41/30/62	41.9/17.9/13.1/27.1
N0/N1/N2/N3	132/25/72/0	57.6/10.9/31.4/0
Overall stage I/II/III/IV	76/20/35/98	33.1/8.7/15.3/42.8
Initial treatment		
Surgery only	79	34.5
Surgery + postoperative RT/CRT	53	23.1
RT only	44	19.2
CRT	53	23.1
Induction chemotherapy	29	12.7
Follow-up information		
Follow-up period, median (range) in months	35 (12–86)	
Recurrence, local/regional/distant[a]	24/10/13	10.5/4.4/5.7
NED/AD/DOD/DOC	172/7/37/13	75.1/3.1/16.2/5.7

BMI body mass index, *CCI* Charlson comorbidity index, *CRT* concurrent chemoradiotherapy, *RT* radiation therapy, *PIM* potentially inappropriate medication, *TNM* tumor-node-metastasis staging system proposed by the American Joint Committee on Cancer (7th ed.)

[a] These values mutually overlap

Table 2 Prevalence of prescription medications by pharmacological category ($n = 229$)

Pharmacologic category	Prescription medication	*N*	%
Cardiovascular	Alpha-adrenergic agonists/antagonists, antiarrhythmics, beta-adrenergic antagonist, calcium channel antagonists, digoxin, renin–angiotensin aldosterone antagonists, vasodilators	116	50.7
Gastrointestinal	Antiemetics, antispasmodics, constipation/diarrhea, histamine-2 antagonist, protectants, proton pump inhibitors	51	22.3
Endocrine	Oral hypoglycemic agent, insulin, thyroid replacement, antithyroid agents	42	18.3
Antiplatelet/anticoagulant		38	16.6
Neuropsychiatric	Antidepressants, anti-Parkinson agents, antipsychotics, anticonvulsants	30	13.1
Dyslipidemics	Statins, ezetimibe, fenofibrate	29	12.7
Analgesic	Nonsteroidal anti-inflammatory drugs, opioids/nonopioids, neuropathic pain drugs	28	12.2
Vitamin/minerals		22	9.6
Pulmonary/respiratory	Inhalers, oral tablets	22	9.6
Diuretic		16	7.0
Genitourinary		15	6.6
Antimicrobial		9	3.9
Benzodiazepine		6	2.6
Gout		3	1.3
Ophthalmic		2	0.8

Table 3 Prevalence of polypharmacy according to comorbidities ($n = 229$)

Comorbidity by disease status	Comorbidity		Polypharmacy	
	N	%	*N*	%
Cardiovascular				
Hypertension	95	41.5	47	49.5
Dyslipidemia	25	10.9	12	48.0
Arrhythmias	7	3.1	3	42.9
Coronary artery disease	6	2.6	6	100.0
Congestive heart failure	4	1.7	1	25.0
Endocrine				
Diabetes	41	17.9	23	56.1
Thyroid disease	3	1.3	0	0
Respiratory				
Tuberculosis history	11	4.8	2	18.2
Asthma	4	1.7	2	50.0
Chronic obstructive pulmonary disease	3	1.3	2	66.7
Gastrointestinal				
Gastroesophageal cancer	11	4.8	1	9.1
Hepatitis	8	3.5	1	12.5
Peptic ulcer	5	2.2	3	6.0
Cholecystitis, cholelithiasis	4	1.7	1	25.0
Irritable bowel syndrome	2	0.8	1	50.0
Neurological				
Stroke history	11	4.8	9	81.8
Parkinson's disease	2	0.8	1	50.0
Epilepsy	1	0.4	1	100.0
Urological				
Benign prostate hypertrophy	11	4.8	6	54.5

PP was significantly associated with age ($P = 0.001$), body mass index ($P = 0.030$), and the number of comorbidities ($P < 0.001$) (Table 4). PIMs were significantly associated with sex ($P = 0.040$), body mass index ($P = 0.036$), and number of comorbidities ($P < 0.001$). Other variables, such as education level, residence, smoking and alcohol habits, serum hemoglobin and albumin levels, performance status, and functional status were not significantly associated with PP or PIM ($P > 0.1$).

Associations between medication measures and treatment-related toxicity, hospitalization or NCHE

Twenty-one patients (9.2 %) had grade 3–4 CTCAE toxicity, and the common complications included dysphagia (42.9 %) followed by dry mouth (38.1 %), oral mucositis (14.3 %), and shoulder pain (4.7 %). Twenty patients (8.7 %) required prolonged hospitalization for more than 1 month due to any cause during the primary and/or adjuvant treatments. Noncancer health events developed in 66 patients (28.8 %) within 2 years after initial treatments, and the most common cause of NCHE was pneumonia (24.2 %) followed by airway obstruction (18.1 %), gastrostomy due to severe dysphagia (10.6 %), radiotherapy-induced complications (7.6 %), odontitis (6.1 %), stroke (6.1 %), or other cause (27.3 %). PP and PIM were not significantly associated with treatment-related toxicity, but modestly associated with an increase in PH (OR 2.30; 95 % CI 0.89–5.95; $P = 0.080$) and noncancer health event (OR 1.81, 95 % CI 0.99–3.31; $P = 0.052$), respectively (Table 5). Of the high-risk medications, the use of benzodiazepine (OR 5.09; 95 % CI 1.21–21.5; $P = 0.015$) and calcium channel blocker

Table 4 Patient characteristics associated with PP and PIM use ($n = 229$)

Variable	PP < 5 *N* (%)	PP ≥ 5 *N* (%)	*P*	No PIM *N* (%)	PIM *N* (%)	*P*
Age						
Mean ± SD	72.2 ± 5.3	74.9 ± 5.4	**0.001**	72.6 ± 5.3	74.2 ± 5.8	0.064
Sex						
Male	135 (83.3)	57 (85.1)	0.745	141 (81.0)	51 (92.7)	**0.040**
Female	27 (16.7)	10 (14.9)		33 (19.0)	4 (7.3)	
BMI (kg/m^2)						
Mean ± SD	22.7 ± 3.4	23.8 ± 3.0	**0.030**	22.8 ± 3.3	23.8 ± 3.2	**0.036**
Education						
≥High school	75 (46.3)	33 (49.3)	0.683	80 (46.0)	28 (50.9)	0.523
<High school	87 (53.7)	34 (50.7)		94 (54.0)	27 (49.1)	
Residence						
Urban	94 (58.0)	35 (52.2)	0.422	96 (55.2)	33 (60.0)	0.529
Rural	68 (42.0)	32 (47.8)		78 (44.8)	22 (40.0)	
Smoking, pack-years						
<30	84 (51.9)	29 (43.3)	0.238	91 (52.3)	22 (40.0)	0.112
≥30	78 (48.1)	38 (56.7)		83 (47.7)	33 (60.0)	
Alcohol, drink/day						
<1	74 (45.7)	30 (44.8)	0.901	81 (46.6)	23 (41.8)	0.539
≥1	88 (54.3)	37 (55.2)		93 (53.4)	32 (58.2)	
Hemoglobin (g/dL)						
≥12	136 (84.0)	57 (85.1)	0.832	146 (83.9)	47 (85.5)	0.784
<12	26 (16.0)	10 (14.9)		28 (16.1)	8 (14.5)	
Albumin (g/dL)						
≥3.5	151 (93.2)	59 (88.1)	0.199	159 (91.4)	51 (92.7)	0.752
<3.5	11 (6.8)	8 (11.9)		15 (8.6)	4 (7.3)	
No. of comorbidities						
Mean ± SD	0.73 ± 0.83	1.69 ± 1.16	**<0.001**	0.80 ± 0.87	1.67 ± 1.22	**<0.001**
ECOG PS scale						
0–1	143 (88.3)	63 (94.0)	0.187	157 (90.2)	49 (89.1)	0.806
2–3	19 (11.7)	4 (6.0)		17 (9.8)	6 (10.9)	
Functional status						
Fit	134 (82.7)	53 (79.1)	0.618	147 (84.5)	40 (72.7)	0.102
Vulnerable or frail	28 (17.3)	14 (20.9)		27 (15.5)	15 (27.3)	

Bold values indicate statistically significant *P*-values ($P < 0.05$)

CCI Charlson comorbidity index, *CI* confidence interval, *ECOS PS* Eastern Cooperative Oncology Group performance status, *PIM* potentially inappropriate medication, *PP* polypharmacy, *SD* standard deviation

(OR 5.69; 95 % CI 1.07–33.25; $P = 0.031$) was significantly associated with prolonged hospitalization but not associated with treatment-related toxicity or noncancer health event ($P > 0.05$). Other drugs, such as antiplatelet medications, were not significantly associated with treatment-related toxicity, prolonged hospitalization, or noncancer health event ($P > 0.05$).

Discussion

The use of multiple medications is a common problem among older adults. In our current study cohort, all patients were receiving a mean of 2.8 medications, and those with PP were receiving a mean of 6.6 medications. Our cohort demonstrated a 29.3 % prevalence of PP and 1.7 % prevalence of excessive PP. These rates are lower than those reported recently (Maggiore et al. 2014; Nightingale et al. 2015). Maggiore et al. (2014) reported a mean of 5 daily medications (range 0–23) and a 60.6 % prevalence of PP (as defined as ≥4 medications) in 500 adults with cancer who were ≥65 years and undergoing chemotherapy. Nightingale et al. (2015) reported a mean of 9.2 medications and 41 % prevalence of PP among 248 ambulatory senior adults with cancer. These differences result from some variations in the study cohorts in

Table 5 Association between medication measures and treatment-related toxicity, hospitalization, or NCHE ($n = 229$)

Variables	Toxicity[a] *N* (%)	No toxicity *N* (%)	Odds ratio (95 % CI)	*N*	PH[b] *N* (%)	No PH *N* (%)	Odds ratio (95 % CI)	*P*	NCHE *N* (%)	No NCHE *N* (%)	Odds ratio (95 % CI)	*P*
PP												
0–4	13 (61.9)	149 (71.6)			12 (60.0)	150 (71.8)			42 (61.8)	120 (74.5)		
≥5	8 (38.1)	59 (28.4)	1.55 (0.61–3.94)	0.350	8 (40.0)	59 (28.2)	1.70 (0.66–4.36)	0.269	26 (38.2)	41 (25.5)	1.81(0.99–3.31)	0.052
PIM												
Absent	15 (71.4)	159 (76.4)			12 (60.0)	162 (77.5)			49 (72.1)	125 (77.6)		
Present	6 (28.6)	49 (23.6)	1.30 (0.48–3.53)	0.608	8 (40.0)	47 (22.5)	2.30 (0.89–5.95)	0.080	19 (27.9)	36 (22.4)	1.346 (0.71–2.57)	0.366
Use of high-risk medications												
Antiplatelet medication												
No	17 (81.0)	184 (88.5)			16 (80.0)	185 (88.5)			58 (85.3)	143 (88.8)		
Yes	4 (19.0)	24 (11.5)	1.80 (0.56–5.81)	0.317	4 (20.0)	24 (11.5)	1.93 (0.60–6.24)	0.267	10 (14.7)	18 (11.2)	1.37 (0.60–3.15)	0.457
Benzodiazepine												
No	20 (95.2)	202 (97.1)			17 (85.0)	202 (96.7)			63 (92.6)	156 (96.9)		
Yes	1 (4.8)	6 (2.9)	1.68 (0.19–14.6)	0.634	3 (15.0)	7 (3.3)	5.09 (1.21–21.50)	**0.015**	5 (7.4)	5 (3.1)	2.48 (0.69–8.85)	0.120
Calcium channel antagonist												
No	21 (100.0)	202 (97.1)			18 (90.0)	205 (98.1)			68 (100.0)	155 (96.3)		
Yes	0 (0.0)	6 (2.9)	0.90 (0.87–0.95)	0.430	2 (10.0)	4 (1.9)	5.69 (1.07–33.25)	**0.031**	0 (0.0)	6 (3.7)	0.70 (0.64–0.76)	0.107
NSAIDs												
No	19 (90.5)	202 (97.1)			20 (100.0)	201 (96.2)			64 (94.1)	157 (97.5)		
Yes	2 (9.5)	6 (2.9)	3.54 (0.67–18.8)	0.114	0 (0.0)	8 (3.8)	0.91 (0.87–0.95)	0.373	4 (5.9)	4 (2.5)	2.45 (0.60–10.11)	0.419

Bold values indicate statistically significant *P*-values ($P < 0.05$)

CI confidence interval, *NCHE* noncancer health event, *NSAIDs* nonsteroidal anti-inflammatory drugs, *PH* prolonged hospitalization, *PIM* potentially inappropriate medication, *PH* prolonged hospitalization, *PP* polypharmacy

[a] CTACE grades 3–4

[b] Prolonged hospitalization defined as treatment lasting >1 month

[c] NCHE was defined as admission to the hospital within 2 years after initial treatments for any cause that was not directly related to the index cancer or newly developed second primary cancer (Ryu et al. 2013; Kwon et al. 2014)

terms of disease groups, comorbidity status, regional medicinal interests, medical and insurance systems, etc.

In our current cohort, the use of PIM was also common (24.0 % prevalence) according to the 2012 Beers criteria. Maggiore et al. and Nightingale et al. also evaluated the use of PP and PIM in elderly cancer patients using the 2012 Beers criteria and reported prevalences of 29 % (Maggiore et al. 2014) and 40 % (Nightingale et al. 2015), respectively. Another study reported a mean number of 7.3 daily medications, 80 % prevalence of PP, and 41 % prevalence of PIM according to the 2003 Beers criteria (Prithviraj et al. 2012). The prevalence of PIM in elderly patients might differ according to which criteria are used. Nightingale et al. (2015) reported that the prevalences of PIM were 40, 38, and 21 % among 173 senior cancer patients who were evaluated using the 2012 Beers criteria, the Screening Tool of Older Person's Prescriptions (STOPP) (Gallagher et al. 2008), and the Healthcare Effectiveness Data and Information Set criteria, respectively. The 2012 Beers and STOPP criteria were the most inclusive, and each detected 118 occurrences of PIM (Nightingale et al. 2015). The prevalence of PIM also appeared to improve from the 2003 Beers version (17 %) to 2012 version (29 %) according to a recent study (Maggiore et al. 2014). Although our study only used the 2012 Beers criteria to evaluate PIM, a high prevalence of PIM was found among elderly HNC patients and particularly among those patients receiving PP. However, because the use of the Beers criteria could underestimate proportion of PIM (Chang et al. 2011), new to the criteria may be advisable, by including the lists of select drugs that should be avoided and select drug–drug interactions associated with harms in older adults (Fick et al. 2015).

The revised 2012 Beers criteria list 34 PIMs and classes to avoid administering to older adults. Although many medications may exacerbate underlying conditions, PIM does not contain indications for when medications should not be used. When clinicians are unable to find alternatives, drugs might be taken by individual patients. However, patients receiving a PIM should be closely monitored during and after cancer therapy in order to detect early any adverse drug effects from the PIM itself or any drug-to-drug interactions. In our current cohort, common PIMs include aspirin, calcium channel blockers, and benzodiazepine. Aspirin is classified as category 1, meaning that it is inappropriate for older adults. Avoiding the chronic use of aspirin is recommended, unless otherwise alternatives are ineffective and gastroprotective agents are also being administered (e.g., proton pump inhibitors or misoprostol) (Herings and Goettsch 2004; Scheiman 2013). According to a 2005 US Food and Drug Administration report summarizing nonsteroidal anti-inflammatory drug safety trials, gastrointestinal bleeding or perforation caused by the drugs occurs in approximately 1 % of patients treated for 3–6 months and approximately 2–4 % of patients treated for 1 year. Nifedipine, a calcium channel blocker, is also classified as category 1 and carries the potential risk for hypotension and myocardial ischemia. Benzodiazepines are classified as both category 1 and category 2. Avoiding benzodiazepines during the treatment for insomnia, agitation, or delirium is also recommended. Category 2 means that the drug is inappropriate for specific coexisting illnesses. Older patients with delirium, dementia, or a history of falls or fracture should also avoid benzodiazepines. All of the above-mentioned medications may affect cancer therapy toxicity, length of hospital stay, and readmission for noncancer health events.

We found in our present analyses that PP and PIM are associated with modest increases in prolonged hospitalization and noncancer health event, respectively. However, although the use of PP and PIM was commonly seen in our cohort, they were not significantly associated with cancer therapy-related toxicity. The use of PP and PIM was more frequently found in patients with $\geq$1 comorbidities, but did not negatively influence the treatment or posttreatment courses in elderly HNC patients. We used the Charlson comorbidity index score as a comorbidity evaluation scale but did not use others such as a cumulative illness rating scale for geriatrics (Miller et al. 1992) that seems to be an indispensable tool for prioritizing treatments (Rougé Bugat et al. 2015). However, both the comorbidity scales were reportedly well correlated each other in terms of medication burden, and can be used for comorbidity evaluation in clinical practice with elderly patients (Beloosesky et al. 2011).

A few studies have attempted to evaluate the potential associations between PP, PIM, and clinical outcomes in elderly cancer patients, none of which could confirm an association (Maggiore et al. 2010, 2014). Maggiore et al. (2014) reported no association between the number of daily medications, PIM use, chemotherapy toxicity, and hospitalization. In addition, no medication class was associated with toxicity or hospitalization. However, our present analysis shows that the use of benzodiazepine and calcium channel blockers is significantly associated with prolonged hospitalization. The potential adverse effects of these drugs are described above. Benzodiazepine is commonly used to treat vertigo, insomnia, and agitation in patients undergoing prolonged hospitalization. Although we found no significant association between PP or PIM and cancer therapy toxicity or noncancer health event in or present analysis, specific drug classes could potentially impact the treatment and posttreatment courses in HNC patients.

This study had several limitations of note. First, medications were assessed at the time of the initial diagnosis and treatment in our cohort but could have changed during or after cancer treatments. These changes can affect analyses of

the associations between PP, PIM, and treatment outcomes. Second, our analyses did not include the dose, frequency, or combinations of medications that might affect the clinical course in elderly cancer patients. Third, our study included various tumor sites and treatment modalities. Primary tumor location may affect metastatic potential, natural course, and clinical behavior. In addition, the treatment modalities differed throughout the study population. However, our head and neck oncologic teams applied a team approach to ensure administering proper planning and multimodal treatment to each HNC patient. Our study cohort did not include the elderly patients with other cancer types arising outside the head and neck but only those with HNC who might be not the good cohort to study elderly cancer. However, the selection of a single specific organ site cancer might help to minimize potential biases from the analyses of relationship between PP or PIM and treatment and posttreatment courses. Our present study included a relatively large cohort of elderly patients with HNC who underwent definitive treatment and is the first study to evaluate PP and PIM use in elderly HNC patients using the most current 2012 version of the Beers criteria in order to determine the clinical importance of these drug indicators. Our results require further confirmation by future prospective multi-institutional studies. Furthermore, the role of PP and PIM, during and after HNC treatment, should also be investigated further.

In conclusion, the use of PP and PIM is frequently found in elderly HNC patients. Neither PP nor PIM are significantly associated with treatment-related toxicity in elderly HNC patients, but these are associated with modest increases in prolonged hospitalization and noncancer health events. The use of specific drug classes, such as benzodiazepine and calcium channel blockers, might increase the hospital stay in these patients. These results could be used to provide guidance on the administration of other drugs in elderly patients with HNC.

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Compliance with ethical standards

Conflict of interest The authors have no conflict of interests to disclose.

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