Clinical Investigation Into the Prevalence and Associated Factors for Second Primary Tumor of the Esophagus in Oral Tumor Patients

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Development of a second primary tumor（SPT）contributes to a poor prognosis, even if the primary oral tumor（OT）was adequately managed. SPT develops as synchronous or metachronous esophageal cancers in 1–20% patients with oral squamous cell carcinoma（OSCC）. This study aimed to evaluate the prevalence and associated factors for SPT of the upper digestive tract in 80 Japanese patients with OT（OSCC, oral intraepithelial neoplasia/carcinoma *in situ* : OIN/CIS, and verrucous carcinoma : VC）. SPT were detected in 67 patients, 8 with esophageal carcinoma（EC）, 2 with intraepithelial neoplasia（IN）, 3 with gastric carcinoma（GC）, 7 with epithelial dysplasia（ED）, and 47 with other diseases. Malignant tumors（EC, IN, GC）, were detected in 13/80 patients（16.3%）. Univariate analysis showed that Brinkman index（BI）was a candidate associated factor. In the multivariate analysis, BI as a continuous variable was also a significant associated factor. We strongly suggest that endoscopic screening be performed to identify malignancies of the upper digestive tract in patients with OSCC, OIN/CIS and VC.

Key words: oral cancer, esophageal cancer, second primary cancer, associated factor

INTRODUCTION

The development of modern surgical techniques and adjuvant therapy for the management of oral cancer, especially oral squamous cell carcinoma（OSCC）, has resulted in improved disease-specific survival rates［1］. However, patients with advanced（Stage III or IV）disease have a 5-year survival rate of 0–40%［2］. Three major causes of the death following cancer treatment are locally recurrent tumor（50–60%）, distal metastases（20–30%）and second primary tumor（SPT）［3, 4］. SPT develops as a synchronous or metachronous esophageal cancer in 1–20% of patients with OSCC［5-7］. Development of SPT is a major predictor of poor prognosis, even if the primary oral carcinoma has been managed adequately［2］.

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Licciardello *et al*. [8] presented a comprehensive and detailed review on SPT risks and patterns in patients with head and neck cancer. They suggested that the site of the primary head and neck cancer may correlate with the site of the SPT within the aerodigestive tract, that is, the primary oral cancer appears to be associated with head and neck cancer SPT, while primary laryngeal cancers are associated with lung SPT. These associations support the concept that the pattern of SPT development may be related to the type of epithelial tissue involved: the oropharynx (primary tumor) and esophagus (SPT) are both lined with squamous epithelia, while the larynx (primary tumor) and lung (SPT) are both lined with columnar epithelia [2].

Other risk factors for SPT are perhaps more important, such as the duration and amount of continuous tobacco use and the type of tobacco (e.g., smokeless tobacco correlates with oral SPT) and the concurrent abuse of alcohol and tobacco (correlating with esophageal or head and neck SPT) [9].

In this study, we evaluated the prevalence of and the associated factors for SPT of the upper digestive tract in oral tumor (OT) patients.

PATIENTS AND METHODS

Participants

Consecutive patients with OT were selected from those who had visited the Department of Oral and Maxillofacial Surgery, Shimane University Hospital, between January 2007 and December 2014. All study participants provided their written informed consent. The study protocol was approved by the Ethics Committee of Shimane University Hospital, Japan (Approval No. 1779, 11 March 2015). Approval from the Institutional Review Board was not necessary because the data obtained from the database of Shimane University Hospital were evaluated in an anonymous manner. The unlinked anonymity of the patients was ensured by the president of Shimane University Faculty of Medicine in this study.

Esophagogastroduodenoscopy examination

All study participants underwent esophagogastroduodenoscopy (EGD) before surgical treatment. EGD were performed using the CV-260SL system (Olympus, Japan) with a high-resolution GIF-H260Z endoscope (Olympus, Japan) at the Department of Gastroenterology, Shimane University Hospital. The final endoscopy report could be checked using the hospital patient record system after the examiner had uploaded it.

In this study, as the SPT synchronous with OT, neoplastic diseases of the upper digestive tract were categorized into four subgroups: esophageal carcinoma (EC) including intraepithelial neoplasia (IN), gastric carcinoma (GC), epithelial dysplasia (ED) and other diseases, following the WHO classification of tumors of the digestive system [10]. The final diagnosis was based on the pathologic examination result.

Evaluation of factors associated with EGD findings

The association between EGD findings and the participants' age; sex; Brinkman index (BI) [11]; Sake index (SI) [12]; and decayed, missing, filled (DMF) index were evaluated. Information on participants' smoking habit and alcohol consumption were collected from the medical records. The consumption of tobacco was assessed using the BI, which was defined as the number of cigarettes smoked per day multiplied by the number of years. The quantity of alcohol consumption was evaluated by SI, which was calculated by multiplying daily alcohol consumption by the number of years.

Oral examinations were carried out by the fourth, fifth and sixth authors with the aid of a dental mirror and explorer under optimal lighting while the subjects were seated in a dental chair. Four factors were examined: primary OT, oral hygiene, dentition, numbers of healthy, decayed, treated (i.e., filled), and missing teeth, which were determined using the DMF index [13].

STATISTICAL ANALYSIS

Univariate logistic regression analysis was performed to evaluate the candidate associated factors for malignant or pre-malignant conditions of the upper digestive tract in patients with OT. Candidate associated factors were those with $p<0.10$. The odds ratios, corresponding 95% confidence intervals and p-values based on the Wald test were calculated.

Multivariate logistic regression analysis was performed by backward selection method to identify the associated factors with $p<0.05$.

RESULTS

Participants' characteristics

The study included 80 Japanese patients with OT (53 men, 27 women) with a mean age of 66.2 (range 23–89) years. The primary sites of OT were upper and lower gingiva (39 patients), tongue (33 patients), mouth floor (3 patients), buccal mucosa (2 patients), maxillary sinus (2 patients) and mandible (1 patient). The histopathological diagnoses were OSCC (74 patients), oral intraepithelial neoplasia/carcinoma in situ (OIN/CIS, 4 patients) and verrucous carcinoma (VC, 2 patients) (Table 1). All diagnoses were based on the pathological result (Table 2). Of the 80 patients, 41 (51.3%) were smokers, the majority of which were men (38/41, 92.7%), while 34 (42.5%) had a history of alcohol consumption, of which 30 were men (88.2%).

Esophagogastroduodenoscopy examination

EC including IN and GC was diagnosed in 13 of 80 patients (16.3%) and ED was diagnosed in 7 patients (8.8%); these two conditions were found in 25.0% of patients (Table 3). In the category of malignant tumors, 11 of 13 (16.9%) patients had EC or GC and 2 patients had IN (15.4%). Other lesions such as Barrett's esophagus, gastroesophageal reflux disease and esophageal candidiasis were seen in 47 patients (58.8%). No other lesions were found in 13 patients (16.3%).

Factors associated with existence of malignant or pre-malignant lesions in the upper digestive tract

The results of logistic regression analysis that explored the association between malignancy and other conditions such as epithelial dysplasia, other diseases and no disease are shown in Table 4, respectively. The univariate analysis of malignant tumor in the esophagus showed that sex and BI (as a continuous variable) were candidate associated factors (Table 4). In the multivariate analysis, BI as a continuous variable was selected as an associated factor (OR 3.61, 95% CI 1.28–10.20, $p=0.015$).

The DMF index was 82 in the malignant group and 74.4 in the other condition group, showing no statistical difference between the two groups. Also, the univariate analysis for malignant lesions and ED in the upper digestive tract showed that sex, BI (as a continuous variable and a categorical variable, comparing <1000 vs. >1000) and SI (0 vs. >0) were selected as candidate associated factors. In the multivariate analysis, BI as a continuous variable was a significant associated factor (OR 2.98, 95% CI 1.17–7.57, $p=0.022$).

DISCUSSION

The subjects of this study were 74 patients with OSCC, 4 with OIN/CIS and 2 with VC. When considering the differential diagnosis for oral lesions, neoplasia of the squamous epithelium should always be considered because most oral neoplasms originate from this tissue [14]. Some of the oral neoplasms are associated with a 0.4–0.6% rate of malignant transformation to OSCC [15, 16]. Neoplasia including IN can be defined as focal proliferative lesions, benign tumors, primary cancers, and metastases with the potential to affect a given cell system and can undergo malignant transformation [14]. OSCC is commonly preceded by a range of tissue and cellular alterations that are consistent with carcinoma but are restricted to the surface epithelial layer; this is termed oral epithelial dysplasia.

Recently, the classification of many of these alterations has been based on the classification for other epithelial sites; for example, OIN is based on cervical intraepithelial neoplasia [17] and squamous intraepithelial lesions of the cervix [18]. CIS is also defined as dysplastic epithelial cells extending from the basal layer to the mucosal surface, with features of malignancy [19]. On the other hand, VC is a low-grade variant of OSCC [19]. For maxillofacial surgeons, OIN/CIS and VC are both resectable lesions [20]. We grouped VC and OIN/CIS within the same category as OSCC from the viewpoint of malignancy in this clinical study.

In this study, malignant conditions including IN and ED in upper digestive tract were seen in 20 OT patients (25%). In patients with OSCC, 19 of 74 had either EC including IN and GC (n=12) or

Table 1. Characteristics of participants and their oral primary tumors

Variable	Category	Number of patients
Age	Mean (range)	66.2 (23–89)
Sex	Male	53
	Female	27
Site	Gingiva	39
	Tongue	33
	Mouth floor	3
	Maxillary sinus	2
	Buccal	2
	Mandible	1
Histopathological type	OSCC	74
	OIN/CIS	4
	VC	2

OSCC:oral squamous cell carcinoma , OIN/CIS: oral intraepithelial neoplasia/carcinoma in situ, VS: verrucous carcinoma

Table 2. Number of patients categorized by pathological diagnosis of oral tumor

	Pathological diagnosis	Number of patients
Differentiation of OSCC	OIN/CIS or VC	6
	Well	32
	Moderate	34
	Poor	8

OSCC: oral squamous cell carcinoma , OIN/CIS: oral intraepithelial neoplasia/carcinoma in situ, VS: verrucous carcinoma

Table 3. Prevalence of malignancy, epithelial dysplasia and other lesions

		Patients n=80	%
Malignant tumor	Esophageal carcinoma	8	16.3
	Intraepithelial neoplasia	2	
	Gastric carcinoma	3	
Epithelial dysplasia		7	8.8
Other diseases		47	58.8
No disease detected		13	16.3

Table 4. Logistic regression analysis for malignant tumors of the upper digestive tract

Variable (reference or unit)	Category	M	ED+OD+NDD	Univariate logistic regression			Multivariate logistic regression		
n=80		n=13	n=67	OR	95% CI	P-value	OR	95% CI	P-value
Age (1)		65.6 (15.2)	69 (14.9)	1.02	0.97-1.06	0.463			
Sex (ref: female)		12 (92.3)	41 (61.2)	7.61	0.93-62.0	0.058			
Brinkman index/1000		778.5 (785.8)	341.1 (457.1)	3.61	1.28-10.20	0.015	3.61	1.28-10.20	0.015
Brinkman index (ref: 0)	0 to 1000	4 (30.8)	22 (32.8)	1.59	0.36-7.02	0.540			
	1000 or >1000	5 (38.5)	10 (14.9)	4.37	0.99-19.4	0.052			
Brinkman index (ref: 0)	>0	9 (69.2)	32 (47.8)	2.46	069-8.78	0.165			
Brinkman index (ref: <1000)	>1000	5 (38.5)	10 (14.9)	3.56	0.97-13.10	0.056			
Sake index (1000)		883.1 (1015.4)	591.5 (920.5)	1.35	0.76-2.42	0.308			
Sake index (ref: 0)	0 to 1500	4 (30.8)	12 (17.9)	2.73	0.63-11.80	0.178			
	1500 or >1500	4 (30.8)	14 (20.9)	2.34	0.55-9.97	0.249			
Sake index (ref: 0)	>0	8 (61.5)	26 (38.8)	2.52	0.74-8.55	0.137			
Number of teeth checked (1)		28.7 (1.0)	28.7 (1.2)	1.01	0.58-1.77	0.977			
Number of teeth present (1)		13 (9.4)	14.4 (10.7)	0.99	0.93-1.05	0.674			
Number of healthy teeth (1)		4.82 (6.57)	7.65 (8.68)	0.95	0.87-1.05	0.311			
Number of decayed teeth (1)		1.36 (2.73)	1.17 (2.26)	1.04	0.8-1.35	0.794			
Number of missing teeth (1)		15.3 (9.3)	14.1 (10.2)	1.01	0.95-1.08	0.715			
Number of filled teeth (1)		6.8 (6.3)	5.6 (6.3)	1.03	0.93-1.14	0.563			
DMFT (1)		23.5 (6.8)	20.9 (8.3)	1.05	0.95-1.15	0.340			
DMF indices (1)		82 (24.0)	74.4 (28.5)	1.01	0.98-1.04	0.405			

DMFT: total number of decayed, missing and filled teeth. M: malignant condition including esophageal carcinoma and intraepithelial neoplasia and gastric carcinoma, ED: epithelial dysplasia, OD: other diseases including Barrett's esophagus, gastroesophageal reflux disease, esophageal candidiasis, NDD: no disease detected

ED (n=7) in the upper digestive tract. In patients with OIN/CIS of the oral cavity, 1 of 4 showed a malignant tumor. In patients with VC of the oral cavity, neither malignancy nor ED was found in the esophagus. Generally, the rates of synchronous and metachronous carcinoma ranged between 8% and 21% [1], or from 16% to 36% in OSCC patients [21, 22]. The rate of developing synchronous and metachronous carcinoma in the head and neck mucosa depends on the initial mucosal sites [23, 24].

In 1953, Slauter *et al*. [25] proposed the concept of "field cancerization", referring to continuous exposure of the upper aerodigestive tract epithelium to unknown carcinogenic agents, in an attempt to define carcinogenesis of multiple neoplasm of the aerodigestive tract. This investigation using histopathological slides from 783 patients with HNC in an effort to understand the gross changes found in epithelia surrounding primary tumors and to explain their clinical behavior [25]. It was discovered that all of the epithelium beyond the boundaries of the primary tumor had more than one independent area of malignancy. The conclusion drawn was that the mucosa of the head and neck had undergone a change because of carcinogen exposure [25]. Therefore, it may be more susceptible to the development of multiple foci of malignant transformation from high grade IN or ED by diffuse mucosal spread [14, 26, 27]. On the other hand, diffuse mucosal initiation and promotion would be induced by oxygenous carcinogenic factors such as tobacco and alcohol, which is also referred to as field cancerization [28-31]. We tested the hypothesis that tobacco and alcohol are risk factors for SPT in the esophagus in OSCC patients including those with OIN/CIS and CIS.

Some studies suggested that tooth loss and periodontal disease associated with carcinogenesis in not only the oral cavity but also the upper digestive tract [32]. So we analyzed DMF indices as one of risk factors. However in our study, DMF indices were not associated with SPT occured in the upper digestive tract synchronous with OT.

In this study, smoking was associated with the development of EC, IN , GC and ED in patients with OT on univariate regression analysis, suggesting that smoking is an independent risk factor. McDonald *et al*. [9] reported that the duration and amount of continued tobacco use and the type of tobacco (e.g., smokeless tobacco correlates with oral second malignant tumors while concurrent abuse of alcohol and tobacco correlates with esophageal second malignant tumors). Our study showed that an increase in BI raises the risk of gastrointestinal cancer, especially for patients with BI over 1000.

However, our study showed no connection between SPT in the upper digestive tract and daily alcohol consumption over the years. Though alcohol is also considered a risk factor for SPT in the upper digestive tract [29-31, 33, 34], alcohol consumption was reported to be an independent risk factor for cancer development instead of smoking [33]. It has been reported that patients with head and neck cancer have a high risk of developing esophageal ED and IN, especially those who have a history of alcohol consumption and prior pharyngeal/laryngeal cancer. Actually, in this study, esophageal carcinoma was present in a patient with OSCC and laryngeal carcinoma, supporting the results of the report by Lim *et al*. [34]. Recently, daily treatment with high doses of isotretinoin is reported to prevent SPT in head and neck cancer patients, although it does not prevent recurrence of the original tumor [35, 36]. Further investigation is needed to prevent SPT of the esophagus in OSCC patients.

CONCLUSION

We strongly suggest that endoscopic screening be performed to identify malignancies or premalignancies such as ED within the upper digestive tract in patients with OSCC, OIN/CIS and VC.

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