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Original Article

Upper Gastrointestinal Tract Cancers as Double-cancers in Elderly Patients with Oral Squamous Cell Carcinoma

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Abstract

Against a background of a rapidly aging society, the number of patients with oral cancers in Japan is increasing yearly. The number of double-cancers with oral cancer as the first malignancy is also reportedly on the rise. Esophageal and gastric cancers are the most common second malignancies. At our institution, our policy is to proactively perform upper gastrointestinal (GI) fiberscopy (GIF) in patients with oral cancer. In anticipation of a probable further increase in the number of patients with double-cancers consisting of oral and GI tract malignancies, we retrospectively analyzed the occurrence of upper GI tract cancers in patients with oral squamous cell carcinoma (OSCC). The cohort consisted of 171 patients in whom OSCC had been diagnosed and who had undergone upper GIF between March 1996 and August 2008. Multivariate analysis was performed. Upper GIF identified 8 patients (7 men, 1 woman, totaling 4.7% of 171 patients) with double-cancer in the upper GI tract. One patient had a triple malignancy consisting of oral, esophageal and gastric cancers. Seven patients had esophageal cancer, while two had gastric cancer. An age of over 65 years was significantly higher in patients with double-cancers including esophageal cancer than in patients without esophageal cancer (OR = 10.454, 95% CI = 1.143–95.621). None of the other analyzed patient factors (sex, smoking habit, drinking habit, site of OSCC, TNM classification, staging results) showed a significant difference. These results indicate that, when treating elderly patients with oral cancers, physicians need to devise suitable treatment plans which take into account the possibility of upper GI tract cancer, particularly esophageal cancer, as a double-cancer.

Key words: Case-control study — Endoscopy — Oral cancer — Esophageal cancer — Gastric cancer

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Introduction

Malignant tumors that develop in the oral cavity are said to represent 2–3% of all malignant tumors[10]. In addition, the number of patients with oral cancers in Japan is increasing yearly[7], and this is occurring against a background of a rapidly aging society.

The number of patients with double-cancers, with oral cancer as the first malignancy, is also on the rise[8]. This trend may be related to factors such as aging, improved survival, and increased exposure to multiple carcinogenic agents due to diet and/or environmental factors. Numerous reports have investigated the relationship between oral cancers and upper gastrointestinal (GI) tract cancers[3,18,20,22]. Yamane *et al.*[22] found that upper GI tract cancers occurred as double-cancers in 10.3% of patients with oral malignancies. Chuang *et al.*[3] reported that the standardized incidence ratio for double-cancers of the oral cavity in patients with esophageal cancer was 3.94. Oral cavity, pharyngeal, esophageal, and gastric cancers all share the same carcinogenic environment, and one report has described widespread carcinogenesis in multiple fields[18].

The number of elderly cancer patients in Japan is predicted to increase. Treatment results for oral cancers in elderly patients have been relatively good[17,19]. The prognosis in elderly patients with esophageal and gastric cancers is similar to that in younger patients, provided that they receive treatment[16]. Therefore, early detection of malignant tumors is the key to effective treatment in elderly patients. Moreover, GI cancers detected by upper GI fiberscopy (GIF) performed at the time of treatment of oral cancers are often relatively early-stage malignancies[21]. We conducted a retrospective investigation of upper GI tract cancers in patients with oral squamous cell carcinoma (OSCC) with the aim of improving our understanding of and ability to treat such cases.

Materials and Methods

1. Patients

The cohort comprised 171 patients who were first examined at the Department of Oral Medicine, Oral and Maxillofacial Surgery, Tokyo Dental College Ichikawa General Hospital (Ichikawa City, Chiba Prefecture, Japan) between March 1996 and August 2008. After a definitive diagnosis of OSCC, all patients underwent upper GIF. Patients in whom a diagnosis of esophageal or gastric cancer had been reached prior to further examination and a diagnosis of OSCC at our department were excluded from the study.

2. Gastrointestinal fiberscopy, staging, and diagnosis-related groups

Gastrointestinal fiberscopy was performed by inserting an endofiberscope (GIF-Q260; Olympus, Tokyo, Japan) through the mouth and observing the sites of interest. Sites predicted to yield abnormal findings were stained with an iodine spray for the esophagus (potassium iodide, 7.2 g; iodine, 3.6 g; liquefied phenol, 1.5 ml; peppermint water, 13.5 ml; purified water, 285 ml). Biopsy was performed when deemed necessary and a definitive diagnosis reached. Gastrointestinal fiberscopy was performed on initiation of treatment for OSCC and then as deemed appropriate once annually postoperatively.

Oral squamous cell carcinoma was classified according to the TNM staging system put forth by the Unio Internationalis Contra Cancrum. Diagnosis-related groups were determined in accordance with the International Classification of Diseases for Oncology, Third Edition, issued by the World Health Organization. Histopathological diagnoses were made at the Pathology Department of our hospital. Evaluations were performed independently by the physicians in charge of pathological diagnosis, performance of GIF, and assessment of medical records. This study was carried out in accordance with the Helsinki Declaration.

3. Definition of double-cancer

Double-cancers are defined as primary

Table 1 Characteristics of patients with oral squamous cell carcinoma

	Total (n=171)	Controls (n=163)	Cases (n=8)	Secondary cancer location	
				Esophageal cancer	Gastric cancer
Sex					
Male	110	103	7	6	2
Female	61	60	1	1	0
Age (years) (Range)	62.2 (26–83)	61.7 (26–83)	72.0 (63–81)	71.7 (63–81)	76.0 (76)
Smoking habits					
Smoker	80	74	6	6	1
Non-smoker	91	89	2	1	1
Drinking habits					
Drinker	104	97	7	6	2
Teetotaler	67	66	1	1	0
Primary cancer location					
Tongue	92	91	1	1	0
Lower gingiva	30	28	2	2	0
Upper gingiva	16	15	1	0	1
Mouth floor	15	12	3	3	1
Buccal	12	12	0	0	0
Soft palate	2	1	1	1	0
Lip	2	2	0	0	0
Sinus	2	2	0	0	0

cancers occurring in different organs and are classified as simultaneous, synchronous, or metachronous on the basis of time of occurrence[12]. For this study, a modification of these criteria was used.

4. Experimental methods

This study was carried out as a hospital-based case-control study, compared OSCC with double-cancer. The assessment parameters were 1) sex; 2) age; 3) smoking history; 4) drinking history; 5) OSCC site; 6) TNM classification; and 7) stage. All cases consisted of patients with OSCC in whom a further diagnosis of double-cancer in the upper GI tract was made. The controls consisted of patients with no double-cancer. Analysis was performed using the age of the patient on the day when the definitive pathological diagnosis was made. Parameters 3) and 4) were based on medical information collected at the time of the initial examination of the patient. Patients who had not smoked in the last 20 years were classified as non-smokers, whereas those who had smoked in the last 20 years were classified as smokers. Similarly, patients who regularly consumed alcohol were classified as having a drinking history, whereas those who consumed alcohol only occasionally or did not drink at all were classified as not having a drinking history.

5. Statistical analysis

Comparisons with the control group were performed using the χ^2 test, and the level of significance was defined as $p<0.05$.

In addition, logistic regression analysis (SPSS version 8; IBM Co., NY, USA) was performed using the data for sex, age, smoking history, drinking history and OSCC site. Odds ratios and 95% confidence intervals were calculated.

Results

1. Experimental group and incidence of upper GI tract double-cancers

Table 1 shows the results for OSCC patients

Table 2 Statistical analysis of second primary cancer after oral squamous cell carcinoma by sex, age, smoking habits, drinking habits and site of primary cancer (logistic regression analysis)

	Controls	Esophageal cancer	OR	95%CI	p Value	Gastric cancer	OR	95%CI	p Value
Sex									
Male	103	6	.909	.058–14.220	.946	2			.997
Female	60	1				0			
Age									
Below 65	87	1	10.454	1.143–95.621	.038	0			.994
65 or 65 above	76	6				2			
Smoking habits									
Smoker	74	6	5.338	.488–58.383	.170	1			.995
Non-smoker	89	1				1			
Drinking habits									
Drinker	97	6	2.426	.152–38.740	.531	2			.997
Teetotaler	66	1				0			
Site of primary cancer									
Mouth floor	12	3	4.926	.796–30.468	.086	1			.994
The other sites	151	4				1			

Independent variable: sex (male = 0, female = 1), age (below 65 = 0, 65 or 65 above = 1), smoking habit (non-smoker = 0, smoker = 1), drinking habit (teetotaler = 0, drinker = 1), site of primary cancer (the other sites = 0, mouth floor = 1)
Dependent variable: esophageal cancer, stomach cancer.

who underwent GIF, representing a total of 171 patients (110 men, 61 women) with a mean age of 62.2 years (range, 26–83 years). Upper GIF identified 8 patients (7 men, 1 woman) with double-cancers in the upper GI tract, with a mean age of 72.0 years (range, 63–81 years). One patient showed a triple malignancy consisting of oral, esophageal and gastric cancers, while 7 patients had esophageal cancer, and 2 had gastric cancer. As a result, 8 of the 171 patients (4.7%) had double-cancers of the upper GI tract that included esophageal or gastric cancer.

2. Stage of upper GI tract double-cancers (9 sites in 8 patients)

Staging of the 9 cancers of the upper GI tract that were detected in this study showed that the 7 esophageal cancers comprised 5 Stage 0 and 2 Stage I, while both gastric cancers were Stage I. All 9 cancers were thus detected at an early stage.

3. Statistical analysis of assessment parameters

Table 2 shows the statistical analysis of secondary primary cancer after OSCC by sex, age, smoking habit, drinking habit and OSCC location.

Age was compared between patients in whom a double-cancer was detected in the upper GI tract and those in whom no double-cancer was found. No significant difference in age was seen for patients with gastric cancer as the double-cancer, but a significant difference in age was seen for double-cancer patients with esophageal cancer (OR = 10.454, 95% CI = 1.143–95.621). With stratification on the basis of sex, smoking habit, drinking habit and OSCC site, no significant difference was observed in either esophageal or gastric cancer double-cancer cases.

None of the other assessment parameters (TNM classification and stage) showed any significant difference on stratified analysis (Table 3).

Discussion

According to a statistical report released for 2007 by The Japanese Society of Gastroentero-

Table 3 Number of cases and statistical analysis of primary cancer location and Unio Internationalis Contra Cancrum (UICC) TNM classification (χ^2 test)

	Total (n=171)	Controls (n=163)	Cases (n=8)	Esophageal cancer	p Value	Gastric cancer	p Value
T category							
T1	26	25	1	1		0	
T2	93	86	7	6	.140	2	.483
T3	21	21	0	0		0	
T4	31	31	0	0		0	
N category							
N0	115	110	5	4		1	
N1	30	29	1	1		1	
N2a	2	2	0	0	.276	0	.677
N2b	15	14	1	1		0	
N2c	7	7	0	0		0	
N3	2	1	1	1		0	
M category							
M0	171	163	8				
M1	0	0	0				
UICC tumor stage							
Stage I	25	24	1	1		0	
Stage II	71	67	4	3	.996	1	.477
Stage III	30	29	1	1		1	
Stage IV	45	43	2	2		0	

logical Cancer Screening[9], the nationwide detection rate of esophageal cancer was 0.02%, while the detection rate of gastric cancer was 0.088%. Although a simple comparison of examinees is not possible, the present survey found a considerably higher detection rate of 4.7% for upper GI tract cancers in OSCC patients (4.0% for esophageal cancer, 1.2% for gastric cancer). Others have reported incidences of 9.3–10.3% for upper GI tract cancers as double-cancers in OSCC patients[2,3,15]. On the other hand, our detection rate was lower than the rates reported by others. This may be because we excluded patients with a history of esophageal cancer or gastric cancer from the present survey.

In addition, the upper GI tract cancers detected in all of the present patients were early-stage lesions. Earlier detection of upper GI tract cancers permits treatment by less-invasive means. This represents another good reason for performing GIF in OSCC patients.

Many reports in recent years have examined field cancerization[4], and the oral mucosa is exposed to the same environment as the esophageal and gastric mucosas. Similarity of physical and chemical exposure factors can be considered to be a cause of development for double-cancer in the upper GI tract of patients who already have OSCC.

Numerous reports found that the incidence of upper GI tract double-cancers in OSCC patients was higher in males than in females. Likewise in the present survey, the number of men with upper GI tract double-cancers was larger than the number of women, but the difference was not significant.

Heterotopic double-cancers in OSCC patients do not show a significant difference for cancer risk as a function of patient age[22]. However, in the present study, patients aged over 65 years with esophageal double-cancers did show a significant difference for cancer risk ($p<0.05$, OR=10.454, 95% CI=1.143–95.621), whereas, because of fewer cases,

patients with gastric double-cancers did not. Conversely, as noted earlier, performance of GIF in OSCC patients leads to a higher likelihood of detecting a double-cancer while still in the early stages[13]. The present survey generated similar findings. Therefore, we can say that, while elderly OSCC patients are at greater risk of developing a double-cancer, monitoring by means of GIF increases the likelihood of any such double-cancer being detected at an early stage. The willingness of elderly cancer patients to undergo treatment is known to vary greatly with the age of the individual, and with increasing age there is a tendency toward not undergoing aggressive treatment[6]. However, the Abridged Life Table[1] issued by the Ministry of Health, Labour and Welfare in Japan shows that the mean life expectancy, even at 80 years, is not short, at 8.49 years for men and 11.43 years for women. In other words, more aggressive therapy should be considered, even among elderly patients, as long as the disease is detected at an early stage. For this reason, GIF of the upper GI tract in OSCC patients has great significance, even in the elderly.

Yamanaka *et al.*[21] reported that smoking and drinking histories did not show any significant associations in patients with upper GI tract double-cancers. In addition, Ako *et al.*[2] reported that neither the Sake index nor the Brinkman index showed significant differences in patients with esophageal double-cancers compared with patients without double-cancers, and no clear associations were found between the Sake index and Brinkman index and the development of esophageal cancer as a double-cancer. However, others found that most double-cancer patients had smoking and drinking habits[22]. Moreover, smoking and drinking have been listed as risk factors for esophageal cancer[11,14], and they are also thought to contribute to the development of OSCC[8]. In the present survey, OSCC patients with esophageal cancer as a double-cancer did not show a significant association with smoking or drinking history. This reason is OSCC patients have risk factors as smoking and drinking history for GI tract cancers originally.

The present study found the esophagus to be the most common site of development of upper GI tract cancers. The esophagus is directly exposed to carcinogens in tobacco smoke entering it from the larynx, and indirectly exposed to carcinogens mixed in saliva[14]. Histological differences are also known to exist between the oral and esophageal mucosas and the gastric mucosa: the former are lined with stratified squamous epithelium, whereas the latter comprises single-layer columnar epithelium. In addition, persistent infection by *Helicobacter pylori* is more strongly involved than smoking and drinking as a factor in the development of gastric cancer[5]. These factors, including the association with smoking, are the reasons that double-cancers detected in OSCC patients were more often esophageal than gastric.

No significant difference was found with regard to the incidence of upper GI tract double-cancers as a function of site of OSCC. However, OSCC floor-of-mouth carcinomas showed a higher incidence of upper GI tract double-cancers than those at other OSCC sites, at 20.0% (3/15 patients with floor-of-mouth SCC). Others have reported similarly high incidences for this association[21,22]. Although the difference was not significant ($p = 0.086$), upper GI tract double-cancers may occur often in patients with OSCC arising in the floor of the mouth.

Stratification on the basis of TNM classification or stage revealed no significant differences in patients with double-cancers consisting of either esophageal or gastric cancer. Stage of OSCC thus does not appear to be involved in the onset of upper GI tract cancers. This means that proactive performance of GIF should be considered for all patients with OSCC, regardless of stage.

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