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Clinicopathological Features of Buccal Squamous Cell Carcinoma with Focus on Patients Who Never Smoke and Never Drink

Yoshiyuki Iida[1,2] Shinichi Okada[1] Yuki Irifune[1] Seiya Goto[1] Kotaro Ishida[1] Fuyuki Sato[3] Takashi Yurikusa[4] Koiku Asakura[5] Ayaka Tsuzuki[1] Takashi Mukaigawa[1]

[1] Division of Head and Neck Surgery, Shizuoka Cancer Center, Sunto-gun, Japan
[2] Division of Otorhinolaryngology, Iida ENT Clinic, Toride, Japan
[3] Division of Diagnostic Pathology, Shizuoka Cancer Center, Sunto-gun, Japan
[4] Division of Dentistry and Oral Surgery, Shizuoka Cancer Center, Sunto-gun, Japan
[5] Division of Diagnostic Radiology, Shizuoka Cancer Center, Sunto-gun, Japan

Address for correspondence Yoshiyuki Iida, MD, Division of Head and Neck Surgery, Shizuoka Cancer Center Hospital, 1007 Shimonagakubo, Nagaizumi-cho, Sunto-gun, Shizuoka 411-8777, Japan (e-mail: iida1967.yi@gmail.com).

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Abstract

Introduction Oral carcinoma has been reported at a substantial proportion in patients who never smoke and never drink. However, the proportion may vary by subsite and ethnicity.

Objective We aimed to determine the clinicopathological features of buccal squamous cell carcinoma (SCC) in a Japanese population.

Methods We retrospectively analyzed the records of patients diagnosed with buccal SCC at our institution from September 2002 to November 2015. We reviewed the gender, age, tumor status, treatment, smoking, alcohol drinking, multiple primary cancers, and prognosis of the patients. The overall and cause-specific survival rates were calculated, and the effects of clinicopathological variables were assessed by univariate analysis. Furthermore, the cause of death was evaluated.

Results Among the 63 patients (men: 38; women: 25) included in the present study, 29 (46.0%) never smoked or drank. Women were almost 5 years older than men ($p = 0.014$). The number of women in the group who never smoked or drank was disproportionately higher than that of those in the smoker or drinker groups ($p < 0.001$). In total, 29 patients (46.0%) had 59 multiple primary cancers, including 26 oral cancers. Surgeries and radiotherapy were performed in 57 (90.5%) and 6 (9.5%) cases, respectively. The 5-year overall survival and disease-specific survival rates were 74.6 and 78.8%, respectively.

Conclusion Our study confirms that buccal SCC may develop in older adult Japanese patients, especially in women who have never smoked or drank. These patients could be at risk for second primary malignancy.

Keywords
- buccal mucosa
- cancer of head and neck
- multiple primary neoplasm
- alcohol drinking
- tobacco cessation
- Japanese

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Thieme Revinter Publicações Ltda., Rua do Matoso 170, Rio de Janeiro, RJ, CEP 20270-135, Brazil

Introduction

Buccal cancer is a common oral malignancy and accounts for almost all squamous cell carcinoma (SCC) cases. There is a wide geographical variation in its incidence, and ethnicity influences the prevalence due to associated social and cultural practices. Buccal SCC is among the most common oral cancers in Southeast Asia; however, it is relatively rare in North America and Western Europe, accounting for only 10% of all oral cavity carcinomas.[1] Moreover, although Japan is close to Southeast Asia, the incidence of buccal SCC in Japan may differ from that in Southeast Asia. The incidence and prevalence of SCC could be related to habits rather than to race.

Populations at risk of developing buccal SCC are those who have a long-standing history of tobacco and alcohol use. Betel quid chewing is a major risk factor associated with this disease in typical Southeast Asian countries, such as India, Malaysia, Pakistan, and Taiwan, and this accounts for a significant proportion of patients with oral cancers. These habits are considered factors associated with field cancerization that could induce multiple primary cancers (MPCs). In contrast, several reports on patients who never smoke and never drink (NSND) with oral cancers have been published. Previous reports have shown that most elderly female patients with gingival/buccal cancers were NSND patients.[2] However, the prevalence of multiple cancers in NSND patients has not been reported. The cause of death and prognosis are also unknown. Therefore, we aimed to determine the clinicopathological features of buccal SCC and to analyze the cause of death in a Japanese population.

Methods

Patient selection

Patients with previously untreated buccal SCC admitted to our institution between September 2002 and December 2015 (13 years and 4 months) were enrolled. Sixty-six consecutive Japanese patients underwent initial treatment with curative intent. Among these patients, 3 who were lost to follow-up within 1 year without available details were excluded. A total of 63 patients with buccal SCC were finally included in the present study. All patients who were alive were followed up for >5 years.

All patients underwent computed tomography (CT) and/or magnetic resonance imaging (MRI). Neck status was routinely evaluated with cervical ultrasonography. Chest X-rays were also obtained.

Experienced surgeons, a pathologist (Sato F.), and a radiologist specialized in head and neck imaging (Asakura K.) reviewed the clinical and pathological data. They reclassified all patients according to the proposals of the 8th edition of the American Joint Committee on Cancer (AJCC/8th edition)[3] and of the Union for International Cancer Control (UICC/8th edition)[4] Staging Manual. The diagnosis of MPCs was based on the Warren and Gates criteria, which determine that lesions must be distinct and separated by normal tissue or located in a similar region if >3 years have elapsed.[5]

The present study was approved by the Institutional Review Board (Authorization Number: 30-J83) and meets the standards set forth in the Declaration of Helsinki. Written informed consent has been waived.

Treatment

The clinical information of all patients was discussed in multidisciplinary head and neck cancer meetings. The standard treatment for buccal SCC at our institution involves radical surgeries. Although prophylactic neck dissection (ND) was not performed for N0 cases, simultaneous ND was performed in patients requiring reconstructive surgery. Tumor depth of invasion (DOI) was not considered when deciding on ND, so DOI was not integrated into the tumor, nodes, and metastasis (TNM) staging system for the present study. Radiotherapy with or without chemotherapy is adopted for patients with unresectable or borderline resectable (estimated low curability) tumors. Patients were prescribed 70 Gy, in 35 fractions, with curative intent.

Statistical Analysis

Statistical analyses were performed using StatMateIV software version 4.01 (GraphPad Software, San Diego, CA, USA). Differences and relationships between categorical parameters were evaluated using the Mann-Whitney U test and the Fisher exact test. Overall survival (OS) was defined as the time in months from diagnosis to death due to any cause, or to the time of last contact. Disease-specific survival (DSS) was measured as the time from the date of completion of treatment until the date of death due to primary buccal SCC. Survival curves were plotted using the Kaplan-Meier method, and the log-rank test was used to determine significance. Factors affecting OS in 5 years were evaluated by Cox proportional hazard models. The relative risk for survival was presented as hazard ratio (HR), confidence interval (CI), and p-value. A p-value <0.05 (two-tailed) was considered statistically significant.

Results

Demographics

The demographic and clinical information of patients is listed in ►**Table 1**. Among the 63 patients, 38 (60.3%) were men and 25 (39.7%) were women. At the time of diagnosis, the median age of all patients was 71 years old (men: 68 years old, range 45 to 89 years old; women: 74 years old, range: 51 to 91 years old). Female patients were almost 5 years older than male patients ($p=0.014$). Our study group did not include adolescents and young adults. In total, 41 (65.1%) patients (men: 20; women: 21) had cancers localized in the buccal mucosa (ICD10; C06.0), and 22 (34.9%) patients (men: 18; women: 4) had cancers of the retromolar trigone (ICD10; C06.2). Skin infiltration was detected in 3 patients (men: 2; women: 1). The numbers of patients with T1, T2, T3, and T4 tumors were 13 (20.6%), 26 (41.3%), 5 (7.9%), and 19 (30.2%), respectively. All patients with T4 tumors underwent CT and MRI. Among the 19 patients diagnosed with T4 tumors, 9 exhibited expansion to the CT masticator space; however,

Table 1 Demographic and Clinical Features ($n = 63$)

	Total		Male	Female	*p-value*
	63		**38**	**25**	
			(60.3%)	**(39.7%)**	
Age (years old)					0.014*[a]
Median	71		68	74	
Range	45–91		45–89	51–91	
Site					0.015*[b]
Buccal mucosa	41	(65.1%)	20	21	
Retromolar	22	(34.9%)	18	4	
Skin invasion					0.819[a]
Present	3	(4.8%)	2	1	
Absent	60	(95.2%)	36	24	
Clinical tumor (T) status					0.181[a]
T1	13	(20.6%)	6	7	
T2	26	(41.3%)	16	10	
T3	5	(7.9%)	2	3	
T4	19	(30.2%)	14	5	
Clinical nodal (N) status					0.887[a]
N0	35	(55.6%)	20	15	
N1	8	(12.7%)	7	1	
N2	20	(31.7%)	11	9	
N3	0	(0%)	0	0	
Clinical stage					0.618[a]
I	13	(20.6%)	6	7	
II	13	(20.6%)	9	4	
III	9	(14.3%)	6	3	
IV	28	(44.4%)	17	11	
Tobacco					< 0.001**[b]
Never	33	(52.4%)	8	25	
Smoker	30	(47.6%)	30	0	
Alcohol					< 0.001**[b]
Never	31	(49.2%)	8	23	
Drinker	32	(50.8%)	30	2	
Tobacco and alcohol					< 0.001**[b]
NSND	29	(46.0%)	6	23	
Smoke/drink	34	(54.0%)	32	2	
MPCs					1[a]
Present	29	(46.0%)	18	11	
Absent	34	(54.0%)	20	14	

Abbreviations: MPC, multiple primary cancer; NSND, never smoke and never drink.
[a]Mann-Whitney U test; [b]Fisher's exact test
Female patients were almost 5 years older than male patients ($p = 0.014$)

infiltration was detected only in 3 patients by MRI. In patients with T4 tumors, 16 (84.2%) and 3 (15.8%) patients were diagnosed with T4a and T4b tumors, respectively. The numbers of patients with N0, N1, N2, and N3 tumors were 35 (55.6%), 8 (12.7%), 20 (31.7%), and 0 (0%), respectively. A total of 35 (55.6%) and 28 (44.4%) patients were clinically designated to have N0 and N+ tumors, respectively. The cases were categorized as follows: stage I, 13 (20.6%); stage II, 13

(20.6%); stage III, 9 (14.3%); and stage IV, 28 (44.4%). The differences in TNM between male and female patients were not significant.

Never Smoke and Never Drink versus Smoker/Drinker

The status of habits included former and current ones. A total of 30 (men: 30; women: 0) patients had a smoking history, and 32 (men: 30; women: 2) patients had a history of alcohol use (►**Table 1**). No patients had betel quid chewing or smokeless tobacco use habits. In total, 29 (46.0%) were NSND patients. The comparison between smoker/drinker and NSND patients is shown in ►**Table 2**. The percentage of women in the NSND group was disproportionately larger (92.0%) than in the smoker/drinker group ($p < 0.001$).

Multiple Primary Cancers

Multiple primary cancers developed in 29 patients (46.0%; men: 18; women: 11). Among these patients, 16 (42.1%) and 13 (44.8%) comprised the smoker/drinker and NSND groups, respectively. No statistical difference was confirmed between the smoker/drinker and NSND groups in MPCs. Overall, MPCs were observed in 59 lesions. In the smoker/drinker group, the number of cases with lip and oral cavity, pharynx and larynx, esophagus, and other MPCs was 10 (27.0%), 12 (32.4%), 4 (10.8%), and 11 (29.7%), respectively. In the NSND group, the number of cases with lip and oral cavity, pharynx and larynx, esophagus, and other MPCs was 17 (77.3%), 0 (0%), 1 (4.5%), and 4 (18.2%), respectively. Multiple primary cancers were equally observed in both smoker/drinker and NSND groups. However, these groups had apparent differences in the content of MPCs. In the NSND group, oral MPC (except the oral floor) was frequently observed, while MPCs in the pharynx, larynx, and esophagus were rare.

Table 2 Habits and Multiple Primary Cancers ($n = 63$)

	Smoker/ drinker	NSND	
	34	**29**	
	54.0%	**46.0%**	***p-value***
Gender			< 0.001** [a]
Male	32	6	
Female	2	23	
MPCs			1.0
Present	16	13	
Absent	18	16	
Number of MPCs			(Total)
Lip	0	1	1
Oral cavity	10	16	26
Tongue	4	4	8
Floor of tongue	1	0	1
Gingiva	3	10	13
Buccal mucosa	2	2	4
Pharynx, larynx	12	0	12
Esophagus	4	1	5
Other site	11	4	15
	37	22	59

Abbreviations: MPC, Multiple primary cancer; NSND, never smoke and never drink.
[a]Fisher exact test
The percentage of women in the NSND group was disproportionately larger (92.0%) than that in the smoker/drinker group ($p < 0.001$). Multiple primary cancers were equally observed in both the smoker/drinker and in the NSND group. In the NSND group, oral MPC (except the oral floor) was frequently observed, while MPCs in the pharynx, larynx, and esophagus were rare.

Treatment

Surgeries were performed in 57 (90.5%) cases (►**Table 3**). Mandibulectomies were performed in 28 (marginal: 13;

Table 3 Treatment

Surgery Group ($n = 57$; 90.5%)	
Primary resection	
Tumor resection alone	29
Marginal mandibulectomy	13
Segmental mandibulectomy	15
Reconstruction	
Anterior lateral thigh flap	17
Rectus abdominis flap	5
Fibular flap	3
Scapula flap	2
Without reconstruction	31
Neck dissection (ND)	
Ipsilateral	32
Bilateral	1
Without ND	24
Adjuvant therapy	
None	54
RT	1
CRT	2
Radiotherapy Group ($n = 6$; 9.5%)	
RT alone	3
3D-RT	1
IMRT	1
Proton	1
CRT	3
Concurrent CRT	1
IC–CRT	1
Intra-arterial CRT	1

Abbreviations: 3D-RT, three-dimentional radiotherapy; CRT, concurrent chemoradiotherapy; IC, induction chemotherapy; IMRT, intensity modulated radiation therapy; RT, radiotherapy.
Surgeries were performed in 57 (90.5%) cases, and adjuvant therapy was performed in 3 (5.3%) patients. Six (9.5%) patients received radiotherapy as initial treatment.

Table 4 Pathological Examinations ($n = 57$)

Surgical margin		
Negative	37	(64.9%)
CIS	13	(22.8%)
Positive	7	(12.3%)
Depth of invasion		
≤ 5 mm	25	(43.9%)
> 5 mm, ≤ 10 mm	14	(24.6%)
> 10 mm	18	(31.6%)
Lymph node metastasis		
Negative	18	(31.6%)
Positive	15	(26.3%)
Number of nodes = 1		5
Number of nodes > 1		10
ENE (-)		9
ENE (+)		6
Without ND	24	(42.1%)

Abbreviations: CIS, carcinoma in situ; ENE, extra nodular extension; ND, neck dissection.
The surgical margin of 7 (12.3%) patients tested positive for invasive carcinoma. Among the 15 patients with pathological metastasis, 6 showed extranodular extension.

segmental: 15) patients depending on the extent of bone invasion. A free flap-based reconstruction was performed in 26 patients (anterior lateral thigh flap: 17; rectus abdominis flap: 5; fibular flap: 3; scapula flap: 2), including double-flap (fibular and rectus abdominis) reconstruction in 1 patient. Neck dissection was performed ipsilaterally in 32 cases and bilaterally in 1 case.

Pathological findings of 57 patients in the surgery group were examined (►**Table 4**). For the primary tumor status, the surgical margin and the depth of invasion were evaluated. The surgical margin of 13 (22.8%) and 7 (12.3%) patients tested positive with carcinoma in situ and invasive carcinoma, respectively, while that of 37 (64.9%) patients tested negative. Depths of invasion ≤ 5, between 5 and 10, and > 10 mm were observed in 25 (43.9%), 14 (24.6%), and 18 (31.6%) patients, respectively. Regional lymph node status was examined in 33 patients who underwent ND. Among these 33 patients, 15 (45.5%) showed defined pathological metastasis. Among these 15 patients with pathological metastasis, 6 showed extranodular extension.

Radical surgeries with adjuvant therapy were performed in three patients (radiotherapy: one; chemoradiotherapy: two) (►**Table 3**). Among the seven patients with a positive surgical margin, two received adjuvant therapy. Among the six patients with an extranodular extension in the pathological specimen, two received adjuvant therapy. Depth of invasion was not considered when deciding on adjuvant radiotherapy. In total, three patients received adjuvant therapy. Other patients were denied or not prescribed adjuvant therapy due to their condition.

Six patients who received radiotherapy as initial treatment were included in the radiation group. Proton therapy was performed in one patient (T2N0) who refused to undergo surgical therapy. Two patients had poor general conditions; thus, they underwent radiation therapy alone (three-dimensional radiation therapy [3D-RT]: 1; intensity-modulated radiation therapy [IMRT]: 1). Concurrent chemoradiotherapy (CRT) with curative intent was performed in three patients (T4N+) with an estimated low curability. Among these three patients, intravenous CRT was performed in two patients and intra-arterial CRT (RADPLAT) in one patient.

Cause of Death

No deaths occurred due to treatment complications. All patients who were alive were followed-up for > 5 years. The median follow-up period was 69 months (range: 2 to 194 meses). The 5-year OS and DSS rates were 74.6 and 78.8%, respectively. The 5-year DSS rates in different stages and T categories were: stage I, 100%; stage II, 84.6%; stage III, 88.9%; stage IV, 66.9% ($p = 0.084$); T1, 100%; T2, 80.1%; T3, 80.0%; and T4, 68.4% ($p = 0.210$) (►**Table 5**). Eight patients developed local recurrences and six underwent curative surgeries, five of whom were disease-free during the follow-up period. Among 13 patients with carcinoma in situ (CIS) on surgical margin, 5 patients developed local recurrences, and all underwent curative surgery. No patients with CIS on surgical margin died. Four of seven patients with positive surgical margins died of buccal SCC. Two patients developed both local and regional recurrences, and one patient developed both local and distant recurrences. In four patients, tumor control was not achieved with initial chemoradiation therapy. Distant metastases without locoregional recurrences were not observed.

Neck dissection was performed in 33 cases (32 ipsilateral and 1 bilateral) (►**Table 3**). Among patients with early buccal SCC (stages I and II), 3 and 23 patients underwent ND and observation, respectively. No pathological metastases were observed in the ND group. Regional recurrences were observed in five patients, and salvage ND was performed in all of them, two of whom died of buccal SCC. The occult

Table 5 Cause of Death ($n = 63$)

	Alive		Died		
Stage	DFS		DOD	DSC	DID
I	13	10	0	3	0
II	13	6	2	3	2
III	9	8	1	0	0
IV	28	16	9	1	2
	63	40	12	7	4
		(63.5%)	(19.0%)	(11.1%)	(6.3%)

Abbreviations: DFS, disease-free survival; DID, dead of intercurrent disease (noncancer); DOD, dead of disease (primary cancer); DSC, dead of second primary cancer.
At the time of analysis, 12 (19.0%) and 7 (11.1%) patients died of buccal SCC and second primary cancers, respectively.

Table 6 Univariate Analyses Estimating 5-Year Overall Survival

	HR (95%CI)	*p-value*
Male versus female	0.93 (0.34–2.57)	0.9
Age (< 70 versus ≥ 70 years old)	1.40 (0.51–3.86)	0.51
Buccal versus retromolar	1.12 (0.41–3.07)	0.83
T1, T2, and T3 versus T4	1.49 (0.54–4.10)	0.44
Pathological DOI (< 5 versus ≥ 5)	2.64 (0.71–9.77)	0.14
Surgical margin (positive versus negative, CIS)	1.12 (0.41–3.07)	< 0.01**
N0 versus N1, N2, and N3	1.82 (0.67–4.89)	0.23
ENE (present versus absent)	6.04 (1.80–20.27)	< 0.01**
NSND versus smoke and/or drink	1.06 (0.39–2.85)	0.91
MPCs (present versus absent)	0.33 (0.11–1.03)	0.06

Abbreviations: CI, confidence interval; DOI, depth of invasion; ENE, extranodular expression; HR, hazard ratio; MPC, multiple primary cancer; NSND, never smoke and never drink.
Univariate analysis shows a significant difference in extranodular expression status and surgical margin.

metastasis rate in patients with early buccal SCC was 19.2% (5 out of 26). Three of six patients with extranodular expression (ENE) underwent adjuvant therapy, and patients who did not undergo adjuvant therapy died of the disease.

At the time of analysis, 40 patients (63.5%) were alive and disease-free, and 12 (19.0%), 7 (11.1%), and 4 (6.3%) patients died due to buccal SCC, other cancers, and intercurrent diseases (noncancer), respectively (►**Table 5**). This implies that 11 (17.5%) patients died of diseases other than buccal SCC.

Outcome Measures

The parameters of the patients were statistically analyzed using Cox regression hazard models to estimate 5-year OS (►**Table 6**). The univariate analysis showed a significant difference in ENE status ($p = 0.0036$) and surgical margin ($p = 0.0027$). Conversely, age, habit (smoking and alcohol drinking), tumor location, pathological DOI, and multiple cancer statuses showed no statistical differences in survival. The 5-year OS determined using the Kaplan-Meier method in patients with buccal cancer as MPCs was of 86.2% and, in those not classified as MPCs, the 5-year OS was 64.7% ($p = 0.043$).

Discussion

There is a wide geographical variation in the incidence of buccal SCC. The present article reports the clinicopathological features of buccal SCC in a Japanese population. Our study found that most women with buccal SCC were elderly NSND patients, and oral MPC was frequently observed. Of our 63 patients, 12 died due to buccal SCC and 11 died from conditions other than buccal SCC.

Cancers occurring in the buccal mucosa and in the retromolar area account for 40.6% of all oral cancers recorded in the Mumbai Cancer Registry (India).[6] In turn, buccal SCC accounts for only ~ 10% of oral cancers in Europe and North America.[1] Between 2011 and 2017, 57,862 patients were registered in the national Head and Neck Cancer Registry of Japan, including our data, of which 15,593 (26.9%) patients had oral cavity cancers. The registry currently includes almost one-half of the estimated annual number of head and neck cancers in Japan.[7–15] Among 15,593 cases of oral cavity cancer, 1,420 (9.1%) patients primarily diagnosed with buccal mucosa and retromolar area cancers were enrolled. Among the patients with buccal SCC, 845 (59.5%) were men and 575 (40.5%) were women. The proportion of female patients > 70 years old was 69.7%. The Japanese population distribution of buccal SCC is similar to that observed in Europe and in North America.

Tobacco consumption and alcohol abuse are widely recognized as the most important causes of head and neck SCCs. At least 75% of head and neck cancers diagnosed in Europe, the United States, and other industrialized regions are attributable to the combination of cigarette smoking and alcohol consumption.[16] Almost 75 to 90% of the patients from various Asian countries have been tobacco users.[17] People who smoked > 1 packet of cigarettes a day had a 13-fold higher risk than nonsmokers, and those who consumed > 1.5 liters of wine per day had a 34-fold higher risk of developing head and neck cancers.[18] Furthermore, the high incidence of buccal SCC in Southeast Asia is considered to be associated with the traditional habit of betel quid chewing.[19] Although Japanese are racially similar to Taiwanese, the Japanese population distribution of buccal SCC is distinct from that in the Taiwanese population.[20] It is important to distinguish between cases in Southeast Asia and other countries.

However, a substantial proportion of oral carcinomas have been reported in NSND patients. A previous report has shown that young women with oral tongue cancer and elderly women with gingival/buccal cancer were commonly NSND patients.[2] Nonsmokers included a disproportionate number of women and there was a subgroup of NSND patients comprising older females with buccal SCC.

A significant proportion of MPCs were recognized in our study population. Slaughter et al. initially reported multicentric oral carcinoma in 1946, and the term "field cancerization" was subsequently introduced in 1953.[21,22] The prevalence of MPC was high (29 patients; 46.0%) and the mortality rate of MPC was relatively low (7 patients; 11.1%) in our cases. Interestingly, MPCs did not worsen the prognosis as indicated by the 5-year OS; in fact, they improved it. We assume that second primary carcinomas could be diagnosed at an early stage after buccal SCC treatment. Careful examination by clinicians is of paramount importance to improve the prognosis and screening for premalignant or early-stage oral cancers. Management of MPCs plays a key role in the prognosis of patients with buccal SCC.

To improve the prognosis of buccal SCC, locoregional control is essential. It has been known for decades that tumor thickness or DOI is considered a predictive parameter of lymph node metastases in patients with N0 oral

cancers.[23] However, our univariate analysis could not confirm pathological DOI as a risk factor. Extranodular expression was the most significant predictive factor of the 5-year DSS rate. The National Comprehensive Cancer Network (NCCN) has recommended adjuvant systematic chemoradiation therapy for extracapsular spread (guideline 2008, volume 2).[24]

Locally advanced buccal SCCs are also a crucial issue. Surgery should be considered as the primary tumor treatment modality when clear margins are achievable. Although the adequacy of the deep margin of the excision conflicts with the cosmetic outcome, wide excision with adequate margins followed by adjuvant treatment is the key to good locoregional control in buccal SCC. The NCCN guideline cites positive surgical margins as adverse features. Several studies suggested neoadjuvant chemotherapy followed by surgery in locally advanced (T4b) oral cavity cancers.[25,26] However, in our MRI study, invasion of the masticator space was relatively rare. To evaluate the invasion of the masticator space, the use of MRI simultaneously with CT is important. The NCCN guideline has also recommended adjuvant systematic chemoradiation therapy for extracapsular spread since 2008 (guideline 2008, volume 2).[24]

However, MPC is a frequent issue in buccal SCC. Therefore, radiation therapy could be reserved as the next treatment strategy.

Among the limitations of the present study is the fact that the population was small and limited to a Japanese population. In addition, this is a single center study. Although our study represented well the characteristics of Japanese buccal SCC, there was still a lack of comparison with other countries.

Conclusion

Our study confirms that buccal SCC may develop in older adult Japanese patients, especially NSND women. These patients could be at risk for second primary malignancy. The factors underlying the disease in this subgroup with no obvious risk factors are difficult to understand. More research on NSND patients is required to elucidate the mechanisms of their predisposition to the development of multiple tumors. It is important to examine other potential risk factors, such as environmental carcinogens and previous viral infections. In particular, elucidation of molecular biological aspects is required.

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Conflict of Interests
The authors have no conflict of interests to declare.

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