Buccinator muscle invasion is a risk factor for cervical lymph node metastasis in squamous cell carcinoma of the buccal mucosa: A retrospective study

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Abstract. The present study aimed to determine the risk factors associated with cervical lymph node metastasis (CLNM) in patients with buccal mucosa squamous cell carcinoma (BMSCC). This retrospective study included patients with primary BMSCC who underwent surgery at the Department of Oral and Maxillofacial Surgical Oncology of Tokyo Medical and Dental University (Tokyo, Japan) between January 2008 and December 2017. The following data were collected and analyzed: Sex, age, primary lesion subsite, tumor/node/metastasis stage, clinical growth patterns, tumor differentiation, lymphovascular and perineural invasion, mode of invasion, pathological depth of invasion, extent of tumor invasion, and clinical outcome of patients with BMSCC. Multivariate analysis was performed to identify the possible risk factors for CLNM. A total of 75 patients were included in the present study, among whom 30 (40%) were found to have histological CLNM. Of the 33 patients with buccinator muscle infiltration by the tumor, 24 (72.7%) had CLNM. Multiple logistic regression analysis revealed that buccinator muscle invasion was the most significant predictive risk factor for CLNM in BMSCC. The present study found that tumor invasion of the buccinator muscle was the most significant predictive risk factor for CLNM in BMSCC. Therefore, elective neck dissection should be performed if buccinator muscle invasion is identified in patients with BMSCC.

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Key words: buccinator muscle, buccal mucosa, cervical lymph node metastasis, squamous cell carcinoma, elective neck dissection

Introduction

Cancer in the oral cavity is the sixth most common type of malignancy worldwide, with approximately 275,000 cases diagnosed annually (1). In Japan, buccal mucosa squamous cell carcinoma (BMSCC) accounts for approximately 10% of oral cancers (2). The buccal mucosa is a large component of the oral cavity extending from the line of attachment between the upper and lower alveolar ridges to the pterygomandibular raphe. It is divided into the buccal mucosa, retromolar area, buccal-alveolar sulcus, and lip mucosa (3).

Cervical lymph node metastasis (CLNM), which significantly impacts the prognosis of patients with head and neck cancers, is encountered in >20% of squamous cell carcinomas (SCCs) (4). Tumor thickness has been reported to be significantly associated with the presence or absence of lymph node metastasis in BMSCC (5). Appropriate neck management in patients with head and neck SCC is important because CLNM is the most significant independent indicator for survival (6).

A new parameter, depth of invasion (DOI), was introduced in the 8th edition of the Union for International Cancer Control (UICC) guidelines, which is strongly correlated with CLNM (7,8). DOI has been reported to be an independent prognosticator of occult cervical metastasis, recurrence, and disease-specific survival (DSS) with the literature supporting an optimal cut-off depth of 4 mm for elective neck dissection (END) (9,10). There is general agreement that END is indicated when there is a high likelihood of occult, clinically undetectable lymph node metastases, when the neck needs to be entered for surgical treatment of the primary tumor, or when the patient will be unavailable for regular follow-up (11). This study aimed to investigate the risk factors for developing CLNM and the indications for END in BMSCC.

Materials and methods

Patients. This retrospective study included patients with BMSCC who underwent surgery at the Department of Oral

and Maxillofacial Surgical Oncology of Tokyo Medical and Dental University between January 2008 and December 2017. Patients who were previously treated at other hospitals or who underwent radiotherapy were excluded. The Institutional Review Board of the Faculty of Dental Hospital of Tokyo Medical and Dental University approved this clinicopathological study, and written informed consent was obtained from all of the patients (approval no. D2015-600). The authors confirm that all experiments were conducted in accordance with the relevant guidelines and regulations.

Data collection. The following data were collected and analyzed: sex, age, primary lesion subsite, tumor/node/metastasis stage (UICC 8th edition), clinical growth patterns, tumor differentiation, lymphovascular invasion, perineural invasion, pathological DOI (p-DOI), extent of tumor invasion, clinical outcomes, and Yamamoto-Kohama mode of invasion (YK classification) (12). Tumor differentiation, lymphovascular invasion, perineural invasion, mode of invasion, p-DOI, and extent of tumor invasion were determined using tissue blocks with the maximum cross-sectional area by two pathologists with more than 15 years of experience.

Treatment strategy. Resection of the primary tumor was performed with a margin of at least 1 cm. If bone invasion was observed, we performed marginal mandibulectomy or segmental mandibulectomy together. END was performed in cN0 patients who underwent reconstruction using a vascularized free flap. We performed supraomohyoid neck dissection (SOHND) as END. Postoperative treatment was performed in patients with positive margins, pathological CLNM in at least four nodes, or the presence of pathological extranodal extension (ENE), which may cause dissemination to the surrounding tissues outside the neck dissection area (13). Postoperative radiotherapy was performed at a dose of 50 Gy in all patients (13). If the renal function was within the normal limits, platinum-based anticancer agents (cisplatin 80-100 mg/m^2, two courses) were co-administered in combination with radiotherapy.

Statistical analysis. The primary endpoint was DSS. The follow-up period was 8-135 months (mean, 58.3±34.2 months). The end of the follow-up period was December 2019, and the median follow-up time was 58 months. Survival rates were calculated from the time of diagnosis until the end of the follow-up period, and Kaplan-Meier curves were plotted. Log-rank tests were used to determine statistical differences between patients with and without CLNM. Receiver operating characteristic (ROC) curve analysis was used to analyze the optimal cut-off value of p-DOI in predicting CLNM. Univariate analyses were performed using the χ^2 test or Fisher's exact test and the Mann-Whitney U non-parametric test, as appropriate. Multivariate analysis was performed using multiple logistic regression to determine significant independent predictive risk factors for CLNM in BMSCC. All statistical analyses were performed using PASW Statistics 18 software for Windows (SPSS Japan, Tokyo, Japan). Statistical significance was set at $P<0.05$.

Results

Subject for study. A total of 778 patients with primary oral SCC were examined at our department during the study period, of whom 86 (11.1%) were diagnosed with BMSCC. Of these, 75 underwent surgery for the primary lesion. Eleven patients who underwent radiotherapy were excluded from the study.

Patient characteristics. Table I shows the clinical and pathological characteristics of 75 patients who underwent surgery. There were 43 males and 32 females, with a mean age of 68.8 years (range, 26-89 years). Furthermore, 48 patients presented with lesions in the buccal mucosa, 14 in the retromolar area, 12 in the buccal-alveolar sulcus, and one in the lower lip mucosa. In the clinical T stage (cT), cT2 was the most common classification (48.0%). In the clinical N stage (cN), cN0 was the most in 50 patients (66.7%), and cN (+) was 25 patients (33.3%). Distant metastasis was not found in any patient (M0).

Clinicopathological findings. In the pathological T stage (pT), pT1 increased (26.7%). In the pathological N stage (pN), pT3b increased significantly (29.3%). Of the clinical growth patterns, the endophytic type was the most common in 43 patients (57.3%). There were six poorly differentiated tumors (8.0%). Lymphovascular and perineural invasion were found in 26 (34.7%) and seven (9.3%) patients, respectively. Mode of tumor invasion was classified as grade 4C in 13 patients (17.3%) and grade 4D in six patients (8.0%) (8). Postoperative treatments were performed in 21 patients (28%); 11 patients underwent chemoradiotherapy, 5 received chemotherapy, and 5 underwent radiotherapy.

Mode of CLNM. Neck dissection was performed at 51 sites among 49 patients (65.3%) as the initial treatment. Of the 49 patients, 25 with cN(+) disease underwent therapeutic neck dissection (level I-V). The remaining 24 patients with cN0 disease underwent both excision of the primary tumor and reconstruction using a vascularized free flap, with SOHND performed as END. CLNM developed subsequently in five patients (10%) with cN0 disease, who then underwent neck dissection.

Histological CLNM was confirmed at 31 sites in 30 patients. The incidence of CLNM in BMSCC was 40% (30/75 patients). The number of metastatic lymph nodes ranged from 1 to 10 (mean 3.2, median 3), and ENE was found in 25 patients (83.3%). All but four patients had lymph node metastasis at ipsilateral levels I-III. Metastasis at level IB was noted in 29 patients (96.7%). The remaining four patients had lymph node metastasis at the mandibular node, buccinator node, lateral retropharyngeal lymph node, and contralateral level IB and III nodes (Table II).

Risk factors for CLNM. The p-DOI ranged from 0-23.0 mm, with a mean of 5.3 mm and a median of 2.7 mm. Histopathologically, 31 patients (41.3%) had tumor invasion to the submucosal tissue, 33 (44.0%) had invasion to the buccinator muscle, and 11 (14.7%) had invasion to the mandible. Extent of tumor invasion, p-DOI, and CLNM values are shown in Table III. Among the 33 patients with buccinator

Table I. Clinical and pathological characteristics of patients.

Classification	Value (%)
Sex	
Male	43 (57.3)
Female	32 (42.7)
Age, years	
Mean	68.8
Range	26-89
Subsite	
Buccal mucosa	48 (64.0)
Retromolar area	14 (18.7)
Buccal-alveolar sulcus	12 (16.0)
Lower lip mucosa	1 (1.3)
cT stage	
T1	11 (14.7)
T2	36 (48.0)
T3	10 (13.3)
T4a	14 (18.7)
T4b	4 (5.3)
pT stage	
T1	20 (26.7)
T2	27 (36.0)
T3	14 (18.7)
T4a	11 (14.6)
T4b	3 (4.0)
cN stage	
N0	50 (66.7)
N1	10 (13.3)
N2b	12 (16.0)
N2c	1 (1.3)
N3b	2 (2.7)
pN stage	
N0	24 (32.0)
N1	2 (2.7)
N2a	3 (4.0)
N2b	3 (4.0)
N3b	22 (29.3)
NX	21 (28.0)
Clinical growth patterns	
Superficial type	18 (24.0)
Exophytic type	14 (18.7)
Endophytic type	43 (57.3)
Tumor differentiation	
Well	42 (56.0)
Moderate	27 (36.0)
Poor	6 (8.0)
Lymphovascular invasion	
No	49 (65.3)
Yes	26 (34.7)
Perineural invasion	
No	68 (90.7)
Yes	7 (9.3)
YK classification	
Grade 1	5 (6.7)
Grade 2	16 (21.3)
Grade 3	35 (46.7)
Grade 4C	13 (17.3)
Grade 4D	6 (8.0)
Adjuvant therapy	
No adjuvant therapy	54 (72.0)
Chemoradiotherapy	11 (14.7)
Chemotherapy	5 (6.7)
Radiotherapy	5 (6.7)

cT, clinical T; pT, pathological T; cN, clinical N; pN, pathological N; YK classification, Yamamoto-Kohama mode of invasion.

Table II. Mode of cervical lymph node metastasis.

Number and level of metastatic lymph nodes	Patients with pN(+) (n=30)
Number	
1	6
2	6
3	6
≥4	12
Level[a]	
Level IA	3
Level IB	29
Level II	17
Level III	4
Others[b]	4

[a]Levels may overlap: Patients with multiple metastases may also have metastases in multiple levels. [b]Others: mandibular node, buccinator node, lateral retropharyngeal lymph node, and contralateral side.

muscle involvement of the tumor, 24 (72.7%) developed CLNM, which was significantly different from those with submucosal tissue involvement and mandibular involvement ($P<0.001$ and $P<0.05$, respectively). No significant difference was found in the p-DOI of each group with different regions of extent of tumor invasion upon comparison of their CLNM status ($P>0.05$ for each group). The ROC curve indicated that the best cut-off value for p-DOI in predicting CLNM was 1.9 mm (sensitivity 80%, specificity 55.5%, area under the curve 0.711). Univariate analysis was used to evaluate the tumor classification, tumor differentiation, clinical growth patterns, subsite, extent of tumor invasion, p-DOI, lymphovascular invasion, perineural invasion, and mode of invasion to investigate the risk factors for developing CLNM.

Table III. Extent of tumor invasion, p-DOI, and CLNM.

Extent of tumor invasion	Incidence of CLNM, % (n)	P-value	Mean p-DOI, mm		P-value
			CLNM(+) (n=30)	CLNM(-) (n=45)	
Submucosa (n=31)	9.7 (3)	<0.001[a]	1.2	1.1	>0.05
Buccinator muscle (n=33)	72.7 (24)		8.5	8.8	>0.05
Mandible (n=11)	27.3 (3)	<0.05[b]	8.1	7.1	>0.05

[a]P-value for the incidence of CLNM in the submucosal invasion group vs. buccinator muscle invasion group. [b]P-value for the incidence of CLNM in the mandible invasion group vs. buccinator muscle invasion group. Incidence of CLNM was analyzed using the χ^2 test and mean p-DOI was analyzed using a Mann-Whitney U test. Statistical significance was set at P<0.05. p-DOI, pathological depth of invasion; CLNM, cervical lymph node metastasis.

Table IV. Multiple logistic regression analysis of CLNM.

Variables	Univariate[a] P-value	Multivariate[b]	
		P-value	OR (95% CI)
T classification (T1-T2 vs. T3-T4)	0.071		
Tumor differentiation (well vs. moderate, poor)	0.097		
Growth pattern (superficial, exophytic vs. endophytic)	0.002[c]	0.992	1.0 (1.0-1.0)
Subsite (buccal mucosa vs. others)	0.222		
Extent of tumor invasion (buccinator muscle vs. others)	<0.001[c]	<0.001[a]	12.3 (2.8-53.2)
p-DOI (≥1.9 mm vs. <1.9 mm)	0.004[c]	0.753	0.8 (0.2-4.0)
Lymphovascular invasion (positive vs. negative)	<0.001[c]	0.011[c]	6.3 (1.5-25.7)
Perineural invasion (positive vs. negative)	0.015[c]	0.325	4.4 (0.2-85.3)
YK classification (Grade 1, 2 vs. Grade 3, 4C, 4D)	0.001[c]	0.248	3.2 (0.5-22.8)

CLNM, cervical lymph node metastasis; OR, odds ratio; CI, confidence interval; YK classification, the Yamamoto-Kohama mode of invasion. [a]Fisher's exact test. [b]Multiple logistic regression analysis. [c]Statistically significant (P<0.05).

Of these, the significant predictors of CLNM were clinical growth patterns, extent of tumor invasion, p-DOI, lymphovascular invasion, perineural invasion, and the mode of invasion. Multiple logistic regression analysis revealed that the extent of tumor invasion and lymphovascular invasion were significant predictors of CLNM (P<0.001 and P=0.011, respectively; Table IV), of which the extent of tumor invasion was confirmed as the most predictive risk factor for CLNM in patients with BMSCC.

Clinical outcomes. Local, regional, and locoregional recurrences were observed in four, three, and two patients, respectively. The recurrence rate of BMSCC was 12%. In local recurrences, three patients underwent additional surgical treatment, and two were salvaged. In regional recurrences, two patients underwent additional surgical treatment and chemoradiotherapy, and both were salvaged. Two patients with locoregional recurrences had a policy of best supportive care. Furthermore, distant metastasis was confirmed in five patients (6.7%), and all patients were pN(+) with buccinator muscle invasion. Thus, total ten patients (13.3%) died due to primary disease (local-related death in four, cervical-related death in one and distal metastases-related death in five), six patients (8.0%) died due to other diseases, and 59 patients (78.7%) achieved no-evidence-of-disease status.

The cumulative overall and 5-year DSS were 78.8 and 86.5%, respectively. The cumulative 5-year DSS was significantly different between patients without buccinator muscle invasion (97.6%; n=42) and with buccinator muscle invasion (72.0%; n=33) (P<0.01) (Fig. 1).

Discussion

The treatment of choice for BMSCC differs based on the extent and location of the disease and geographic location (14). In some areas of Southeast Asia, radiotherapy is the treatment of choice. However, surgery is the treatment of choice in Western countries (14,15). In this study, 87% of patients (75/86 patients) underwent surgery, and the remaining underwent radiotherapy.

Oral SCC has a strong tendency for developing CLNM, which is well-known to be its most significant prognostic factor (16). Therefore, CLNM has a significant impact on treatment strategy and prognosis in patients with BMSCC.

In this study, the incidence of CLNM was 40% (30/75 patients), which is consistent with previous reports (5,17). A previous study reported that metastatic lymph nodes were

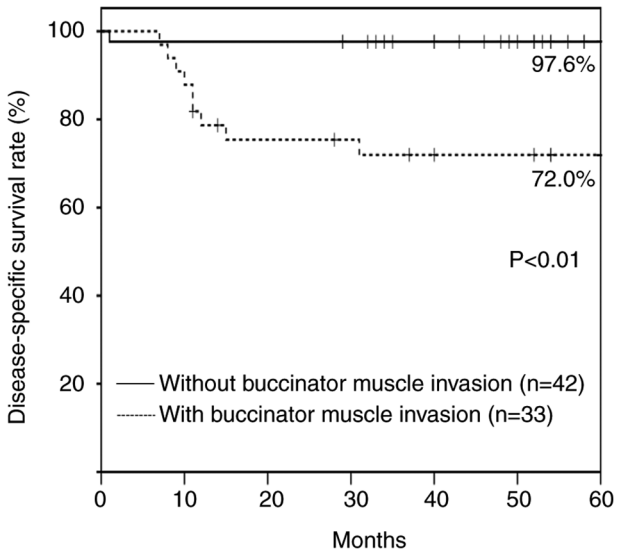

Figure 1. Disease-specific survival with or without buccinator muscle invasion.

most often found at levels I-III (18). The lymphatic system of the buccal mucosa drains primarily into the submandibular space through collectors that pierce through the buccinator muscle toward the facial artery and vein (19-21). In this study, metastasis to level IB was confirmed in 96.7% of patients with pN(+) (29/30 patients). Hence, the level IB node should be carefully monitored in patients with BMSCC. The buccinator and mandibular nodes were recognized as the other metastatic sites by Tomioka *et al* (22), who reported that 0.4% of patients with oral SCC had metastases at these sites. Additionally, buccinator and mandibular node metastases were found in 1.9 and 5.8% of patients who had BMSCC without and with CLNM, respectively (22). BMSCC is characterized by being more likely to metastasize to these lymph nodes than other oral SCCs. Therefore, treatment of these lymph nodes is important for improving survival. These lymph nodes are usually outside the dissection area in a typical neck dissection. When we performed neck dissection to excise the primary tumor of the buccal mucosa, we performed an *en-bloc* resection of the primary lesion and the dissected tissue, including the adipose tissue surrounding the facial artery and vein. Thus, we were able to dissect the lymphatic tissue from the cheek to the neck, including the buccinator and mandibular nodes. Lateral retropharyngeal lymph node metastasis was identified in one patient. Oikawa *et al* (23) reported that the incidence of retropharyngeal lymph node metastasis in patients with oral cancer was 1.2%, and the prognosis was significantly poor. In this study, no adhesions in the internal carotid artery were found in the patient with retropharyngeal lymph node metastasis; hence, surgical resection was performed. However, tumor recurrence occurred in the neck.

Previous studies have reported that tumor thickness is a more reliable predictor of CLNM (5,6). Ahmed *et al* (5) reported that the risk of CLNM in BMSCC increased in tumors with a thickness ≥2 mm. Soni *et al* (24) also reported that a DOI in SCC of the buccal-alveolar sulcus increased the incidence of CLNM, but the trend was not statistically significant. In this study, CLNM was found in three out of 31 patients (9.7%) with submucosal tissue invasion, three out of 11 patients (27.3%) with mandibular invasion, and 24 out of 33 patients (72.7%) with buccinator muscle invasion. These values were significantly different from each other. This time, we focused on the fact that the anatomical structure of the buccal mucosa differs depending on the subsite. The submucosal group is superficial and does not involve the buccinator muscle. The retromolar area carcinoma can easily invade the mandible. As shown in Table III, the mandible group had a p-DOI comparable to that of the buccinator muscle group, but there was a clear and significant difference in CLNM. This indicates that the extent of tumor invasion (i.e., buccinator muscle invasion), not p-DOI, affects CLNM in BMSCC. Previous studies have reported that lymphovascular invasion is a risk factor for CLNM in oral SCC (25,26). In the multivariate analysis of this study, lymphovascular and buccinator muscle invasion showed significant differences, but buccinator muscle invasion was found to be a more significant predictive risk factor for CLNM in BMSCC. In addition, buccinator muscle invasion can be evaluated preoperatively using computed tomography, magnetic resonance imaging, and ultrasound, and it is a useful factor in determining treatment strategy.

D'Cruz *et al* (27) reported the significance of performing END for clinical stage I/II disease (T1-2N0). However, it may be unnecessary in approximately 70% of patients without metastasis (28). Okura *et al* (29) reported that END was recommended if the probability of occult metastasis was >44.4%. In the present study, 24 out of 33 patients (72.7%) with buccinator muscle involvement had CLNM. Hence, END should be performed if buccinator muscle invasion is clinically identified.

In the previous studies, the 5-year survival rates for BMSCC have been reported to range from 54.1-74.5% (30-32). In this study, the cumulative 5-year DSS was 86.5%, which is more favorable than that reported in previous studies. Among 10 deaths from primary disease, CLNM was identified in nine patients. Metastases in multiple regions were also found in seven patients. The poor prognosis for patients with CLNM is consistent with that reported in previous studies (33,34). Since buccinator muscle invasion is an independent risk factor for CLNM, in this study, the cumulative 5-year DSS rates were 97.6 and 72% for patients without and with buccinator muscle invasion, respectively. Furthermore, five patients were found to have died due to distant metastases. All five patients who died were in the group with buccinator muscle invasion and CLNM. Hence, adjuvant chemotherapy should be considered for patients with CLNM in multiple regions.

The most significant limitation of this study was the relatively small sample size and its retrospective nature. Moreover, since the surrounding tissues in BMSCC differ according to the subsite, it is difficult to measure the p-DOI of the mandible and buccinator muscles in a standardized manner. For prospective studies, it is necessary to classify tumors by subsite and to include more cases to overcome these limitations.

We evaluated 75 patients with BMSCC who underwent surgery. We found that tumor invasion of the buccinator muscle was the most significant predictive risk factor for CLNM in BMSCC. The survival rate of patients with BMSCC may be improved by performing END in patients with buccinator muscle invasion and adjuvant chemotherapy for patients with CLNM in multiple regions.

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Availability of data and materials

The datasets used and/or analyzed during the current study are available from the corresponding author on reasonable request.

Authors' contributions

HHi and HHa conceptualized this study. HHi, NN, TO, TKug, TKur and YM curated and investigated the data. HHi, HT and YO developed the statistical analysis plan and conducted statistical analysis. KK and TI performed the pathological investigation. HT and HHa supervised and organized this study. HHi wrote the first draft of the manuscript. HHi and HHa reviewed and edited the manuscript. HHi and HHa confirm the authenticity of all the raw data. All authors read and approved the final manuscript.

Ethics approval and consent to participate

The Institutional Review Board of the Faculty of Dental Hospital of Tokyo Medical and Dental University approved this clinicopathological study, and written informed consent was obtained from all of the patients (approval no. D2015-600).

Patient consent for publication

Not applicable.

Competing interests

The authors declare that they have no competing interests.

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