Int. J. Oral Maxillofac. Surg. 2018; xxx: xxx–xxx
https://doi.org/10.1016/j.ijom.2017.12.007, available online at https://www.sciencedirect.com

International Journal of Oral & Maxillofacial Surgery

Clinical Paper
Head and Neck Oncology

Small size of metastatic lymph nodes with extracapsular spread greatly impacts treatment outcomes in oral squamous cell carcinoma patients

C. Michikawa[1,2], T. Izumo[3], J. Sumino[1], T. Morita[1,4], Y. Ohyama[1,5], Y. Michi[1], N. Uzawa[6]

[1]Maxillofacial Surgery, Maxillofacial Reconstruction and Function, Division of Maxillofacial and Neck Reconstruction, Graduate School of Medical and Dental Sciences, Tokyo Medical and Dental University, Tokyo, Japan; [2]Department of Head and Neck Surgery, The University of Texas MD Anderson Cancer Center, Houston, Texas, USA; [3]Division of Oral Diagnosis, Dental and Maxillofacial Radiology and Oral Pathology Diagnostic Service, The Nippon Dental University Hospital, Tokyo, Japan; [4]Head and Neck Oncology Department, The Cancer Institute Hospital of JFCR, Tokyo, Japan; [5]Oral and Maxillofacial Surgery, Shizuoka City Shizuoka Hospital, Shizuoka, Japan; [6]Department of Oral and Maxillofacial Surgery II, Graduate School of Dentistry, Osaka University Osaka, Japan

C. Michikawa, T. Izumo, J. Sumino, T. Morita, Y. Ohyama, Y. Michi, N. Uzawa: Small size of metastatic lymph nodes with extracapsular spread greatly impacts treatment outcomes in oral squamous cell carcinoma patients. Int. J. Oral Maxillofac. Surg. 2018; xxx: xxx–xxx.

Abstract. Extracapsular spread (ECS) of metastatic lymph nodes from oral carcinoma is the most significant prognostic predictor of a poor treatment outcome. However, only a few reports on prognostic factors in ECS-positive cases have been investigated. To address this problem, a detailed examination of ECS pathology was conducted to determine the prognostic factors of oral squamous cell carcinoma (OSCC) with ECS of metastatic lymph nodes. This study involved 63 OSCC patients with at least one pathologically metastatic node with ECS. Among the 229 metastatic lymph nodes, 149 exhibited ECS. Univariate analysis revealed that a poor outcome and recurrence were significantly associated with the number of ECS-positive nodes, density of ECS, and the minor axis of the smallest ECS-positive node. However, multivariate analysis identified only small size of ECS-positive nodes as a significant and independent factor predicting recurrence and a poor outcome. Thus, small size of ECS-positive nodes is the most important prognostic indicator for OSCC with ECS in metastatic lymph nodes. The classification of ECS status using the minor axis of ECS-positive nodes may be useful for further prediction of a poorer prognosis in OSCC cases. Standardization of ECS diagnosis and multicenter prospective studies will be required to confirm and refine these findings.

Key words: oral cancer; extracapsular spread; lymph node; metastasis; size.

Accepted for publication 19 December 2017

0901-5027/000001+06

Head and neck squamous cell carcinomas (HNSCCs), including oral cancer, are common causes of cancer-related deaths worldwide[1,2]. It is widely accepted that the presence of extracapsular spread (ECS) of lymph node metastasis is the most pivotal prognostic indicator of survival, disease recurrence, and distant metastasis in these types of malignancies. In 2011, the present investigators retrospectively examined 127 patients with oral squamous cell carcinoma (OSCC). Multivariate analysis indicated that the presence of ECS, rather than the existence of a metastatic lymph node, was a significant predictor of disease recurrence and a poor prognosis[3]. This finding is in accordance with other important findings indicating that ECS is a discriminatory and significant predictor of the prognosis in patients with HNSCCs[4–8]. Based on these observations, postoperative concurrent high-dose single-agent chemoradiotherapy with cisplatin is recognized worldwide as the standard treatment for patients with resectable advanced HNSCCs who are at high risk of recurrence and metastases due to ECS or positive surgical margins[9–11].

Previous studies have shown that the incidence of ECS in metastatic lymph nodes of patients with HNSCCs is associated with increased lymph node size[12]. Thus, it is generally accepted that ECS is the result of local progression in the metastatic lymph node, owing to mechanical rupture of the lymph node capsule in many cases. However, although ECS has been detected in 60–100% of lymph nodes >3 cm in diameter, it has also been found in 39–59% of nodes <3 cm in diameter and in 23% of nodes <1 cm in diameter. In addition, ECS has been seen in 13–60% of patients with clinically negative (cN0) necks[13]. Alvi and Johnson reviewed 109 HNSCC patients with cN0 necks and found occult nodal metastasis in 37 (34%) patients; ECS was present in half of these patients[14]. Hosal et al. reported ECS in 17 out of 71 occult nodal metastases (24%) among 300 selective neck dissections for 210 HNSCC patients[15].

A previous study by the present authors investigated the association between the presence of ECS and the size of metastatic lymph nodes, and determined that ECS occurs more frequently in larger nodes in both the minor and major axes, although these differences were not statistically significant[3]. Therefore, ECS does not necessarily occur only in large lymph nodes, but can also occur in small metastatic lymph nodes. It seems unlikely that ECS is caused by local progression in metastatic small lymph nodes. Thus, ECS of large lymph nodes develops via a different mechanism from ECS of small lymph nodes, suggesting that the clinical course differs between these two types of ECS and that different adjuvant therapy may be required depending on these types.

This study was conducted to evaluate the clinical impact of small ECS-positive metastatic lymph nodes in OSCC patients.

Methods

Patient characteristics

Sixty-three patients with OSCC who had at least one pathologically metastatic node with ECS were evaluated. All patients underwent primary surgical excision in the Department of Oral and Maxillofacial Surgery, Tokyo Medical and Dental University Hospital (Tokyo, Japan) between February 2004 and August 2012. No patient underwent preoperative treatment. All protocols were reviewed and approved by the Research Ethics Committee of Tokyo Medical and Dental University. Detailed patient characteristics are shown in Table 1.

Pathological T staging, cellular differentiation, and mode of invasion of the primary tumours were defined based on the Union for International Cancer Control TNM Classification of Malignant Tumors[16], the World Health Organization (WHO) classification[17], and the modified malignancy grading system of Jakobsson et al.[18], respectively. All histological data obtained from neck dissection specimens were re-evaluated independently by two authors (C.M. and T.I.), both of whom were blinded to the patients' clinical data.

Table 1. Correlations between clinicopathological parameters and disease-free survival/overall survival.

Clinicopathological parameters	Disease progression			Overall survival		
	Negative	Positive	*P*-value[a]	Alive	Dead	*P*-value[a]
Sex						
Male	24	21	0.169	25	20	0.222
Female	13	5		13	5	
Age (years)						
≤62	12	12	0.270	13	11	0.434
>62	25	14		25	14	
Tumour site						
Tongue	19	16	0.423[b]	20	15	0.565[b]
Lower gingiva	7	3		8	2	
Floor of the mouth	5	4		4	5	
Buccal mucosa	3	2		3	2	
Upper gingiva	3	1		3	1	
Pathological T stage						
1–2	30	19	0.452	31	18	0.371
3–4	7	7		7	7	
Cellular differentiation						
Well/moderately differentiated	26	16	0.469	27	15	0.363
Poorly differentiated	11	10		11	10	
Mode of invasion						
1–3	13	9	0.928	14	8	0.662
4C/4D	22	16		22	16	
Number of positive nodes						
1	11	3	0.087	11	3	0.113
≥2	26	23		27	22	
Number of nodes with ECS						
1	18	4	0.006	18	4	0.011
≥2	19	22		20	21	
Highest anatomical level						
I/II	27	15	0.205	27	15	0.363
III/IV	10	11		11	10	
Density of ECS						
≤50%	13	3	0.034	13	3	0.048
>50%	24	23		25	22	
Size of smallest nodes with ECS (minor axis)						
≤5 mm	10	17	0.002	10	17	0.001
>5 mm	27	9		28	8	

ECS, extracapsular spread.
[a] *P*-value determined using the χ^2 test.
[b] Tongue versus other sites.

Please cite this article in press as: Michikawa C, et al. Small size of metastatic lymph nodes with extracapsular spread greatly impacts treatment outcomes in oral squamous cell carcinoma patients, *Int J Oral Maxillofac Surg* (2018), https://doi.org/10.1016/j.