Journal of Oral Cancer and Research

Original Article   **Open Access**

Cervical Lymph Node Metastatic Factors in the Preoperative Diagnosis of Oral Squamous Cell Carcinoma

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Abstract

The cervical lymph node (N) status is an important determinant of the prognosis of oral squamous cell carcinoma (SCC). The treatment strategy administered with regard to the N status of a patient greatly affects prognosis. However, it is difficult to completely diagnose the N status preoperatively and the development of secondary cervical lymph node metastasis. In this study, we aimed to analyze whether it was possible in the preoperative clinical diagnosis to determine the presence or absence of cervical metastatic extension. In this study, we followed 169 patients with untreated oral SCC for more than 1 year after they had undergone radical treatment at the Miyazaki University Hospital (Miyazaki, Japan). The patients were treated from 2005 to 2015. Among the 169 patients who were assessed preoperatively, 142 patients had an N0 status. Among these 142 patients, 16 patients had secondary cervical metastasis. The factors associated with cervical secondary metastases and predominance were the World Health Organization (WHO) grade, Yamamoto-Kohama (YK) classification, sectional margin, and local recurrence. If a preoperative biopsy showed a poor WHO grade and YK classification, then metastasis extension was possible. It may be necessary to consider prophylactic neck dissection for enforcement.

Keywords

Oral squamous cell carcinoma, Lymph node metastasis, Prognosis, Diagnosis

Introduction

Oral squamous cell carcinoma (SCC) affects 3 million people globally [1]; however, the overall survival rate is low at 40%-66% [1,2]. A patient's cervical lymph node (N) status at the initial diagnosis of oral SCC is an important factor determining prognosis [3,4]. Reports frequently suggest that patients without cervical lymph node metastasis undergo neck dissection [5]. However, approximately 20%-25% of patients who have undergone cervical dissection and a clinical status of N0 have metastatic lymph nodes, and 75%-80% of patients are overtreated [6,7]. The clinical or histopathological characteristics of the primary tumor could aid in determining whether it will develop into cervical lymph node metastasis, and may become a key solution to the problem of overtreatment. In our study, we aimed to determine whether it was possible in the preoperative diagnosis to judge the presence or absence of cervical lymph node metastasis. Therefore, we retrospectively investigated patients with secondary cervical lymph node metastasis of oral SCC, and extracted the risk of cervical lymph node metastasis

extension by examining clinicopathologic factors.

Material and Method

Included in this study were 169 patients who had untreated oral SCC and had undergone radical treatment at the Department of Oral Maxillofacial Surgery of Miyazaki University Hospital (Miyazaki, Japan) from 2005 to 2015. We followed these patients for more than 1 year after treatment.

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Table 1: Characteristics of patients.

Characteristics		No. of patients (% of total)	
		N0	N (+)
Sex	Male	84 (59)	13 (48)
	Female	58 (41)	14 (52)
Age (y)	Range	28-96	33-90
	Mean	68.5	67.3
Primary site	Tongue	79 (56)	14 (52)
	Mandibular gingiva	31 (22)	5 (19)
	Maxillary gingiva	12 (8)	1 (4)
	Floor of mouth	9 (6)	4 (14)
	Buccal mucosa	9 (6)	2 (7)
	Soft palate	1 (1)	1 (4)
	Lip	1 (1)	0
	Total	142 (100)	27 (100)

Table 2: Characteristics of patients detected secondary cervical lymph node metastases.

Characteristics		No. of patients (% of total)
Sex	Male	9 (56)
	Female	7 (44)
Age (y)	Range	36-80
	Mean	64.4
Primary site	Tongue	10 (63)
	Mandibular gingiva	1 (6)
	Maxillary gingiva	1 (6)
	Floor of mouth	1 (6)
	Buccal mucosa	3 (19)
	Total	16 (100)

For the clinicopathologic characteristics, we investigated age, sex, tumor (T) status, N status, histopathological differentiation (based on the World Health Organization [WHO] classification), invasive type (based on the Yamamoto-Kohama [YK] classification), therapy, presence or absence of sentinel lymph node biopsy (SNB), resection margin, and presence or absence of local recurrence. The treatment modality was surgery or radical chemoradiotherapy. When the treatment strategy for patients with stage N0 was prophylactic dissection, the patient only received a temporary neck dissection for primary tumor resection (i.e., pull-through operation) from April 2005 to March 2007 and from July 2012 to March 2015.

From April 2007 to July 2012, we performed SNB. We used cystography computed tomography, magnetic resonance imaging, and ultrasonography to determine a clinical diagnosis of lymph node metastasis. The statistical examination assumed a significant difference at $p < 0.1$ using the Mann-Whitney test and the Kruskal-Wallis test.

Results

The patients comprised 97 men and 72 women whose mean age was 67.9 years (age range, 28-96 years). The primary site was the tongue in 93% of patients, the man-

dibular gingiva in 36% of patients, the maxillary gingiva in 5% of patients, the mouth floor in 13% of patients, the buccal mucosa in 11% of patients, the soft palatal in 1% of patients, and the lip in 1% of patients. The N status was N0 in 142% patients, and N+ in 27% patients (Table 1). The T status among the 142 patients with an N0 status was T1 in 38 (27%) patients, T2 in 65 (46%) patients, T3 in 4 (3%) patients, and T4 in 35 (24%) patients.

Histopathological differentiation (using the WHO classification) among the 142 patients with an N0 status was Grade 1 in 87 (61%) patients, Grade 2 in 41 (29%) patients, Grade 3 in 4 (3%) patients, and unknown in 10 (7%) patients. The Yamamoto-Kohama (YK) classification among 142 patients with an N0 status was YK-2 in 12 (8%) patients, YK-3 in 55 (39%) patients, YK-4C in 32 (23%) patients, YK-4D in 3 (2%) patients, and unknown in 40 (28%) patients.

The treatment strategy among the 142 patients with an N0 status was only surgery in 108 (76%) patients and chemoradiotherapy (with salvage) in 34 (24%) patients. Among the 142 patients with an N0 status, 44 (31%) patients had an SNB, and the remaining 98 (69%) patients did not have an SNB.

The sectional margin among the 142 patients with an N0 status who received surgery or salvage was negative in 100 (70%) patients, revealed dysplasia in 10 (7%) patients, was positive in 13 (9%) patients, and unknown in 19 (14%) patients. Sixteen (11%) patients had a local recurrence, whereas 126 (89%) patients did not have a local recurrence.

Among the 142 patients with an N0 status, 16 (11%) patients had secondary cervical lymph node metastasis; these patients comprised nine men and seven women, and their mean age was 64.4 years (age range, 36-80 years). Among the 169 patients, 97 were men and were 72 women, and their mean age was 67.9 years (age range, 28-96 years). There was no correlation between secondary cervical lymph node metastasis and late departure, sex, and age. The primary site of secondary cervical lymph node metastasis was the tongue in 10 (63%) patients, the mandibular gingiva in one (6%) patient, the maxillary gingiva in two (12%) patients, and the buccal mucosa in three (19%) patients. There was no correlation between secondary cervical lymph node metastasis and the primary site (Table 2).

The T status among patients with secondary cervical lymph node metastasis was T1 in five (31%) patients, T2 in seven (44%) patients, and T4a in four (25%) patients. There was no correlation between secondary cervical lymph node metastasis and the T status. Histopathological differentiation (using the WHO classification) of the secondary cervical lymph node metastasis patients

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Table 3: Factor of secondary cervical lymph node metastases.

Factor	No. of patients (% of total)	
T status		
T1	38 (27)	5 (31)
T2	65 (46)	7 (44)
T3	4 (3)	0
T4a	33 (23)	4 (25)
T4b	2 (1)	0
WHO grade		
Grade1	87 (61)	7 (44)
Grade2	41 (29)	7 (44)
Grade3	4 (3)	2 (12)
Unknown	10 (7)	0
YK classification		
YK-2	12 (8)	0
YK-3	55 (39)	7 (44)
YK-4C	32 (23)	8 (50)
YK-4D	3 (2)	1 (6)
Unknown	40 (28)	0
Treatment		
Surgery	108 (76)	13 (81)
CCRT (+salvage)	34 (24)	3 (19)
SLN biopsy		
+	44 (31)	3 (19)
-	98 (69)	13 (81)
Sectional margin		
Negative	100 (70)	8 (50)
Dysplasia	10 (7)	3 (19)
Positive	13 (9)	2 (12)
Unknown	19 (14)	3 (19)
Local recurrence		
Negative	126 (89)	13 (81)
Positive	16 (11)	3 (19)
Total	142 (100)	13 (100)

Table 4: After treatment & outcome of characteristics of patients with secondary cervical lymph node metastases.

After treatment & outcome		No. of patient (% of total)
After treatment	TND	7 (44)
	TND + CRT	3 (19)
	CRT	3 (19)
	TND (both side)	1 (6)
	BRT	1 (6)
	Proton	1 (6)
Outcome	Dead	9 (63.5)
	Alive	5 (26)
	Cancer bearing	2 (10.5)
	Total	16 (100)

was Grade 1 in seven (44%) patients, Grade 2 in seven (44%) patients, and Grade 3 in two (12%) patients. Histopathological differentiation and secondary cervical lymph node metastasis accepted a significant difference by Kruskal-Wallis test (p < 0.01), and it followed that it became easy to occur the secondary cervical lymph node metastasis if degree of was poor.

The YK classification of patients with secondary cervical lymph node metastasis was YK-3 in seven (44%) patients, YK-4C in eight (50%) patients, and YK-4D in one (6%) patient. For the YK classification and secondary cervical lymph node metastasis, p < 0.1 indicated a significant difference (based on the Kruskal-Wallis test). Secondary cervical lymph node metastasis was likely if the YK classification was poor.

The treatment of secondary cervical lymph node metastasis involved only surgery in 13 (81%) patients and chemoradiotherapy (with salvage) in three (19%) patients. There was no correlation between the secondary cervical lymph node metastasis and the treatment modality. Three (19%) patients with secondary cervical lymph node metastasis underwent an SNB test, and 16 (81%) patients did not undergo an SNB. Therefore, SNB could not inhibit the secondary cervical lymph node metastasis. In patients with secondary cervical lymph node metastasis who underwent surgery or salvage therapy, the sectional margin was negative in eight (50%) patients, showed dysplasia in three (19%) patients, and was positive in two (12%) patients. The Kruskal-Wallis test showed a significant difference (i.e., p < 0.05).

Secondary cervical lymph node metastasis was likely if the sectional margin showed dysplasia and was positive. Thirteen (81%) of 16 patients did not have a local recurrence, but the remaining three (19%) patients had a local recurrence. The Mann-Whitney test revealed a significant difference. Patients with a local recurrence was were more likely to develop secondary cervical lymph node metastasis (Table 3). The secondary cervical lymph node metastatic site, time, treatment, and outcome are presented in Table 4.

Discussion

The patients whose necks were treated after the secondary cervical lymph node metastasis had a poorer prognosis than treated patients for whom the neck was treated during the initial treatment [5]. In addition, prophylactic neck dissection for patients with an N0 status improves the prognosis, but it may be overtreatment and remain only a postoperative disorder [8]. The treatment strategy for patients with oral SCC and an N0 status is important for a prognosis [5,8,9].

The aim of our study was to determine whether a judgment of the presence or absence of cervical lymph node metastatic development was possible in the preoperative diagnosis. Secondary cervical lymph node metastasis was not correlated with age, sex, and T status. It followed that it was easy to occur the secondary cervical lymph node metastasis in predominance so that the histopathological differentiation and the invasive style of the primary tumor worsened. Shingaki, et al. [10] reported that when

secondary cervical lymph node metastasis develops the degree of differentiation is poor, which is similar to the findings of our study. The mean time to the development of secondary cervical lymph node metastatic time was 8.7 months after treatment; therefore, most patients may have latent lymph node metastases before treatment.

Most cases of secondary cervical lymph node metastasis of oral SCC occur within 1 year; therefore, the primary cause of late departure metastasis is an oversight of latent metastases at the initial diagnosis [11]. Sentinel lymph node biopsies have been performed to decrease unnecessary neck dissection [10-12]. However, in our study, 44 patients underwent SNB tests, which detected secondary cervical lymph node metastasis in three patients. Therefore, the enforcement of SNB did not inhibit the secondary cervical lymph node metastasis to late departure.

The technique of SNB has recently been developed [12,13], and good results have been obtained in a large-scale investigation. This technique may have a role in the discovery of latent lymph node metastases [10-14]. Therefore, the immediate operative method of SNB that is unified is expected. However, SNB is an invasive diagnostic procedure, and postoperative disorder is concerned about. In this study, the resection margin-positive patients were easy to occur the secondary cervical lymph node metastasis in predominance, and the local recurrence patients turned out similar. These factors may be correlated, and it may be that the perioperative appropriate resection was important for controlling secondary cervical lymph node metastasis.

The prognosis of patients with secondary cervical lymph node metastasis was poor: nine (56%) patients died and the two (12.5%) patients had cancer-bearing survival. In order to control without having to over-treatment the secondary cervical lymph node metastatic rate, it is necessary to determine the presence or absence of the possibility of neck metastasis progress in the preoperative clinical diagnosis.

This study showed the possibility of neck metastasis if a patient has a poor degree of histological differentiation and invasion style. When the degree of histological differentiation and invasion style were poor in the preoperative clinical diagnosis, even in patients with an N0 status, prophylactic neck dissection can be performed and may improve the secondary cervical lymph node metastatic rate if we choose follow up when it is not so. However, it is difficult to completely diagnose cervical metastatic extension. The development of a new diagnostic procedure is expected in future.

Gene diagnosis after tissue biopsy is a method that could potentially be used to determine the likelihood of cervical metastatic extension [15,16]. The invasion depth

of a tumor is also a method that could be used to diagnose the likelihood of metastasis [10,17]. However, there is no unified method for judging the invasion depth by echo, and it is problematic that the determination of invasion depth varies among doctors. It is also impossible to determine the histopathological invasion depth preoperatively. Settling these problems can greatly assist in determining a preoperative metastatic diagnosis. For a long time, a preoperative diagnosis of cervical metastasis of oral SCC has been a problem and has not been settled. This study solves this problem. However, the development of other solutions is expected in the future.

Conflicts of Interest

None.

Ethical Approval

The study protocol was approved by the Research Ethics Committees of University of Miyazaki Hospital (approved No,2014-107.).

Patient Consent

Not required.

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