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Oral squamous cell carcinoma with microscopic extracapsular spread in the cervical lymph nodes

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Abstract. The purpose of this study was to determine the detailed background of cases of oral squamous cell carcinoma (OSCC) with microscopic extracapsular spread (ECS) in the cervical lymph nodes. The cases of 78 patients with primary OSCC, who attended hospital from October 2007 to July 2011 and underwent resection of the primary tumour with neck dissection, were reviewed. The subjects were classified into three categories: pN0, pN+/ECS−, and pN+/ECS+; the outcomes of pN+/ECS+ patients were compared in detail with those of the other categories. Thirty-one cases (39.7%) were pN0, 25 cases (32.1%) were pN+/ECS−, and 22 cases (28.2%) were pN+/ECS+. The 3-year overall survival rate was 82.1% in pN0, 74.1% in pN+/ECS−, and 39.8% in pN+/ECS+ (pN0 vs. pN+/ECS+, $P = 0.0004$; pN+/ECS− vs. pN+/ECS+, $P = 0.0086$). The 3-year disease-specific survival rate was 96.2% in pN0, 77.2% in pN+/ECS−, and 39.8% in pN+/ECS+ (pN0 vs. pN+/ECS+, $P < 0.0001$; pN+/ECS− vs. pN+/ECS+, $P = 0.0038$). Patients with poorly differentiated carcinoma, those with three or more ECS+ nodes, and those with ECS+ node(s) located at levels III, IV, and V, had the worst prognosis among pN+/ECS+ subjects.

Keywords: oral cancer; squamous cell carcinoma; extracapsular spread.

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Cervical lymph node metastasis is an important prognostic factor influencing survival in patients with oral squamous cell carcinoma (OSCC). In particular, extracapsular spread (ECS) in the cervical lymph nodes, which is defined as the penetration of a tumour through the capsule of an involved lymph node, is thought to be a significant adverse prognostic factor.

The pathology of ECS was first described by Willis in 1930.[1] Bennett et al. showed that ECS was a distinct adverse prognostic factor in patients with laryngeal and hypopharyngeal cancer.[2] Woolgar et al. demonstrated that OSCC patients with intra-nodal metastases had a 5-year overall survival rate of 64%, which went down to 21% in patients having microscopic ECS.[3] In a previous study, we found cases of OSCC with more than 10 pathologically positive lymph nodes (pN+) in the unilateral side to show a low overall survival rate of 20.8%; all of these cases had microscopic ECS.[4] Of note, cases with macroscopic ECS have a more unfavourable prognosis than those with microscopic ECS. Shaw et al. reported macroscopic ECS to have a 5-year overall survival rate of 19%, compared with 31% in microscopic ECS.[5] The diagnosis of macroscopic ECS must be made from subjective observation at the time of surgery, however the diagnostic

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criteria for microscopic ECS have been defined clearly.[6]

In this study we examined cases of OSCC with microscopic ECS (pN+/ECS+) and compared these with cases without pathologically positive neck lymph nodes (pN0) and cases without microscopic ECS (pN+/ECS−). Further, we investigated the detailed backgrounds of pN+/ECS+ cases, including tumour pathological differentiation, clinical distribution and number of cervical lymph nodes, and postoperative adjuvant therapies, to determine the prognosis in pN+/ECS+ cases.

Patients and methods

The cases of 78 patients with primary OSCC, who attended the study hospital from October 2007 to July 2011 and underwent resection of the primary tumour with neck dissection, were retrospectively reviewed. All of these patients were followed up until July 2013 and provided informed consent to participate in the study. This study was exempted from the need for ethical approval by the institutional medical ethics committee because of the retrospective method. The study was performed in conformity with the Declaration of Helsinki.

The subjects included 53 males and 25 females, with a mean age of 68.9 years and an age range of 40–89 years at the time of surgery. The primary tumour site was located on the tongue in 29 cases (37.2%), lower gingiva in 12 cases (15.4%), upper gingiva in 12 cases (15.4%), buccal mucosa in 11 cases (14.1%), and oral floor in 11 cases (14.1%); the primary tumour was a central carcinoma of the mandible in three cases (3.8%). T-stages, except for the central carcinoma cases, included T1 (one case), T2 (39 cases), T3 (14 cases), and T4 (21 cases). The tumour was pathologically well differentiated in 35 cases (44.9%), moderately differentiated in 32 cases (41.0%), and poorly differentiated in 11 cases (14.1%).

Among the 78 cases, eight were treated with bilateral neck dissections, which were indicated by preoperative physical or imaging examinations. All lymph nodes detected by palpation from neck dissection specimens were submitted for pathological analysis. Each lymph node was sectioned, put in different cassettes, and embedded in paraffin. The maximum profile diameter of the lymph node was measured and the specimen was evaluated microscopically; these evaluations were done by more than one pathology specialist.

Table 1. Distribution of cases in each subgroup (pN0, pN+/ECS−, and pN+/ECS+) by pathological grading.

Subgroup	Pathological grading		
	Well differentiated	Moderately differentiated	Poorly differentiated
pN0	18 cases	12 cases	1 case
pN+/ECS−	10 cases	9 cases	6 cases
pN+/ECS+	7 cases	11 cases	4 cases

Statistical methods

Microsoft Excel (Microsoft, Redmond, WA, USA) was used for the data analysis. Survival curves were constructed using the Kaplan–Meier survival analysis method, and a log-rank test was used to compare the survival distributions among the different groups. All statistics were two-sided, and a value of $P < 0.05$ was considered to indicate statistical significance.

Results

Of the 78 subjects, 31 (39.7%) were without pathologically positive neck lymph nodes (pN0) and 47 (60.3%) had pathologically positive neck lymph nodes (pN+). In the pN+ group, 25 (32.1%) were pN+/ECS−, while 22 (28.2%) were pN+/ECS+. The distribution of cases in each subgroup by pathological grading is shown in Table 1.

The profiles of pN+/ECS+ cases

pN+/ECS+ cases included 15 males and seven females, with a mean age of 68.7 years and an age range of 52–88 years at the time of surgery. The primary tumour site was located on the tongue in 11 cases, lower gingiva in one case, upper gingiva in two cases, buccal mucosa in two cases, and the oral floor in six cases (Table 2). The highest probability of pN+/ECS+ according to the primary tumour site was 54.5% for the oral floor, followed by 37.9% for the tongue.

With regard to the T-stage, 11 cases were T2, seven were T3, and four were T4; no case was T1. The maximum diameter of the ECS node ranged from 7 mm to 30 mm (mean 13.5 mm). Among pN+/ECS+ cases, three underwent postoperative adjuvant chemotherapy, five underwent radiotherapy with a total dose of 60–66 Gy, and eight underwent chemoradiotherapy (radiotherapy with a total dose of 66 Gy), while no postoperative adjuvant therapy was performed in six cases (Table 3).

The 3-year overall survival rate in pN0 was 82.1% (95% confidence interval (CI) 64.8–99.5%) and in pN+/ECS− was 74.1% (95% CI 55.9–92.3%), whereas it was 39.8% (95% CI 18.8–60.8%) in pN+/ECS+. There were significant differences between pN0 and pN+/ECS+ ($P = 0.0004$), and between pN+/ECS− and pN+/ECS+ ($P = 0.0086$) in the overall survival curves (Fig. 1).

The 3-year disease-specific survival rate in pN0 was 96.2% (95% CI 88.8–100.0%) and in pN+/ECS− was 77.2% (95% CI 59.2–95.1%), whereas it was 39.8% (95% CI 18.8–60.8%) in pN+/ECS+. There were significant differences between pN0 and pN+/ECS+ ($P < 0.0001$), and between pN+/ECS− and pN+/ECS+ ($P = 0.0038$) (Fig. 2).

The postoperative outcomes of pN+/ECS+ cases in July 2013 are shown in Table 3. These cases were divided into two groups based on the outcome: cases numbered 1–15 died or were still alive with distant metastasis, and these patients were categorized as the adverse prognosis group; cases 16–22 were all living without any disease, and these patients were categorized as the favourable prognosis group. Among pN+/ECS+ subjects, four were diagnosed pathologically to have poorly differentiated carcinoma, and all of these patients belonged to the adverse prognosis group.

Table 2. The probability of ECS+ according to the primary tumour site.

Primary tumour site	ECS+ cases/all subjects (%)
Tongue	11/29 (37.9%)
Lower gingiva	1/12 (8.3%)
Upper gingiva	2/12 (16.7%)
Buccal mucosa	2/11 (18.2%)
Oral floor	6/11 (54.5%)
Central carcinoma of the mandible	0/3 (0.0%)
Total	22/78 (28.2%)