

Clinical Paper  
Head and Neck Oncology

# Prognostic significance of extracapsular spread of lymph node metastasis from oral squamous cell carcinoma in the clinically negative neck

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**Abstract.** The presence of extracapsular spread (ECS) in patients with oral squamous cell carcinoma (OSCC) indicates a poor prognosis and is associated with a higher risk of regional recurrence and distant metastasis. The aim of this study was to analyse this important feature of cervical lymph nodes in the clinically node-negative setting. The study included 61 patients with clinically T1–T3N0 OSCC who underwent primary surgical treatment; 52 were male and nine were female, and their median age was 57 years. The 5-year disease-free survival, disease-specific survival, and overall survival rates were 30.6%, 28.3%, and 14.3%, respectively, in the ECS group compared to 61.9%, 61.9%, and 48.2%, respectively, in the pN+/ECS-negative group and 76.7%, 81.9%, and 47.0%, respectively, in the pN0 group. The differences between the survival curves were highly significant ( $P = 0.023$ ,  $P = 0.003$ , and  $P = 0.029$ , respectively). The incidence of local (50% vs. 14.9%,  $P = 0.011$ ) and regional (28.6% vs. 2.1%,  $P = 0.008$ ) recurrence was significantly greater in the ECS group compared to the other subgroups of patients. Furthermore, the time to recurrence was significantly shorter in the ECS subjects. The presence of ECS in patients with oral cancer indicates a poor prognosis. ECS is a frequent feature in clinically node-negative settings and may be more common in smaller lymph nodes than is generally appreciated.

**Key words:** oral cancer; lymph node metastasis; extracapsular spread; recurrence; survival.

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Oral cancer is common worldwide, representing up to 25% of all malignancies<sup>1</sup>. Squamous cell carcinoma is the most common histological type of oral cancer. It is

associated with high morbidity and mortality rates, which have improved significantly in the last three decades due to early detection and therapeutic advances<sup>2</sup>. The

lymph node status is the most important predictor of survival for patients with oral squamous cell carcinoma (OSCC). The presence of regional metastases reduces

the survival of these patients by up to 50%.<sup>3</sup> Furthermore the presence of extracapsular spread (ECS) indicates an even worse prognosis and is associated with a higher risk of regional recurrence and distant metastasis.<sup>4</sup>

Although most experts agree that ECS is an important adverse prognostic feature in OSCC, there is controversy about the interpretation and clinical relevance of ECS. The aim of the present study was to analyse in detail ECS in cervical lymph nodes within the clinically node-negative setting in terms of incidence, patterns of failure, recurrence rates, and patient survival.

## Materials and methods

The study was conducted with the approval of the Ethics Committee of the University of Zagreb School of Medicine, University Hospital Dubrava. Inclusion criteria were the following: histologically proven OSCC clinically staged as T1–T3, no clinical evidence of regional metastasis (cN0), and no prior treatment for head and neck cancer. The study included 61 consecutive patients with clinically T1–T3N0 OSCC who underwent primary surgical treatment at the Department of Maxillofacial Surgery, University Hospital Dubrava, Zagreb, Croatia between 2000 and 2004. The neck was considered to be cN0 when there were no palpable lymph nodes on physical examination and the lymph nodes were <1 cm in size and without an area of central necrosis (central low density or inhomogeneity) on computed tomography (CT).

All patients underwent elective neck dissection. The policy for the treatment of patients with a cN0 neck at the authors' institution is to dissect levels I–IV/V in oral cavity primaries that are larger than the superficial T2 tumour (T1 and superficial T2 primary tumours are treated by transoral excision with careful observation of the neck during the follow-up period). A bilateral neck dissection was performed in patients with midline or bilateral disease. Disease staging was based on the international TNM classification of 2002.<sup>5</sup>

Patients with adverse histopathological features (positive margins, perineural invasion, ECS, multiple positive lymph nodes, stage pT3 or pT4) underwent postoperative irradiation. A prophylactic dose of 50 Gy was given to the clinically undissected neck levels in daily fractions of 2 Gy. A boost of 60 Gy was applied to the tumour bed and metastases confined to the lymph node and a boost of 62–66 Gy was applied to regions of the neck with

ECS and/or close/involved margins. These latter two features were the indications for the addition of chemotherapy to adjuvant irradiation (concurrent chemoradiotherapy). The chemotherapy regimen was cisplatin 100 mg/m<sup>2</sup> on days 1, 22, and 43. The follow-up protocol consisted of history and physical examinations every 3 months in the first year, every 6 months in the second year, every 8 months in the third year, and every 12 months in the fourth year of surveillance. Post-treatment CT (primary and neck) was performed within 1 and 2 years after surgical treatment. Further imaging studies were performed only for patients with signs/symptoms; these were not done routinely for asymptomatic patients.

## Histopathological evaluation

Perioperatively, the neck dissection specimen was separated into lymph node levels using steel clips. The specimen was fixed in formaldehyde solution and each of the isolated lymph nodes was cut into slices approximately 2–3 mm thick, which were then embedded in paraffin blocks. Each paraffin block was sliced into sections 3–4 µm thick and these were stained with haematoxylin and eosin (HE); every isolated lymph node was examined histologically.

ECS was defined as the presence of any extension of tumorous tissue through the nodal capsule, with or without the presence of a desmoplastic stromal reaction. The finding of tumour tissue within the nodal capsule was not considered as ECS. Tumour thickness was measured from the luminal surface of the tumour to the deepest point of stromal invasion in the HE-stained slices. Margin status was defined as negative when the tumour was ≥4 mm from the marked surgical margin on the histological slide. The mode of cancer invasion was evaluated according to the classification proposed by Yamamoto et al.,<sup>6</sup> in which only the most invasive parts of the tumour (deep invasive margins) are graded.

## Statistical analysis

Follow-up intervals were calculated in months from the date of first treatment to the date of last follow-up or death. To assess the association of lymph node status and clinicopathological parameters, a  $\chi^2$  test or Fisher's exact test was performed. The main outcome measures were disease-free survival (DFS), disease-specific survival (DSS), and overall survival (OS). A DFS event was defined as a pathologically

confirmed recurrence. A DSS event was defined as a death resulting from OSCC; death from other causes was censored at the date of death. An OS event was defined as a death resulting from any cause. DFS, DSS, and OS were calculated using the Kaplan–Meier method, while the log-rank test was used to test differences between the actuarial curves. All statistical analyses were done using MedCalc statistical software (ver. 13.0.2; MedCalc Software bvba, Ostend, Belgium). *P*-values of <0.05 were considered statistically significant.

## Results

Of 153 patients with OSCC treated by surgery, 61 underwent elective neck dissection as part of the primary surgical treatment. Ninety-two patients underwent intraoral excision solely and were excluded from further analysis. Of the 61 patients, 52 were male and nine were female (median age 57 years, range 37–85 years). The clinicopathological characteristics of the study cohort are summarized in Table 1.

## Incidence of ECS and impact on survival

Fourteen (22.9%) of the study patients had ECS, 12 (19.7%) had an involved lymph node without ECS (pN+/ECS-negative), and the remaining 35 (57.4%) were node-negative (pN0). The influence of ECS on survival is shown in Figs. 1–3. The 5-year DFS, DSS, and OS was 30.6%, 28.3%, and 14.3%, respectively, in the ECS group compared to 61.9%, 61.9%, and 48.2%, respectively, in the pN+/ECS-negative group and 76.7%, 81.9%, and 47.0%, respectively, in the pN0 group. The differences between survival curves were highly significant (*P* = 0.023, *P* = 0.003, and *P* = 0.029, respectively).

## Impact of ECS on patterns of failure and time to recurrence

The incidences of local recurrence (50% vs. 14.9%, *P* = 0.011) and regional recurrence (28.6% vs. 2.1%, *P* = 0.008) were significantly higher in ECS subjects than in the subjects in the other subgroup of patients (Table 2). Also, a higher rate of distant metastasis was identified in the ECS group than in the other subgroup, although this did not reach statistical significance (28.6% vs. 10.6%, *P* = 0.093). Furthermore, the time to recurrence was significantly shorter in the ECS group (median 17.5 months) than in patients with metastases confined to lymph nodes

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