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Lymph node density predicts lung metastases in oral squamous cell carcinoma

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Abstract

The association between lymph node density and survival free of lung metastases in oral squamous cell carcinoma (SCC), has not been investigated so far to our knowledge. Lymph node density $\geqq 0.07$ has been reported by a multicentre international study to be a significant predictor of shorter survival in patients with oral SCC who have invaded nodes. We investigated whether a lymph node density of $\geqq 0.07$ correlates with shorter overall survival, survival free of distant metastases, and survival free of lung metastases, in patients with oral SCC and invaded lymph nodes. Thirty-five patients with histologically-confirmed invaded lymph nodes werestudied. Their density was calculated as the ratio of the number of invaded lymph nodes:total number of nodes. A density of $\geqq 0.07$ correlated significantly with shorter overall survival ($p < 0.02$), survival free of distant metastases ($p < 0.01$), and survival free of lung metastases ($p < 0.01$) on log rank testing. On testing by Cox's proportional hazards model of multivariate survival analysis with adjustment for the pathological stage (pstage IV/pstage III), and invaded surgical margins or extracapsular spread, or both, we found that lymph node density $\geqq 0.07$ was associated with significantly shorter survival ($p < 0.02$). We conclude that lymph node density predicts lung metastases in patients with oral SCC.

Keywords: Lymph node density; Oral squamous cell carcinoma; Lung metastasis

Introduction

Lymph node density, which is the ratio of the number of invaded lymph nodes:total number of lymph nodes, reliably predicts the survival of patients with oral squamous cell carcinoma (SCC) and invaded lymph nodes in the neck.[1–5] Although different cut-off values have been used in studies,[1–5] a multicentre international study showed that if the density was $\geqq 0.07$ it was associated with significantly shorter survival, both overall and free of distant metastases, in patients with oral SCC.[1]

Distant metastases after treatment of oral SCC are directly correlated with a shorter overall survival, and lung metastases are the most common.[6–8] Although several investigators have reported that a higher lymph node density is correlated with a shorter survival free of distant metastases,[1,2] the association between density and freedom from lung metastases[8] in oral SCC has not to our knowledge been investigated.

We have therefore investigated whether lymph node density of $\geqq 0.07$ is correlated with shorter overall survival, survival free of distant metastases, and survival free of lung metastases, in patients with oral SCC and invaded lymph nodes.

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Patients and methods

Between February 2008 and July 2013, 50 Japanese patients newly diagnosed at the Department of Head and Neck Surgery, Aichi Cancer Center Hospital, with oral SCC and clinical lymph node metastases were treated by resection of the primary tumour and neck dissection without any preoperative treatment. We excluded 15 patients who did not have lymph node metastases on histopathological examination, which left 35 patients with invaded lymph nodes who were enrolled in the study (tongue=20, upper gum=4, lower gum=4, floor of mouth=3, cheek mucosa=3, and hard palate=1). The study was approved by the institutional review board, and all patients provided their informed consent for all treatments and examinations.

Clinical diagnosis

At the first visit the patient had a routine physical examination, nasopharyngoscopy, and chest radiograph. Clinical staging was based on the results of these examinations, together with enhanced cervical computed tomography (CT) or magnetic resonance imaging, and ^{18}F-fluorodeoxyglucose (FDG)- positron emission tomography CT. The clinical signs of lymph node metastases, which were defined by enhanced CT, were the presence of ringed enhancement or a lymph node $\geqq$ 10 mm in size. We used the TNM classification for staging.[9]

Neck dissection and histopathological diagnosis

En bloc neck dissection as described by the Japan Neck Dissection Study Group was used for patients with clinical lymph node metastases.[10] Bilateral neck dissection was indicated in patients with primary tumours that involved the middle region and those who had clinical lymph node metastases in the contralateral side of the neck. Samples from neck dissections were carefully divided by cervical regions and the total number of lymph nodes was recorded. The pathologists examined all lymph nodes in a single representative cross section. These samples and this record were submitted for the pathological examination. All pathological diagnoses were made by two pathologists.

Postoperative treatment

After the pathological diagnosis had been made, the first choice of treatment for patients with invaded surgical margins, extracapsular spread, or multiple invaded lymph nodes, was cisplatin-based chemoradiation. Postoperative radiation was recommended if they were of advanced age, or had renal insufficiency, or poor general health, or both, and postoperative chemotherapy was recommended if there were distant metastases present. When treatment had been completed the patients were followed up in our outpatient clinic. We made an effort to identify those with early locoregional recurrence and treated such patients with radical salvage operations.

The follow-up protocol comprised routine locoregional examination every 1-3 months, and CT of the neck and chest every 6-12 months in the outpatient clinic. If symptoms or routine examination indicated possible recurrence, we followed these up with other specific tests and biopsy.

Lymph node density

A total of 1621 lymph nodes (level I=333, level II=396, level III=391, level IV=267, and level V=234) were evaluated, 154 (9.5%) of which were histopathologically invaded (level I=39, level II=55, level III=22, level IV=8, and level V=30). The numbers of patients who were diagnosed with invaded lymph nodes at each level were level I=25, level II=27, level III=10,level IV=5, and level V=1. Based on previous reports,[1–5] the density was calculated as the number of invaded lymph nodes:the total number of lymph nodes excised.

Statistical analysis

The statistical analysis was made with the aid of JMP software (version 9; SAS Institute; Cary, NC, USA). In all cases the survival time was defined as the period from resection to the "target event" or date of last contact. The "target events" included death (overall survival), local recurrence (survival free of local recurrence, regional recurrence (survival free of regional recurrence), distant metastases (survival free of distant metastases), and lung metastases (survival free of lung metastases). The Kaplan-Meier technique was used to estimate survival curves, and various cut-off values for density were tested using the log rank test in a univariate overall survival analysis.[11,12] The differences in the survival rates of the two groups ($\geqq$ 0.07 and $<$ 0.07 nodes) were assessed by the log rank test. The significance of differences between the two groups in clinicopathological variables (age, sex, clinical T and N classifications, clinical stage, site of tumour, type of neck dissection, histopathological T and N classifications, histopathological stage, invaded surgical margins, or extracapuslar spread, or both, and postoperative treatment) were compared using Fisher's exact test. A Cox proportional hazards model was used for multivariate survival analyses. We did the multivariate analysis (overall survival, survival free of distant metastases, and survival free of lung metastases) with adjustment for pathological stage (pstage IV /pstage III) and invaded surgical margins, or extracapsular spread, or both. Probabilities of less than 0.05 were accepted as significant.