

Prognostic impact of the level of nodal involvement: retrospective analysis of patients with advanced oral squamous cell carcinoma

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Abstract

We retrospectively evaluated the prognostic impact of the level of nodal involvement in patients with advanced oral squamous cell carcinoma (SCC). Between 2005 and 2010, 105 patients with clinical stage III or IV oral SCC had chemoradiotherapy preoperatively. Clinical (cN) and pathological nodal (pN) involvement was primarily at levels Ib and II. We defined nodal involvement at levels Ia and III–V as anterior and inferior extensions, respectively, and recorded such findings as extensive. With respect to pretreatment variables (age, clinical stage, clinical findings of the primary tumour, and nodal findings), univariate analysis showed that extensive cN was the only significant factor for overall survival (hazard ratio [HR], 3.27; 95% CI 1.50 to 7.13; $p = 0.001$). Univariate analysis showed that all pN findings, including the nodal classification (invaded nodes, multiple, and contralateral) and extensive involvement were significant, and multivariate analysis confirmed that extensive pN (HR 4.71; 95% CI 1.85 to 11.97; $p = 0.001$) and multiple pN (HR 2.59; 95% CI 1.10 to 6.09; $p = 0.029$) were independent predictors of overall survival. Assessment based on the level of invaded neck nodes may be a better predictor of survival than the current nodal classification.

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Introduction

Radiological examinations are widely used for the diagnosis and clinical staging of squamous cell carcinoma (SCC) of the head and neck.^{1–6} The TNM staging system has been updated several times in close cooperation between the Union for International Cancer Control (UICC) and the American Joint Committee on Cancer (AJCC), and is essential for pre-

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dicting prognosis, planning treatment, and comparing clinical trials.^{7,8}

The International Consensus Guidelines for the level of invaded neck nodes are also used to plan radiotherapy and neck dissection.^{9–11} According to the UICC/AJCC criteria for SCC of the head and neck, the staging of nodes takes into consideration single (N1), multiple (N2b), and contralateral (N2c) nodes, but not the level of involvement.

As nodal involvement tends to be stepwise and predictable, detailed anatomical knowledge of the lymphatic network in each area is essential for the development of effective treatments. The lymphatic drainage of each organ, which follows several pathways including the main collection and alternative routes,^{9,10} can be changed by the presence of nodal metastases.¹² We hypothesised that extensive nodal involvement (at uncommon levels) indicates progression and poor prognosis. We therefore retrospectively evaluated the prognostic impact of the level of nodal involvement in patients with advanced oral SCC.

Material and methods

Patients' characteristics

Between September 2005 and December 2010, 116 consecutive patients with newly-diagnosed advanced oral SCC were treated with preoperative chemoradiotherapy and operation. Of them, 105 (62 men, 43 women, median (range) age 70 (28–90) years) fulfilled our inclusion criteria of histologically confirmed SCC of the oral cavity, clinical stage III or IV, no distant metastases, and no previous malignancies. Data on the surgical specimens after preoperative chemoradiotherapy were also available, as were images taken before treatment (ultrasonography, computed tomography (CT), magnetic resonance imaging (MRI), and 18F-fluorodeoxyglucose (FDG) positron emission tomography (PET)/CT). We excluded two patients with a previous malignancy, and nine who had missing FDG-PET/CT data. Primary tumours were in the buccal mucosa (n = 10), upper gingiva (n = 16), lower gingiva (n = 34), hard palate (n = 7), tongue (n = 29), and floor of the mouth (n = 9).

The clinical pretreatment stage according to the UICC/AJCC criteria was identified at a clinical conference of oral surgeons, radiologists, and radiation oncologists, who interpreted the images. We based the radiological diagnosis of nodal involvement on accepted morphological criteria.^{1–3} The criterion for the FDG-PET-based identification of nodal metastases was tracer uptake, which was judged visually to be greater than that in the surrounding normal soft tissue.^{2,3} We took obvious FDG-uptake to indicate invasion even in small nodes, and obscure uptake to be equivocal.¹ Of the 105 tumours, one was T1, 30 were T2, 31 were T3, and 43 were T4. Thirty-two patients had midline involvement of the primary tumour. The clinical nodal (cN) stage was recorded as cN0 in 20 patients, cN1 in 23, cN2b in 51, and cN2c in 11.

The pattern of lymph node involvement according to the clinical findings of the primary tumour was based on the 2013 Consensus Guidelines.¹¹

Preoperative chemoradiotherapy

Under our protocol for preoperative chemoradiotherapy, which we used until July 2009, the total radiation dose (30 Gy) was delivered at daily fractions of 2 Gy over 3 weeks. Concurrently, patients were given S-1, a fluoropyrimidine derivative (Taiho Pharmaceutical, Tokyo, Japan) (80 mg/m²/day for 14 consecutive days) orally, but not during the last week of radiotherapy.¹³ In August 2009 we changed the total radiation dose to 40 Gy, which was delivered in 2-Gy daily fractions, and patients were given S-1 (65 mg/m²/day) orally for 4 weeks on the days of irradiation.¹⁴ The clinical target volume consisted of the tumour extension and levels I and II, even in cN0 necks, and levels with clinically invaded and equivocal nodes were included.

Operation

Operations were done three to four weeks after the completion of chemoradiotherapy. Radical operations were based on the TNM stage before treatment and the patient's condition. Primary tumours were resected with conventional surgical margins according to the ink tattoo that marked the tumour extension before chemoradiotherapy. Reconstruction was done immediately with revascularised free flaps or myocutaneous flaps. Generally, patients with clinically invaded nodes in the neck were treated by modified or radical neck dissection and, depending on the site and extent of the primary tumour, even patients with cN0 disease had a neck dissection. We divided the surgical specimens into the nodal levels, and routinely recorded the pathological nodal (pN) findings at each level. Based on the pathological findings, 4 patients also had postoperative chemoradiotherapy.

Follow-up evaluation

The initial sites of recurrence were classified as local, regional, or distant. Patients whose tumours did not respond to treatment had salvage operations and additional radiotherapy or chemotherapy, or both. Survival was measured from the first day of chemoradiotherapy to recurrence, death, or the last follow up.

Statistical analysis

Pretreatment variables included age, clinical stage, T classification, midline involvement, and cN status. In addition to the cN classification, we considered the level of nodal involvement to be a prognostic factor. The pN findings were evaluated as post-treatment variables.

Disease-free and overall survival were calculated using the Kaplan-Meier method and the log-rank test was used for com-

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