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A clinicopathological study of perineural invasion and vascular invasion in oral tongue squamous cell carcinoma

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Abstract. The risk factors for recurrence of head and neck cancer are classified as being of high or intermediate risk. Those of intermediate risk include multiple positive nodes without extracapsular nodal spread, perineural/vascular invasion, pT3/T4 primary tumours, and positive level IV/V nodes. However, little evidence is available to validate these intermediate risk factors. We analyzed perineural/vascular invasion in 89 patients who underwent radical surgery for oral tongue squamous cell carcinoma, whose records were reviewed retrospectively. Perineural invasion was found in 27.0% of cases and vascular invasion in 23.6%; both had a strong relationship with histopathological nodal status ($P = 0.005$). The 5-year disease-specific survival (DSS) and overall survival rates of patients with perineural invasion were significantly lower than those of patients without perineural invasion ($P < 0.001$ and $P = 0.002$, respectively). The 5-year DSS of UICC stage I and II cases with perineural/vascular invasion was significantly lower than those without ($P < 0.001$ and $P = 0.008$, respectively). Perineural invasion and vascular invasion are risk factors for regional metastasis and a poor prognosis. We recommend elective neck dissection when perineural/vascular invasion is found in clinical stage I and II cases. The accumulation of further evidence to consider intermediate risks is required.

Key words: oral tongue squamous cell carcinoma (OTSCC); perineural invasion; vascular invasion; intermediate risk.

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Extracapsular nodal spread and the presence of positive margins are major adverse prognostic factors for survival in head and neck cancer. Patients with these prognostic factors are considered to be at high risk of recurrence and have a survival benefit of postoperative adjuvant chemoradiotherapy in head and neck squamous cell carcinoma.[1–3] Moreover, intermediate risk factors (multiple positive nodes without extracapsular nodal spread, perineural invasion and vascular invasion,

pT3 or pT4 primary tumours, and oral cavity or oropharyngeal primary cancers with positive level IV/V nodes) are established as indications that patients should undergo postoperative radiation therapy (RT) and that adjuvant chemoradiotherapy should be considered.[1–3] The postoperative management of high-risk disease was clarified in two multicenter randomized trials: the Radiation Therapy Oncology Group (RTOG) trial 9501,[2] and the European Organization for Research and Treatment of Cancer (EORTC) trial 22931.[3] These two trials revealed common risk factors for the recurrence of oral cancer, such as extracapsular nodal spread, positive surgical margins, and multiple positive nodes without extracapsular nodal spread.[4] However, the RTOG recently demonstrated that patients with two or more positive lymph nodes did not benefit from adding chemotherapy to RT.[5]

Thus, the criteria for high or intermediate risk factors that suggest postoperative adjuvant therapy are controversial and need to be studied further. In particular, not many studies have discussed the intermediate risk factors – only the RTOG trial 9501 and EORTC trial 22931.[1–3] Nevertheless, several studies have reported adverse effects associated with chemoradiotherapy.[6,7] Therefore, it is necessary to accumulate evidence regarding the truly effective treatments for patients with oral cancer in order to implement the most appropriate postoperative adjuvant treatments. Perineural invasion and vascular invasion are defined as intermediate risk factors.

Some reports have revealed a relationship between perineural/vascular invasion and the prognosis in oral tongue squamous cell carcinoma (OTSCC) patients.[8–21] However, the contribution of perineural and vascular invasion to the prognosis remains unclear because of contradictory reports.

In this study, we reassessed the high and intermediate risk factors for oral cancer recurrence, in particular the relationship between perineural/vascular invasion and the prognosis.

Materials and methods

Patients and pathological examinations

The records of 89 patients who underwent radical surgery for previously untreated OTSCC between January 2001 and December 2011 were reviewed retrospectively. The study cohort included patients with histologically confirmed OTSCC and a minimum follow-up of 12 months. All study patients underwent extensive pretreatment evaluations, including blood chemistry, complete blood cell count, chest X-ray, computed tomography (CT) and/or magnetic resonance imaging (MRI) of the head and neck area, ultrasonic echo (US), and thoraco-abdominal CT, and provided informed consent to participate in the study. During the study period, surgery alone was preferred for the initial treatment of patients with oral cancer in our institution. However, patients who were unwilling to consent to a surgical intervention and inoperable patients with unresectable cancer and/or a severe systemic illness were selected for chemotherapy, radiation therapy, and/or supportive palliation.

All patients underwent glossectomy with curative intent. A neck dissection was performed for the clinical node (cN)-positive cases and cN-negative cases who required tongue reconstructive surgery because of the size of the primary tumour. No sentinel lymph node biopsy was performed. Postoperative adjuvant chemo/radiotherapy or RT was applied in accordance with the current National Comprehensive Cancer Network (NCCN) guidelines.[1] Patients who had adverse features (high risk features including extracapsular nodal spread and the presence of positive margins; intermediate risk features including multiple positive nodes without extracapsular nodal spread, perineural/vascular invasion, pT3/T4 primary tumours, and positive level IV/V nodes) were treated depending on the degree of the risk. Clinical staging was defined by palpation, inspection, CT, MRI, US, etc., according to the Union for International Cancer Control (UICC) TNM classification system.[22]

Tumours were classified histopathologically as well-, moderately, or poorly differentiated according to their cellular differentiation, as defined by the UICC.[22] The pattern of invasion was examined at the host/tumour interface; pattern of invasion types 1–4 were defined previously by Bryne et al.[23] The depth of invasion was measured as the infiltrative portion of the tumour that extended below the surface of the adjacent mucosa. Previous studies have demonstrated that a depth of invasion $\geq$4 mm has predictive value for cervical lymph node metastasis in patients with OTSCC[24–26]; therefore, depth of invasion was classified as $\geq$4 and $<$4 mm in the current study. A previous large cohort study demonstrated that a pathological margin distance $\leq$4 mm was significantly associated with loco-regional recurrence[27]; therefore, surgical margin status was classified as superficial ($>$4 mm) and deep ($\leq$4 mm) in this study.

Perineural invasion was defined as the presence of tumour cells within any of the three layers of the nerve sheath (the epineurium, perineurium, and endoneurium). Vascular invasion was defined as the clear presence of tumour cells within a vascular space (lymphatic space or blood vessel), and it was required that the tumour be adhered to the vessel endothelium or attached to a thrombus in the vessel. Expert pathologists who were unaware of the clinical outcomes performed all pathological assessments. Disease-specific survival (DSS) was calculated from the time of initial examination to the time of death related to local, regional, or distant recurrence/metastasis of the disease or the time of last follow-up. Overall survival (OS) was calculated from the time of initial examination to the time of death or last follow-up.

Statistical analysis

Statistical analyses were performed using StatMate IV (ATMS Co. Ltd, Tokyo, Japan). Categorical data were assessed using the χ^2 test or Fisher's exact test, as appropriate. The clinicopathological information related to perineural/vascular invasion was compared using the χ^2 test or Fisher's exact test, as appropriate. The clinicopathological information included pT stage, histopathological nodal status, UICC stage, pattern of invasion, local recurrence, and treatment. DSS and OS were calculated using the Kaplan–Meier method, and significance was evaluated using the log-rank test. A value of $P < 0.05$ was considered to be significant.

Results

Patient characteristics

The demographic and clinical characteristics of the study patients are summarized in Table 1. The male-to-female ratio was 1.28; 50 subjects were male. The mean age at diagnosis was 63.4 years (range 28–88 years). Perineural invasion was found in 24 of 89 patients (27.0%), and vascular invasion in 21 (23.6%). Histopathological lymph node metastasis was found in 25 (28.1%) patients. Local recurrence developed in 11 patients (12.4%) during the follow-up period. Postoperative distant metastasis occurred in three (3.4%) patients. The mean follow-up period of the whole series was 49.4 months (range 3–125 months).