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Extranodal extension and thickness of metastatic lymph node as a significant prognostic marker of recurrence and survival in head and neck squamous cell carcinoma

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ABSTRACT

Purpose: We examined the effect of extranodal extension (ENE) and its thickness (ENET) of metastatic lymph node (LN) on the disease course of patients with head and neck squamous cell carcinoma.
Methods: Data from 438 patients who were initially treated surgically at our center was retrospectively analyzed. ENE presence and ENET were examined in metastatic LN from each patient. Clinicopathologic characteristics, recurrence, and survival were then compared.
Results: Of 438 patients, 219 (50%) showed positive nodal status, and ENE was identified in 84 (19.6%). Forty-five of 219 (20.5%) node-positive patients were classified with ENET $\geq$ 2 mm, which was associated with an increase in both the size and number of positive LN, bilateral cervical involvement, and a higher LN ratio. ENE-positive patients had a higher risk of recurrence and a lower overall survival rate; however, multivariate analysis failed to identify a significant difference in cancer-specific survival (CSS) between those with and those without ENE. On the contrary, ENET $\geq$2 mm was significantly associated with a poor CSS, even in multivariate analysis.
Conclusion: ENET $\geq$2 mm might be a complementary prognostic marker in CSS estimation for ENE positivity.

1. Introduction

Cervical lymph node (LN) metastasis is a significant prognostic factor for patients with head and neck squamous cell carcinoma (HNSCC) (Layland et al., 2005). In addition, extranodal extension (ENE) is associated with an increased risk of recurrence and death (Wenzel et al., 2004). Current universal guidelines for HNSCC treatment strongly recommend that HNSCC patients with ENE receive adjuvant chemoradiotherapy (CRT) to reduce the risk of treatment failure (National Comprehensive Cancer Network).

The tumor-node-metastasis (TNM) staging system devised by the American Joint Committee on Cancer defines nodal-stage HNSCC according to largest diameter, number, or laterality of metastasized LNs (Edge et al., 2010). Treatment of HNSCC patients is usually based on TNM staging; however, this system does not provide reliable predictions of prognosis or treatment results (Takes et al., 2010). Therefore, other staging parameters, particularly regarding LN features, have been introduced to overcome these limitations. For example, Prabhu et al. reported that the LN ratio (calculated by dividing the number of positive LN by the total number removed during neck dissection [ND]) was an independent prognostic factor for locoregional recurrence and survival in HNSCC patients (Prabhu et al., 2014a). Another study proposed a modified pathological TNM staging system that accounts for ENE status when making treatment decisions and predicting prognosis (de Juan et al., 2013).

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Recent reports suggest that the mere presence of ENE is a poor predictor of disease recurrence and has little prognostic value because there is little evidence to support the beneficial effects of chemotherapy in addition to adjuvant radiotherapy (RT) in such patients (Lewis et al., 2011; Sinha et al., 2012; Prabhu et al., 2014b). Therefore, a new grading or risk stratification system for ENE is needed to avoid unnecessary treatment and to improve the survival of HNSCC patients. Because greater thickness/invasion depth of tumors in the oral cavity is a risk factor for LN metastasis, we assumed that ENE thickness (ENET) in metastatic LNs would have significant prognostic value. Therefore, the aim of the present study was to examine the association between ENET and other pathologic findings in HNSCC patients, and to analyze whether ENET is a predictor of tumor recurrence and patient survival. Furthermore, we sought to define a cut-off value for ENET, which could then be used to identify patients who would benefit from postoperative adjuvant treatment.

2. Material and methods

2.1. Study patients

The medical records (including pathology reports) of patients diagnosed with HNSCC and treated surgically (primary tumor resection plus ND with curative intent) at our tertiary referral hospital from January 2000 to December 2011 were retrospectively reviewed. The inclusion criteria were as follows: age >18 years; pathologically proven squamous cell carcinoma arising in the oral cavity, oropharynx, larynx, and/or hypopharynx; no distant metastasis at initial presentation; and follow up for more than 1 year after the initial treatment. Therefore, 438 patients were included in the final analysis. The patient selection procedure is depicted in Fig. 1. The study was approved by the institutional review board of our hospital. The requirement for informed consent was waived.

2.2. Treatment and follow-up

All patients underwent radical resection of the primary tumor combined with ND. Patients without clinical cervical LN metastasis underwent elective ND involving levels I–III or II–IV according to the index tumor site. When nodal metastasis was suspected, patients received therapeutic ND (including levels I–V or I–VI) on a case-by-case basis. Bilateral ND was performed if the primary tumor extended across the midline and contralateral neck metastases were suspected. Patients with advanced-stage tumors or adverse pathologic features were usually treated with postoperative RT or CRT (except patients with poor performance status, those who were very old, and those who refused treatment).

After the initial treatment protocol was completed, patients were followed up regularly: clinical examination and imaging were performed every 1–3 months during the first year, every 2–4 months during the second and third years, every 6 months during the fourth and fifth years, and annually thereafter. Clinical or radiologic findings indicative of index cancer recurrence or of the presence of a second primary cancer (SPC) were confirmed by biopsy and additional diagnostic tests. Patients with confirmed recurrence were scheduled for salvage or palliative treatment.

2.3. ENE and other pathologic parameters

The reports from pathological examinations of surgical specimens included the following: primary tumor size, grade, invasion into adjacent structures, lymphovascular invasion (LVI) or perineural invasion (PNI), resection margin status, the number of metastasized LNs harvested at each cervical level, the size (largest diameter) of the metastatic tumor, and the presence of ENE and its thickness. All pathologic reports and data were carefully reviewed and confirmed by reviewing additional slides. A board-certified pathologist (K.-J.C.) with >25 years clinical experience in head and neck pathology checked the metastatic LNs from each patient for the presence of ENE and its thickness.

ENE was defined as extension of the tumor through the LN capsule (as indicated by the finding of cancer cells or an associated peritumoral reaction to extracapsular keratin extension) (Apisarnthanarax et al., 2006). ENET was measured as the linear distance from the border of the external LN capsule to the farthest extent of the tumor, or the peritumoral reaction (Fig. 2). If the capsular structure was completely destroyed, or no residual LN architecture remained, the specimen was regarded as immeasurable and was excluded from the ENET analysis (although the specimen was still included in the ENE analysis).

2.4. Variables

Clinical data obtained from the medical records included patient age and gender, smoking status, alcohol consumption, body mass index (BMI; kg/m^2), initial treatment, and follow-up data. Heavy smokers were defined as those with >20 pack-years, and one drink was defined as 15.6 ml of pure ethanol (100%) (Hashibe et al., 2007). The site and TNM stage of the primary tumor were identified, and the above-mentioned pathologic parameters (including LN ratio) were also evaluated.

2.5. Statistical analysis

The Pearson χ^2 test or Fisher exact test were used to compare categorical variables between groups (clinicopathologic parameters, including ENE and ENET). The Kaplan–Meier method was used to calculate survivals, and data were compared using the log-rank test. The relationship between pathologic parameters (including ENE and ENET) and overall survival (OS) and cancer-specific survival (CSS) was examined using a Cox proportional hazards model, and the hazard ratio (HR) and 95% confidence intervals (CI) were calculated. A log-rank statistic–based cut-off determination method was used to identify the optimal cut-off values for ENET and the LN ratio with respect to CSS (Williams et al., 2006). Statistical analyses were performed using IBM SPSS software version 21.0 (IBM, Armonk, NY, USA) and SAS version 9.3 (SAS Institute Inc., Cary, NC, USA). A two-sided *P*-value of <0.05 was considered statistically significant.

3. Results

3.1. Patient characteristics

The characteristics of the 438 eligible patients (350 men and 88 women; mean age, 58 years [range, 20–82 years]) are summarized in Table 1. Primary tumors were most frequently found in the oral cavity (n = 179), followed by the larynx (n = 149), oropharynx (n = 85), and hypopharynx (n = 25). Of the 438 patients examined, 182 (41.6%) were pathologic stage T3–4 and 219 (50%) were node positive. Adverse characteristics of the primary tumors were also identified: close-to-positive margin in 57 cases (13%), LVI in 59 cases (13.5%), and PNI in 35 cases (8%). ENE was found in 84 patients (19.2%), with a mean ENET of 3 mm (range, 1–18 mm). Postoperative adjuvant treatments comprised RT alone (219 patients [50%]) and CRT (27 patients [6.2%]). The mean follow-up duration for the survivors was 56 months (range, 12–157 months). At follow-up, recurrence of the index HNSCC was found in