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Pretreatment pain predicts perineural invasion in oral squamous cell carcinoma: A prospective study

Chien-Fu Yeh MD [a,b], Wing-Yin Li MD [c], Pen-Yuan Chu MD [a,b], Shou-Yen Kao DDS, MHA, DMSc [d,e], Ya-Wei Chen DDS [d,e], Tsung-Lun Lee MD [a,b], Yen-Bin Hsu MD [a,b], Cheng-Chieh Yang DDS, PhD [d,e], Shyh-Kuan Tai MD, PhD [a,b,f,*]

[a] Department of Otorhinolaryngology-Head and Neck Surgery, Taipei Veterans General Hospital, No. 201, Sec. 2, Shipai Rd., Taipei 11217, Taiwan
[b] Department of Otolaryngology, National Yang-Ming University, No. 155, Sec. 2, Linong St., Taipei 11221, Taiwan
[c] Department of Pathology, Taipei Veterans General Hospital, No. 201, Sec. 2, Shipai Rd., Taipei 11217, Taiwan
[d] Department of Dentistry, School of Dentistry, National Yang-Ming University, No. 155, Sec. 2, Linong St., Taipei 11221, Taiwan
[e] Department of Stomatology, Oral and Maxillofacial Surgery, Taipei Veterans General Hospital, No. 201, Sec. 2, Shipai Rd., Taipei 11217, Taiwan
[f] Infection and Immunity Research Center, National Yang-Ming University, No. 155, Sec. 2, Linong St., Taipei 11221, Taiwan

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ABSTRACT

Objectives: Perineural invasion (PNI) is an established poor prognostic pathological feature for oral squamous cell carcinoma (OSCC). The purpose of this study was to analyze the role of pretreatment parameters in predicting PNI for OSCC.

Materials and methods: We prospectively enrolled into our study 102 newly diagnosed OSCC patients, who were surgically treated from 2011 to 2012. Before treatment, patients completed the European Organization for Research and Treatment of Cancer Quality of Life Questionnaire H&N35 and the visual analogue scale (VAS) for cancer pain. Pathological examination was performed to ascertain PNI status in all patients. Patients were divided into two groups, those with PNI and without PNI. Pretreatment parameters were compared between the two groups.

Results: In univariate analysis, clinical T classification ($P < 0.001$), painkiller use ($P = 0.001$), problem with social eating ($P < 0.001$) and social contact ($P = 0.002$), VAS scores of primary pain ($P < 0.001$) and referred pain ($P = 0.004$) were found to be associated with PNI. Multivariate logistic regression analysis further revealed VAS score of primary pain ($P = 0.001$, OR 2.014) and T3-4 classification ($P = 0.014$, OR 6.422) were independent predictors of PNI. A regression equation incorporating pretreatment pain was developed to predict the probability of having PNI.

Conclusion: PNI can be predicted by higher pretreatment VAS score of primary pain, as well as more advanced clinical T classification. Careful evaluation of pretreatment pain of primary tumor can thus be helpful in improving treatment decision making for OSCC.

Introduction

Oral squamous cell carcinoma (OSCC) remains a common type of cancer worldwide [1]. Patients with early OSCC can be treated by a single modality of either surgery or radiotherapy. However, advanced OSCC with T3-4 classification, N2-3 disease, or extracapsular spread requires a combination of surgery, radiotherapy and chemotherapy. In clinical practice, patient risk stratification mainly relies upon use of the TNM staging system which contains considerable heterogeneity within the same risk group, and no reported biomarkers are now widely used [2]. Thus, it is important to develop novel predictors in an effort to facilitate proper treatment decision making for OSCC.

Perineural invasion (PNI) is a distinct route of tumor spread broadly defined as the presence of tumor cells in the perineural space [3,4]. To date, PNI has been recognized as a poor prognostic pathological feature in several human malignancies including OSCC [5–10]. Earlier studies suggested that PNI was associated with lymph node (LN) metastasis and poor survival in OSCC [7–11]. In OSCC pathology report, PNI is a required element and an adverse feature suggesting the necessity of postoperative adjuvant radiotherapy or chemoradiotherapy, according to the National Comprehensive Cancer Network guidelines [12]. We recently

* Corresponding author at: Department of Otorhinolaryngology-Head and Neck Surgery, Taipei Veterans General Hospital, No. 201, Sec. 2, Shipai Rd., Taipei 11217, Taiwan.
E-mail address: sktai@vghtpe.gov.tw (S.-K. Tai).

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demonstrated that PNI independently predicts LN metastasis, neck recurrence, and poor survival in early OSCC [13,14], and that these negative impacts of PNI occur early in T1 cases [15]. We also reported that PNI is a key determinant for the aggressiveness associated with increased tumor thickness [16]. The important clinical role of PNI in guiding neck management, observation or elective neck dissection (END), was also reported [14,17].

However, it is not possible to use PNI status in guiding presurgical treatment planning, because determining the presence of PNI requires pathological evaluation after excision of primary tumors. To overcome this limitation, strategies in pretreatment prediction of PNI are necessary. Pain is a general and important sensation which can be generated by peripheral nerve stimulation [18]. In pancreatic cancer, PNI has been shown to play a role in the manifestation of associated pain [19]. Previous reports also suggested that there is an association between PNI and pretreatment pain or dysphagia in OSCC [20]. We therefore hypothesize that PNI may induce related presenting symptoms such as pain and influence the quality of life in OSCC. The purpose of this study was to analyze the role of pretreatment parameters including pain in predicting PNI for OSCC.

Materials and methods

Patient population

Between 2011 and 2012, 102 consecutive newly diagnosed OSCC patients who underwent surgical treatment at Taipei Veteran General Hospital were prospectively collected. The exclusion criteria included patients with previous head and neck cancers, or those who received previous chemotherapy or radiotherapy in the head and neck area. All patients completed preoperative assessment including medical history, physical examination, and comprehensive imaging studies. The tumor stage was determined preoperatively by the multidisciplinary head and neck cancer tumor board according to the 2010 seventh edition of the American Joint Commission on Cancer TNM staging system. The study was approved by the hospital's institutional review board. Patients were provided with a full explanation of the study, and written informed consent was obtained from each participant.

Questionnaire

The EORTC quality of life questionnaire, head and neck cancer module (EORTC QLQ - H&N35) was routinely completed by each participant before surgery at our department. The EORTC QLQ - H&N35 questionnaire comprised seven multi-item scales (pain, swallowing, senses, speech, social eating, social contact and sexuality) and eleven single items (teeth, opening mouth, dry mouth, sticky saliva, coughing, felt ill, pain killers, nutritional supplements, feeding tube, weight loss, weight gain). All of the scales ranged in score from 0 to 100, and a high score represented a high level of symptomatology or problems [21]. In addition, visual analogue scale (VAS) was used to evaluate the preoperative pain status. Both primary pain at the primary tumor site and referred pain at other head and neck regions such as otalgia were evaluated. Patients ranked the severity of pain on a 10-cm VAS bar, which clearly indicated 0 as no pain, 2 as mild pain, 4 as discomforting pain, 6 as disturbing pain, 8 as severe pain, and 10 as severe and unbearable pain [22].

Pathological examination

Regular hematoxylin-eosin (H&E) staining was performed on tissue sections from surgery fixed in formalin and embedded in paraffin. All sections were examined by 1 senior pathologist, who was blinded to all clinical data. Tumor tissue sections were cut at 5 mm thickness according to regular pathological diagnostic procedure. PNI was comprehensively examined across all tissue sections with a light microscope, first under $\times 40$ or $\times 100$ magnification, and confirmed under $\times 200$ or $\times 400$ magnification. PNI was defined as tumor cell infiltration in any layer of the nerve sheath, or tumor in close proximity involving more than one-third of the nerve circumference [3].

Statistical analysis

Categorical and continuous variables were summarized with descriptive statistics. Categorical data were compared by using Chi-square analysis or Fisher's exact test, and the differences between two groups with continuous variables were analyzed by use of the Mann-Whitney *U* test. Multivariate logistic regression analysis was performed to examine the predictors of PNI and construct a regression model. Hosmer-Lemeshow test revealed the goodness-of-fit of this model ($P = 0.120$). Receiver-operating characteristic (ROC) curve was established by plotting sensitivity against (1-specificity) and an optimal cut-off point was selected on the basis of Youden's index. Sensitivity, specificity, positive predictive value (PPV) and negative predictive value (NPV) of this cut-off point were assessed. The statistical analyses were performed using the SPSS/PC 17.0 software package (SPSS, Inc, Chicago, IL, USA). The statistical level of significance was defined as $P < 0.05$.

Results

Clinicopathological characteristics

Clinical and pathological characteristics of the 102 patients in our study were listed in Table 1. The mean and median age were 56.3 and 54.5 years, respectively (range 30–87 years), and 92 (90.2%) patients were male. The most common subsites were tongue SCC in 53 (52.0%) patients and buccal SCC in 26 (25.5%) patients. Based on the 2010 TNM staging system, the clinical T classification was T1 in 31 (30.4%), T2 in 42 (41.2%), T3 in 4 (3.9%), and T4 in 25 (24.5%) patients. More than half of the patients (59.8%, 61 cases) were clinical N0 and there was no patient with N3 disease in this population. Pathological examination revealed the presence of PNI in 40 (39.2%) patients.

Parameters predicting perineural invasion

The relationships between preoperative clinical parameters and PNI were analyzed. As shown in Table 1, clinical T classification predicted PNI. The PNI positive rate was higher in T3-4 classification compared with T1-2 classification (65.5% vs 28.8%, $P = 0.001$). None of the other clinical parameters demonstrated predictive value for PNI, including gender ($P = 1.000$), age ($P = 0.105$), tumor subsite ($P = 0.656$), smoking habit ($P = 0.779$), alcohol habit ($P = 0.244$), betel nut habit ($P = 0.186$), and clinical N classification ($P = 0.090$).

The scales of pretreatment questionnaire EORTC QLQ-H&N35 were compared between patients with and without PNI (Table 2). Patients with PNI demonstrated higher scores of pain ($P = 0.047$), painkiller use ($P = 0.001$), problems with social eating ($P < 0.001$) and social contact ($P = 0.002$), indicating more obvious problems with social eating, social contact and more pain at the time of initial diagnosis. To clarify the possible association between pain and PNI, we further analyzed the pain level evaluated by VAS (Table 2). We found that the mean VAS scores for primary pain in patients