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# Prognostic impact of perineural invasion in early stage oral tongue squamous cell carcinoma: Results from a prospective randomized trial

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ABSTRACT

*Background:* Although perineural invasion (PNI) has been recognized as a poor prognostic factor for oral cancer, few studies have focused on tongue squamous cell carcinoma (TSCC). Using a prospective randomized trial, this study investigated the role of PNI in the regional control and survival of the patients with cT1-2N0 TSCC, and clarified the benefit of neck management based on PNI status.

*Methods:* PNI status was reviewed under H&E staining in tumors of 221 patients with cT1–2N0 TSCC, who were randomly assigned into elective neck dissection (END) group (n = 111) and observation group (n = 110). Oncologic and survival outcomes were analyzed by multivariate regression and Kaplan–Meier analyses.

*Results:* PNI was identified in 34 patients and multivariate analyses revealed that PNI remained an independent predictor for cervical lymph node metastasis (CLNM), local relapse, neck relapse and disease-specific survival (DSS) after controlling for T stage and pathologic differentiation. END could not improve the benefit for patients. Stratified analysis revealed that END also could not improve neck control or DSS among patients with PNI.

*Conclusions:* This study demonstrated that PNI was an invaluable pathological parameter to independently predict cervical metastasis, local relapse, neck relapse and poor survival outcomes, but END could not improve benefits compared to observation for the PNI-positive patients.



## 1. Introduction

Tongue squamous cell carcinoma (TSCC) is the most common oral cancer, which is the eighth most frequent cancer-related death worldwide [1]. TSCC is well known for its high propensity to metastasize to cervical lymph nodes, even for clinical T1-2 tumors and node-negative necks (cT1-2N0) amenable for local surgical excision and neck dissection [2]. In patients with TSCC, the presence of cervical lymph node (LN) metastasis is the most important prognostic factor of survival, and regional recurrence after surgical excision is the most frequent cause of treatment failure and poor outcomes [3]. Therefore, the studies are need for exploring novel techniques or pathological indicators that effectively predict LN involvement or neck relapse, and that are capable of guiding optimal neck management for individual patients with TSCC.

Perineural invasion (PNI) is a distinct pathological feature characterized by the presence of tumor cells within the nerve sheath or perineural space [4]. According to the protocol published by the College of American Pathologists, PNI status is a required feature of the regular pathology report for oral cancer [5]. PNI is also regarded as an adverse feature in the National Comprehensive Cancer Network guidelines for head and neck cancers [6]. Although PNI has been recognized as a poor prognostic factor in several

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human cancers including oral and head and neck cancers [7–11], it remains unclear whether differential prognostic significance of PNI can be observed at different subsites and tumor stages of head and neck cancer. Besides, the specific impact of PNI on oncologic outcomes and survival also remains controversial [9,10]. Thus, it is important to clarify the impact of PNI at specific early-stage TSCC in order to better understand and properly apply this commonly used pathologic parameter in head and neck cancers.

In this study, we therefore focused specifically on the impact of PNI in early-stage TSCC. We aimed to investigate the roles of PNI and other parameters in the LN involvement, loco-regional control, and survival of the patients with cT1-2N0 TSCC, and clarify the benefit of neck management based on PNI status used a prospective randomized trial from China.

## 2. Patients and methods

### 2.1. Study patients

The studied subjects who were enrolled onto a prospective randomized single-center trial from the Department of Oral & Maxillofacial-Head & Neck Oncology, Shanghai Ninth People's Hospital, China were eligible for this study. The primary objective of the trial was to estimate the patients with early-stage cT1-2N0 TSCC should be treated with elective neck dissection (END) at the time of the primary surgery or observed with therapeutic neck dissection (TND) after neck metastasis. The trial was approved by the hospital's research ethnic committee, and written permission for the randomization of treatment obtained from all participating subjects.

### 2.2. Study procedures

From November 2008 to September 2014, a total of 221 cT1–2N0 TSCC patients were randomly assigned into END group and observation group with the use of a prepared computerized block design. All patients had preoperative physical examination, ultrasonic scanning, and imaging examinations including computed tomography or magnetic resonance imaging, and had transoral glossectomy with 1.5 cm resection margin of the primary tumor. Primary tumor was defined stage T1 (<2.0 cm) and T2 (2.0–4.0 cm) based on the 2007 edition of the American Joint Commission on Cancer TNM system, and the cN0 status was determined by physical and imaging examination. Those patients who were randomized to END had ipsilateral supraomohyoid levels I to III neck dissection, and other patients who were randomized to observation group had ipsilateral TND levels I to V neck dissection after neck relapse. All patients were followed up regularly with interval of 2 month in the first years, 4 months in the second year, 6 months in the third year, and thereafter once every 6 months to 1 year.

### 2.3. Histologic examination

The pathologic diagnosis including differentiation (well, moderate, or poor), depth of invasion (DOI), and PNI of all cases was determined by an oral pathologist on duty from the Department of Oral Pathology, Shanghai Ninth People's Hospital. PNI was defined as positive when tumor cell infiltration was identified in any layer of the nerve sheath, including the perineural space or epineurium. The confirmation diagnosis focusing on PNI was performed by another oral pathologist who was blinded to all clinical and outcome data.

### 2.4. Study outcomes

The oncologic outcomes including LN metastasis, tongue local relapse, neck relapse, and distant metastasis were studied. LN metastasis was defined as pathological diagnosis of positive nodal metastasis in the END group and positive nodal disease during follow-up period without antecedent local recurrence in the observation group. Neck relapse was defined as the nodal recurrence after neck dissection and the development of first nodal disease after the excision of the primary tumor one year in the observation group. Disease-free survival was defined as the interval between the date of randomization and the date of the first documented evidence of relapse at any site (local, regional, or metastatic) of the disease. Disease-specific survival was defined as the interval between the date of randomization and the date of death from the index tumor or treatment-related events. Follow-up time was defined as the duration between the date of treatment initiation and events or last contact. The mean follow-up period was 44.3 months (range, 21–91 months).

### 2.5. Statistical analysis

Categorical variable were compared with chi-square or Fisher exact tests, where appropriate. Pearson correlation analysis was used to determine the relationship of PNI and DOI over all cases. The independent effect was analyzed by using binary multivariate logistic regression model. The Kaplan–Meier method was used for survival analysis, and the log-rank test was used to evaluate the statistical significance of differences. Multivariate Cox proportional hazards model was applied to test the independent prognostic factors. All tests were two-sided and the level of statistical significance was set at 0.05. All statistical analyses were carried out using the Statistical Package of Social Sciences software version 17.0 (SPSS, Chicago, IL).

## 3. Results

### 3.1. END could not improve the benefit compared to observation for the cT1/2N0 TSCC patients

A total of 221 cT1–2N0 TSCC patients were randomly assigned into END group (n = 111) and observation group (n = 110). Clinicopathological features and outcomes of the cT1/2N0 TSCC patients by neck management are shown in Table S1. There were no significant differences in age, sex, T stage, and pathological grade between the observation and END groups (all $P > 0.05$). The differences in oncologic outcomes including LN metastasis, tongue local relapse, neck relapse, and distant metastasis were not observed between the two groups (all $P > 0.05$). Moreover, differences in 5-year disease-free survival rate (70.0% vs. 66.0%) and 5-year disease-specific survival rate (86.5% vs. 78.5%, Fig. 1A) were also not observed between the observation and END groups (both $P > 0.05$).

### 3.2. PNI was correlated with oncologic outcomes and survivals of the cT1/2N0 TSCC patients

Of the 221 patients, 34 (15.4%) were presented with PNI positive (+). Relationships between PNI status and clinicopathological features and outcomes of the cT1/2N0 TSCC patients were summarized in Table 1. Although PNI was not associated with T stage ($P > 0.05$), PNI (+) was associated with poor differentiation compared to well/moderate differentiation (32.6% vs. 10.9%; $P = 0.001$), and associated with DOI > 5 mm compared to DOI ≤5 mm (30.5% vs. 4.0%; $P < 0.001$). Of note, The positive correlation