Original Research

Pathologic evaluation of tumor budding as a prognostic factor for Stage I–II tongue squamous cell carcinoma

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ABSTRACT

Objective: Tongue squamous cell carcinoma (TSCC) has the tendency of rapid locoregional invasion and high cervical lymph node metastasis compared with other squamous cell carcinomas. Tumor budding has been reported as a useful prognostic factor for various cancers. In this study, we reported the usefulness of tumor budding evaluation as a prognostic factor for Stage I–II TSCC, in comparison with the Yamamoto-Kohama mode of invasion (YK classification).
Materials and methods: A total of 23 patients with Stage I–II TSCC were evaluated for tumor budding and YK classification. Tumor budding was classified as low or high-grade based on presence of < 5 or ≥ 5 tumor buds, respectively, in hematoxylin and eosin-stained specimens (BD classification). YK classification was similarly designated as either low (YK-1/-2/-3) or high-grade (YK-4C/-4D). Statistical analysis was carried out to evaluate the correlation of BD and YK classifications with disease free survival (DFS).
Results: Low-grade BD and YK classifications were confirmed in 15 and 11 patients (65.2% and 47.8%), respectively, while high-grade BD and YK classifications were confirmed in 8 and 12 patients (34.8% and 52.2%), respectively. DFS of patients with low-grade BD and YK classifications were significantly longer than those with high-grades ($p = 0.047$ and $p = 0.017$, respectively).
Conclusion: High-grade BD and YK classifications were associated with poor prognosis in patients with Stage I–II TSCC. Strict follow-up observation or postoperative adjuvant therapy should be considered when high-grade BD and YK classifications are confirmed.

1. Introduction

Tongue squamous cell carcinoma (TSCC) is more aggressive compared with other oral squamous cell carcinomas (OSCCs). Stage I–II TSCC does not always portend a good prognosis, as evidence shows that 20–40% of these cases already have occult cervical lymph node metastasis at presentation [1,2]. To date, various prognostic factors have been suggested for Stage I–II TSCC, however, the most useful clinical factors have not yet been determined.

In Japan, particularly in the field of oral surgery, many institutions use the Yamamoto-Kohama mode of invasion (YK classification) [3], which is based on the Jakobsson criteria [4] and focuses on the tumor-host borderline. Recently, tumor budding has been reported as a significant prognostic factor for OSCC. Tumor budding is defined as either a single cancer cell or a cluster of < 5 cancer cells in the stroma of the invasive front [5] (Fig. 1A and B). In Japan, tumor budding has been recognized as an independent prognostic factor for the lymph node metastasis of submucosal invasive colorectal cancer. According to the Japanese Society for Cancer of the Colon and Rectum (JSCCR) Guidelines 2010 [6], if tumor budding of Grade 2/3 is found after endoscopic resection of submucosal invasive colorectal cancer, such patients are indicated for additional enterectomy with lymph node dissection. In this study, we report the usefulness of tumor budding evaluation as a prognostic factor for Stage I–II TSCC, in comparison with YK classification.
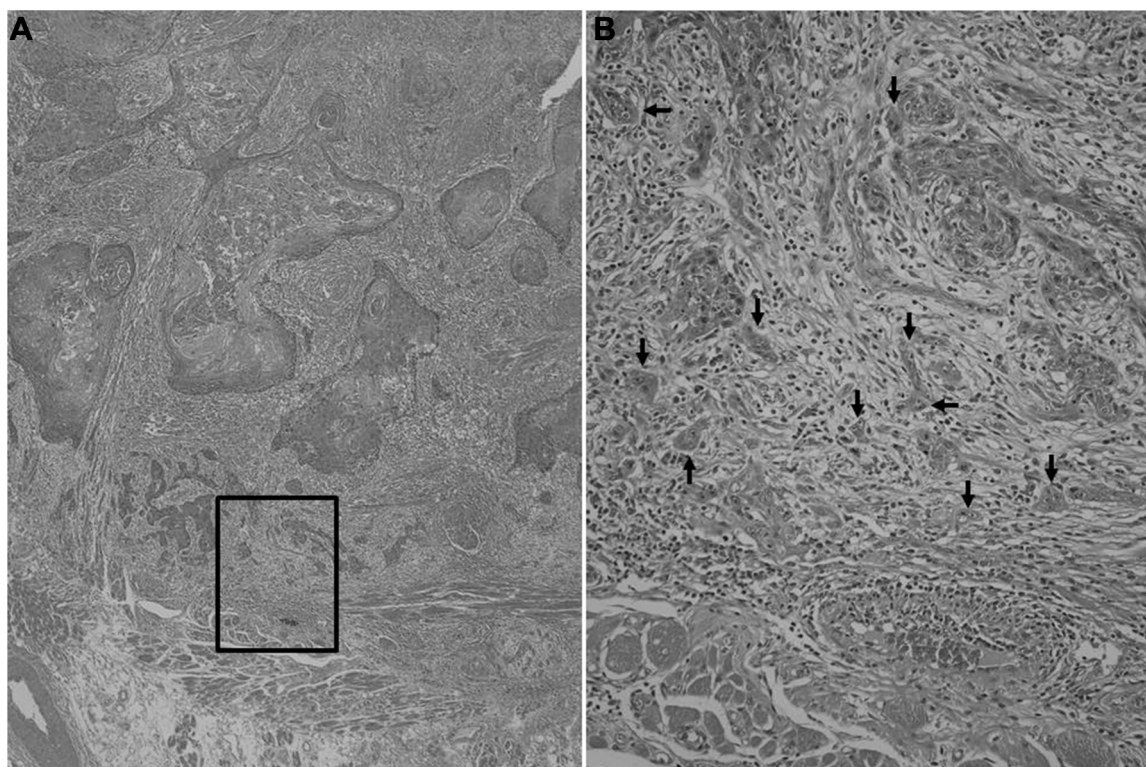

Fig. 1. Pathological appearance of tumor budding at the invasive front of TSCC (H&E, A, ×4; B, ×20). Arrows indicate tumor buds.

2. Materials and methods

2.1. Patients and tissue specimens

Twenty-three patients were diagnosed with Stage I–II TSCC between March 2006 and April 2013 in the Department of Dentistry, Oral and Maxillofacial Surgery, Yamagata University Hospital. All patients underwent glossectomy and/or ipsilateral supraomohyoid neck dissection (SOHND). None of the patients had received any adjuvant therapy prior to their surgery. Duration of follow-up was calculated based on the date of the last follow-up, cervical lymph node metastasis, locoregional recurrence or death. The tumor extent was classified according to the TNM Classification of Malignant Tumors from the UICC [7].

2.2. Evaluation of tumor budding and YK classification

Formalin-fixed and paraffin-embedded surgically resected specimens were sectioned to a thickness of 4 μm and stained with hematoxylin and eosin (H&E). All specimens were histologically confirmed using microscopy by 2 independent observers (pathologist and oral surgeon) blinded to each patient's clinical outcome. To evaluate the intensity of tumor budding, specimens were initially examined under the ×4 objective lens. Subsequently, the numbers of tumor budding foci in each field were counted under the ×20 objective lens. Tumor budding was initially designated as Grade 1 (0–4 tumor buds), Grade 2 (5–9 tumor buds) or Grade 3 (≥10 tumor buds). These labels were then used to generate a BD classification of either low-grade (Grade 1) or high-grade (Grade 2/3), according to the JSCCR Guidelines 2010 [6]. Similarly, we separated YK classification labels into 2 groups, namely low-grade (YK-1/-2/-3) and high-grade (YK-4C/-4D).

2.3. Statistical analysis

Disease free survival (DFS) was calculated using the Kaplan-Meier method and compared by log-rank test. P values < 0.05 were considered statistically significant, and all analyses were performed using SPSS version 23.0.

3. Results

The patient cohort consisted of 16 men and 7 women, with a median age of 59 years (range, 22–100). There were 16 patients with Stage I disease (69.6%) and 7 patients with Stage II disease (30.4%). In terms of pathologic differentiation, the tumors of 18 patients (78.3%) were well-differentiated, 4 patients (17.4%) were moderately-differentiated, and 1 patient (4.3%) had a poorly-differentiated tumor. Nineteen patients underwent glossectomy and 4 patients underwent concomitant ipsilateral SOHND. In 12/19 patients who underwent glossectomy, secondary cervical lymph node metastases were confirmed in 10 patients (1–23 months postoperatively), and locoregional recurrence and cervical lymph node metastases were confirmed in 2 patients (8 and 10 months postoperatively). Four patients who underwent concomitant ipsilateral SOHND were pN0 in terms of pathology and made good clinical progress. The median duration of follow-up was 11 months (range, 1–42). Two patients died of TSCC and 1 patient died of other causes, thus 20 patients were alive at the end of follow-up (Table 1).

In terms of BD classification, 15 patients (65.2%) had Grade 1, 7 patients (30.4%) had Grade 2, and 1 patient (4.4%) had Grade 3. Thus, 15 patients (65.2%) had a low-grade BD classification, while 8 patients (34.8%) had a high-grade BD classification. In terms of YK classification, 1 patient (4.3%) was YK-2, 10 patients (43.5%) were YK-3, 10 patients (43.5%) were YK-4C, and 2 patients (8.7%) were YK-4D; no patients were classified YK-1. Hence, 11 patients (47.8%) had a low-grade YK classification, and 12 patients (52.2%) had a high-grade YK classification (Table 2).

Of the 15 patients with a low-grade BD classification, secondary cervical lymph node metastases were confirmed in 5 cases, and locoregional recurrence and cervical lymph node metastasis was confirmed in 1 case. Of the 8 patients with a high-grade BD classification, secondary cervical lymph node metastases were confirmed in 5 cases,