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Prognostic value of lymph node density in buccal squamous cell carcinoma

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ABSTRACT

Purpose: Lymph node density(LND) has been shown to be a better prognosticator than conventional nodal classification to predict prognosis for squamous cell carcinoma(SCC) of the oral cavity. However, studies focusing on subsites of oral cancer are meager. The role of LND for buccal SCC was evaluated in this study.
Methods: A total of 39 patients with buccal SCC primarily treated surgically with neck dissection were identified. LND was defined as the number of positive nodes over the number of nodal yield. The cut-off of LND was ≤0.07 or >0.07. Patient demographic data and clincopathologic parameters were described. Survival was expressed by Kaplan-Meier method and correlation with survival is analyzed with log-rank test. IBM SPSS Statistics version 22 was used for data computation.
Results: The median follow-up was 79.0 months and median nodes removed was 23 (range 8–93). Positive nodal involvement was found in 19(48.7%) patients. The 5-year and 10-year OS were 67.4% and 42.5% whilst for DSS were 69.2% and 65.5%, respectively. When pT-, pN-, LND-classification and AJCC stage were analyzed for the whole series, only pN- ($p = 0.006$) and LND-classification ($p = 0.002$) were significant factors for OS, while pT-, pN-, LND-classification and AJCC stage were all significant factors for DSS. When only cases with positive nodal spread were considered, the pN-classification (pN1 vs pN2) was not a significant risk factor for either OS ($p = 0.075$, HR 3.10(CI 0.89–10.76)) and DSS ($p = 0.074$, HR 3.58(CI 0.88–14.56)). By contrast, LND-classification (≤0.07 vs >0.07) remained a significant predictor for OS ($p = 0.03$, HR 3.95(CI 1.15–13.63)), but not for the DSS ($p = 0.112$, HR 2.92(CI 0.78–10.99)).
Conclusion: The prognostic value of LND on buccal SCC is supported in this study. The results also suggest that LND is better than the conventional pN-classification to predict OS. Further studies on LND with big sample size for buccal SCC or other subsites of OSCC are worthwhile.

1. Introduction

The lymph node status is the most important prognostic factor for squamous cell carcinoma of the oral cavity (OSCC). However, the pN-classification of TNM system has been challenged regarding its predictability for prognosis. For instance, Wenzel et al. [1] showed no difference in oncologic outcome between pN0 and intra-nodal pN-positive cases. Lymph node density(LND), defined as the ratio of number of nodes involved by malignancy and total number of nodes harvested from neck dissection, has recently been proposed as a reliable prognosticator for OSCC on multivariate analysis [2]. Subsequently, a multi-center trial validated that a modified staging system based on LND outweighed the conventional pN-classification to predict survival [3]. Positive correlation of LND with other prognostic co-variates (depth of primary tumor invasion, perineural invasion and extracapsular nodal spread) [4] as well as lung metastases [5] has been demonstrated.

However, the aforementioned studies on LND evaluating OSCC as a whole which encompasses heterogeneously many subsites of the oral cavity: tongue, floor of mouth, buccal mucosa, alveolar and palate. It is not certain whether the prognostic value of LND can be consistently applicable to the various subsites. Amar et al. [6] first evaluated the value of LND for tongue and floor of mouth cancer and found out that it is a better indicator than the pN-classification. Likewise, the prognostic value of LND in oral tongue SCC has also been validated in subsequent studies [7,8].

To our knowledge, LND has not been studied on buccal SCC. Therefore, we were prompted to investigate the prognostic role of LND for this subsite of OSCC.

2. Methods

All the patients with histopathologically verified buccal SCC were retrieved from our head and neck cancer registry. We undertook this retrospective survey on a prospectively collected database. A total of 40

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patients primarily treated with surgery for buccal SCC from March 2000 to July 2016 were identified. One patient, an 80-year-old man with T1 tumor, was excluded because the buccal SCC was surgically removed without neck dissection. The remaining 39 patients with neck dissection were eligible for evaluation. As all of the primary tumors were ipsilateral, there was no bilateral neck dissection performed in this series.

All enrolled patients underwent surgical extirpation of their tumors. When nodal metastases were evident clinically or radiologically, ipsilateral comprehensive neck dissection from level I to level V was done [9]. Conversely, only elective neck dissection from level I to level III was performed. The cancer was staged in accordance with the 7th edition of AJCC TNM staging system [10]. Adjuvant radiotherapy was given for stage III/IV disease, presence of perineural spread or lymphovascular invasion. Concurrent chemoradiotherapy was offered to patients with positive resection margin or extra-capsular nodal involvement. Patients were followed 3-monthly in the first year, then 4-monthly in the second year, 6-monthly in the third year onward, and annually after 5 years. No patient has defaulted follow-up.

The neck dissection specimen was marked in various levels and fixed in neutral buffered formaldehyde. The lymph node was carefully identified, embedded in paraffin and stained with hematoxylin-eosin, and examined by our pathologists for tumor metastases. The number of involved lymph nodes was recorded in each level. LND was calculated as the number of positive nodes per number of nodes harvested.

The clinicopathologic parameters were described. Margin status was classified into negative if >3 mm, close if ≤3 mm or involved if tumor cell seen at resection margins, respectively. Survival was calculated from the date of surgery to last follow-up or patient expiry. Survival curves were plotted by Kaplan-Meier method. The clinicopathologic variables were expressed in median with range. Risk factors for overall survival (OS) and disease specific survival (DSS) were analyzed by log-rank test. The LND was dichotomized into either ≤0.07 or >0.07 [3,5]. Any differences were statistically significant when p value was <0.05. IBM SPSS Statistics version 22 was used for data computation.

3. Results

The median age of the 39 patients was 70.0 years (range 46.0–95.0). There were 20(51.3%) male patients. Of the surviving patients, the median follow-up duration was 79.0 months (range 5.0–167.0). The other clinicopathologic parameters were summarized in Table 1. The median of nodes removed during neck dissection was 23 (8–93). Positive nodal involvement was found in 19(48.7%) patients and extranodal spread was present in 6 of them. The pN-classification was pN0(51.3%), pN1(25.6%), N2(23.1%) and pN3(0%), respectively. When only node positive patients were counted, the median LND was 0.05 (0.01–0.33). The final tumor stage distribution was stage I(12.8%), stage II(28.2%), stage III(25.6%) and stage IV(33.3%). (Table 1).

Most of the patients were treated by surgery alone (53.8%) while 28.2% of patients underwent surgery followed by radiotherapy. The remaining patients underwent surgery with postoperative chemotherapy or chemoradiotherapy. (Table 2) Local recurrence, regional recurrence or distant metastases occurred in 9(23.1%), 5(12.8) and 3(7.7%) patients, respectively. As in December of 2016, 19 patients have died while 20 were surviving. Of the deceased patients, 12 died of the buccal SCC while the other 7 patients succumbed to other illnesses not related to buccal SCC.

The Kaplan-Meier curves of OS and DSS of the whole series were shown in Fig. 1A and Fig. 1B, respectively. The 5-year and 10-year OS were 67.4% and 42.5% whilst for DSS were 69.2% and 65.5%, respectively. When pT-classification, pN-classification, LND-classification(0 vs ≤ 0.07 vs > 0.07) and AJCC stage were analyzed with log-rank test (Table 3), only pN-classification ($p = 0.006$) and LND-classification ($p = 0.002$) were significant factors for OS. (Fig. 2A and Fig. 2B) On the other hand, pT-classification, pN-classification, LND-classification and AJCC stage were all significant factors for DSS. (Table 3).

Table 1
Clincopathologic parameters.

			Number of patients
Age (year)			39
Median 70.0 (46.0–95.0)			
Gender			39
Male	20 (51.3%)		
Female	19 (48.7%)		
Follow-up duration (month)			19
Median	79.0 (5.0–167.0)		
Depth of invasion (mm)			28
Median	7.0 (1.1–30.0)		
pT			39
T1	9 (23.1%)		
T2	15(38.5%		
T3	7 (17.9%)		
T4	8 (20.5%)		
Node removed			39
Median	23 (8–93)		
pN status			39
Positive	19 (48.7%)		
Median	1(1–17)		
Extracapsular spread	Yes	6	
	No	13	
Negative	20 (51.3%)		
pN classification			39
N0	20(51.3%)		
N1	10(25.6%)		
N2	9 (23.1%)		
N3	0		
LND			19
Median	0.05 (0.01–0.33)		
Tumor differentiation			39
Well	2 (5.1%)		
Moderate	35(89.7%)		
Poor	1 (2.6%)		
Unknown	1 (2.6%)		
Lymphovascular invasion			39
Yes	3 (7.7%)		
No	36(92.3%)		
Perineural spread			39
Yes	5 (12.8%)		
No	34(87.2%)		
Margin			39
Negative	19(48.7%)		
Close	14(35.9%)		
Involved	6 (15.4%)		
Stage			39
I	5 (12.8%)		
II	11(28.2%)		
III	10(25.6%)		
IV	13(33.3%)		

When only cases with positive nodal spread were considered, the pN-classification (pN1 vs pN2) was not a significant risk factor for either OS ($p = 0.075$, hazard ratio 3.10(CI 0.89–10.76)) and DSS ($p = 0.074$, hazard ratio 3.58(CI 0.88–14.56)). By contrast, LND-classification (≤0.07 vs > 0.07) remained a significant predictor for OS ($p = 0.03$, hazard ratio 3.95(CI 1.15–13.63)) (Fig. 3), but not for the DSS ($p = 0.112$, hazard ratio 2.92(CI 0.78–10.99)). (Table 4).

4. Discussion

The results of this study indicate that LND of buccal SCC is, akin to that for overall OSCC, a predictor for oncologic outcomes. It also suggests that LND is a better prognosticator than conventional pN-classification which is determined by size, number and laterality of the positive nodes. The findings are not unexpected as the behavior of buccal SCC is actually similar to other subsites of OSCC after matching for the patients based on a population-base analysis [11]. Huang et al. [12] showed that elective neck dissection is indicated even for early buccal SCC as the neck control rate and 5-year disease-free survival is

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