Incorporation of log odds of positive lymph nodes into the AJCC TNM classification improves prediction of survival in oral cancer

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Objectives: To assess the prognostic performance of a new N classification that incorporates the log odds of positive lymph nodes (LODDS) into the routinely used pathological N classification for oral squamous cell carcinoma (OSCC) patients.

Design: Retrospective cohort study utilising LODDS into pN category was performed, and the AJCC TNM stage and T-New N-M stage were compared with respect to 5-year disease-specific survival (DSS) rates. The discriminability was evaluated from the linear trend chi-square test, Akaike information criterion (AIC) and Harrell's c-statistic.

Setting: Medical centrer in Taiwan.

Participants: A total of 463 patients received primary surgery and neck dissection between 2004 and 2013 for OSCC.

Main outcome measures: The discriminability for 5-year DSS rates.

Results: The median follow-up period was 54 months, the mean patient age was 54 ± 11 years and 428 patients (92.4%) were male. The patients with higher LODDS had worse 5-year DSS rates. Incorporation of LODDS into the prognostic model based on the seventh edition of the TNM classification significantly improved discriminative performance for 5-year DSS with a lower AIC (1883 *versus* 1897), and higher prediction accuracy (Harrell's c-statistic: 0.768 *versus* 0.764).

Conclusions: By utilising a merger of the LODDS and pN classifications to create a new N classification has better discriminatory and predictive ability than pathological TNM staging and could help identify high-risk patients for intense adjuvant therapy.

In Taiwan and some areca quid use area, the incidence of oral squamous cell carcinoma (OSCC) continued to increase.[1] Oral cancer incurred huge utilisation of healthcare services and could result in a serious socio-economic problem due to the increasing number of young patients.[2] Despite great advances in diagnostic workup, surgical techniques, patient care and adjuvant treatment such as chemotherapy or radiotherapy, the long-term survival of patients of OSCC remains stagnant in the recent decades.[3] Besides the public health strategies, such as oral screening, and programmes which help individuals to quit habitually smoked cigarettes, drank alcohol and chewed betel quid, refinement of the present tumour-node-metastasis (TNM) staging system and identification of high-risk patients may be worth trying.

Due to multiple shortcomings of N classification in current American Joint Committee on Cancer (AJCC) staging system (7th edition) such as understaging and stage migration, several new classification methods for nodal status had been developed.[4–6] The lymph node ratio (LNR) had been proven to better predict outcomes in head and neck cancers.[7] Recently, the log odds of positive lymph nodes (LODDS) outperformed AJCC pN category and LNR in major cancers, such as colon cancer, gastric cancer and pancreatic cancers.[8–10] LODDS discriminates patients without positive lymph nodes and better discriminates between

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cancer patients with few positive nodes, or insufficient nodes retrieved.[4,11] The literature related to the LODDS in head and neck cancer was scant. Our previous research first reported the discriminability of LODDS in oral cancer.[12] Yildiz *et al.*[13] also demonstrated that LODDS behaviour better prediction for overall survival in oral cancer in Western countries, compared with LNR or AJCC pN category. However, the pathological factors such as tumour thickness, perineural invasion (PNI) and lymphovascular permeation which played as an important prognostic role were not included in our previous analysis and the number in each subgroup was relatively small in the preliminary 3-year follow-up study.[12] Furthermore, management of OSCC is based on the pathological TNM staging of patient specimens currently. Given this background, we reserve the routinely used pN classification by addition of the LODDS category to establish a 'new N' classification. It had the strengths of pN classification based on lymph node number, size and location and LODDS weighted on the number of pathologic lymph nodes. Therefore, in this context, different to our previous analysis, we evaluated that whether the addition of LODDS into current AJCC TNM classification-based prediction models improved the discrimination of 5-year disease-specific survival (DSS).

Materials and methods

Ethical considerations

This retrospective study was approved by the Institutional Review Board of Kaohsiung Veterans General Hospital in Taiwan. The requirement for informed consent was waived because all identifying information was removed from the dataset before analysis.

Patient demographics and database

Data were collected from the Cancer Registry Dataset of the Kaohsiung Veterans General Hospital from 2004 to 2013. The electronic medical records and cancer registry were retrospectively reviewed. The follow-up deadline was October of 2015 for survivors. The records of all newly diagnosed OSCC patients (n = 463) who were treated by primary surgery and neck dissection, with or without adjuvant therapy, were reviewed. Patents were excluded if they had previous cancer history, received any therapeutic treatments prior to surgery (e.g. chemotherapy or radiotherapy) or if they had distant metastases. The Cancer Registry Dataset format, developed by the Health Promotion Administration of the Ministry of Health and Welfare, provides the date of diagnosis, primary tumour site, age, sex, margin status (positive or negative), degree of differentiation (well, moderately or poorly), number of lymph nodes examined, number of positive lymph nodes, PNI, status of lymphovascular invasion, chemotherapy regimen, radiation dosage, cause of death and clinical/pathological TNM stage. All cases were staged according to the 2009 AJCC stage classification system (7th edition).[6] The clinical endpoint was 5-year DSS rate. Deaths due to cancer were recorded as events, and deaths due to other causes were censored.

The definition and optimal cut-off value for LODDS classification

The LODDS was defined as log of the ratio between numbers of pathological metastatic lymph nodes and the number of pathological non-metastatic lymph nodes from the neck dissection specimen. The formula was as $\log_{10}[(\text{pnod} + 0.5)/(\text{tnod-pnod} + 0.5)]$, where pnod is the number of positive cervical lymph nodes and tnod is the total number of lymph nodes retrieved.[10] In this calculation formula, 0.5 was added to both the numerator and denominator to avoid an infinite number. For this analysis, we tested the use of three different sets of cut-off points (25%, 25%, 25%, 25%; 40%, 25%, 20%, 15%; 35%, 30%, 20%, 15%). At last, we adapted the cut-off points (25%, 25%, 25%, 25%) to define four LODDS groups due to its better prediction ability (Table 1).

Optimal Category for New N classification

We attempted to improve and modified the current AJCC pN classification by adding the LODDS to create a 'new N' classification by the following three steps:

1 OSCC patients were divided into three groups by the pN category (pN0-pN2) and merged with the four different LODDS groups (LODDS1-LODDS4). Thus, this procedure yielded one new N classifications.

2 The 5-year DSS rates for the new N systems were estimated by the Kaplan–Meier method, and patients with similar survival rates were placed into four categories: new N0, new N1, new N2 and new N3 (Table 2).

3 Subgroups with fewer than 10 OSCC patients were not included in the analysis because the small number of patients could lead to unreliable estimates of the 5-year DSS.

Statistical analysis

Statistical analyses and graphics were performed using SPSS software (version 15, SPSS Inc., Chicago, IL, USA). The prognostic influence of LODDS for 5-year DSS rates was examined by Kaplan–Meier methods. The AJCC TNM stage and hypothetical T-New N-M stage were compared with

Table 1. Demographic and clinical characteristics of study patients, $n = 463$

	Numbers *n* (%)
Age (mean ± SD)	53 ± 11
≦40 years	48 (10.4)
>40 years	415 (89.6)
Gender	
Male	428 (92.4)
Female	35 (7.6)
pT stage	
T1	103 (22.2)
T2	176 (38.0)
T3	37 (8.0)
T4	147 (31.7)
Site of primary tumour	
Tongue	166 (35.9)
Buccal	209 (45.1)
Other	88 (19.0)
Margin	
Negative	418 (90.3)
Positive	45 (9.7)
Differentiation	
Well	66 (14.3)
Moderately	356 (76.9)
Poorly	41 (8.9)
Adjuvant therapy	
Nil	205 (44.3)
Radiotherapy	121 (26.1)
Chemotherapy	44 (9.5)
Chemotherapy + radiotherapy	93 (20.1)
Tumour thickness	
≦5 mm	108 (23.3)
>5 mm	355 (76.7)
Perineural invasion	
No	341 (73.7)
Yes	122 (26.3)
Lymphovascular invasion	
No	422 (91.1)
Yes	41 (8.9)
Alcohol	
No	118 (25.5)
Yes	345 (74.5)
Smoking	
No	46 (9.9)
Yes	417 (90.1)
Areca quid	
No	70 (15.1)
Yes	393 (84.9)
pN classification	
N0	279 (60.3)
N1	56 (12.1)
N2	128 (27.6)
LODDS classification	
LODDS 1 (LODDS≦−1.64)	121 (26.1)
LODDS 2 (−1.64 < LODDS≦−1.18)	117 (25.3)
LODDS 3 (−1.18 < LODDS≦−0.70)	105 (22.7)
LODDS 4 (−0.70 < LODDS)	120 (25.9)
New N classification	
New N0 (pN0 and LODDS1-4)	287 (60.3)
New N1 (pN1 and LODDS1-3)	42 (9.1)
New N2 (pN1 and LODDS4, pN2 and LODDS1-3)	71 (15.3)
New N3 (pN2 and LODDS4)	71 (15.3)

LODDS, log odds of positive nodes.

respect to 5-year DSS rates. Cox proportional hazards models were used to compare the 5-year DSS rates for these two stage systems after adjusting for clinicopathologic factors. The discriminability of these two stage models was assessed with Harrell's c-statistic and the linear trend chi-square test.[11,14] The Akaike information criterion (AIC) for each regression model was also used to measure discriminability.[15] In multivariate analysis, the Cox proportional hazards regression model was used to compare outcomes after adjusting for patient characteristics (age, sex), pathological T stage, risk factors (tumour thickness, differentiation, PNI and lymphovascular invasion) and personal factors (smoking, alcohol and chewed betel quid). Harrell's c-statistic for the model prediction was classified as follows: 0.5, equal to chance; 0.7–0.8, acceptable; 0.8–0.9, excellent; and 0.9–1, outstanding. A P-value <0.05 was considered statistically significant.

Results

Table 1 summarises the demographic characteristics and pathological risk factors of the study cohort ($n = 463$), all of whom underwent major surgery and neck dissection with curative intent for OSCC, with or without adjuvant therapy. Overall, the median follow-up time was 54 months, there were 428 males and 35 females, the mean age was 53 ± 11 years and the 5-year DSS was 58%. There were 184 patients (40%) with neck dissection for clinical node-negative disease and 281 patients (60%) with neck dissection for clinical node-positive disease. A total of 279 (60.3%) patients were free of nodal disease, and 184 (39.7%) had nodal disease. Fifty-six patients (12.0%) were classified as pN1 and 128 (27.6%) as pN2.

The mean number of total lymph nodes retrieved was 22.3 ± 16. The overall mean number of metastatic nodes was 1.4 ± 3.4 and was 3.4 ± 4.7 in lymph node-positive patients. The median LODDS value was −1.23 (range: −2 to 1). The patients with higher LODDS were significantly associated with worse survival rates (Fig. 1).

In Fig. 2, when stratified based on AJCC pN category, 5-year DSS was similar in patients with high LODDS and low LODDS (cut-off point: 75% of LODDS or value of −0.7) for pN0 (P = 0·348). However, 5-year DSS was noted a trend in difference for pN1 (P = 0·094) and significant difference for pN2 (P = 0.014) between patients with high and low LODDS. Table 2 shows the 5-year DSS for different combinations of AJCC pN plus LODDS. As described in the 'Material and Methods', subgroups with fewer than 10 OSCC patients were not included in this analysis. This led to a new N category in which each patient was placed into one of four groups: new N0 (pN0 and LODDS1-4); new N1 (pN1 and LODDS2-3); new N2 (pN1 and LODDS4, pN2 and LODDS3); and new N3 (pN2 and LODDS4).

We further explored the stage-specific 5-year DSS (Fig. 3). Performance of AJCC TNM stage and T-New N-M stage was illustrated in Table 3. The T-New N-M stage had better discriminatory performance (linear trend chi-square, 105 *versus* 61; AIC, 1905 *versus* 1937) and higher prediction accuracy (Harrell's c-statistic, 0.730 *versus* 0.692). In multivariate analysis, we evaluated the prognostic effect of AJCC TNM stage and T-New N-M stage after adjusting for age, sex, pathological T classification, margin status, differentiation, PNI, lymph-vascular permeation, personal risk factors and tumour site (Table 4). The new N based regression model performed better than AJCC TNM stage model with a lower AIC (1883), and higher prediction accuracy (Harrell's c-statistic: 0.768). This implies that T-New N-M stage system, which incorporates pN category with LODDS, provides a better classification system for OSCC than current AJCC TNM stage system.

Table 2. The 5-year disease-specific survival rates of patients with oral squamous cell carcinoma according to different pN category plus LODDS combinations

Category	Case	pN category	LODDS	Survival rate (%)
All patients				
New N0	120	N0	LODDS1	81.8
New N0	94	N0	LODDS2	68.7
New N0	29	N0	LODDS3	77.9
New N0	35	N0	LODDS4	84.7
–	1	N1	LODDS1	0.0
New N1	16	N1	LODDS2	37.7
New N1	25	N1	LODDS3	69.3
New N2	14	N1	LODDS4	31.3
–	0	N2	LODDS1	–
–	7	N2	LODDS2	28.6
New N2	51	N2	LODDS3	33.9
New N3	71	N2	LODDS4	17.0

LODDS, log odds of positive nodes.

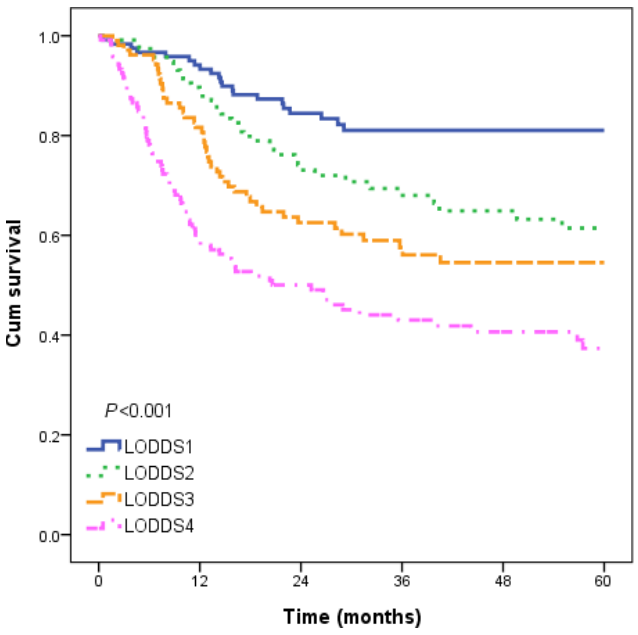

Fig. 1. Impact of LODDS category on 5-year disease-specific survival.

Discussion

Synopsis of the key findings

This is the first study to use and test the prognostic utility of a merger of the LODDS and pN classifications to create a new N classification for patients with OSCC. The present pN classification is deficient in estimating OSCC survival outcomes and incorporation of LODDS into a prognostic model based on the seventh edition of the TNM classification significantly improved risk reclassification for DSS. Thus, this T-New N-M stage system could help to identify high-risk patients who may benefit from more intense adjuvant therapy and allow for more accurate comparisons between different treatment groups.

Strengths of the study

For oral tumours, a main drawback of the current AJCC pN system is that the node category is mostly based on the number of positive nodes. Inadequate neck dissection may lead to stage migration in pN classification.[9,16–18] Although

the pN classification was the best prognostic indicator in previous data, the issue of stage migration was not resolved. Recent research indicated that the LNR better predicted outcome than the pN classification, but the LNR may also be criticised due to same classification of LNR0 and pN0. The limitations of these systems led us to consider LODDS as an alternative.

Previous literatures demonstrated that LODDS could provide a more accurate prediction for prognosis than other systems used for staging of lymph nodes.[4,19] The main reason to explain why the LODDS is superior to the pN and LNR classifications is that the cassociation between the LODDS distribution and the number of pathological-positive nodes.[4] Different to LNR, LODDS is able to discriminate among patients with the same ratio of node metastasis but different survival rates especially for those with insufficient LN examination achieved. Our previous study showed LODDS had better discrimination than pN classification for those with <5 neck metastases.[12] LODDS also had better discrimination than LNR classification in OSCC patients with LNR <0.2 or >0.6. Therefore, LODDS gives a chance to improve the accuracy of lymph node involvement for prognostic assessment.

Our previous study was the first to assess the discriminability of LODDS for OSCC, but LODDS category did not show better discriminability regarding 5-year DSS in current analysis. In Table S1, the pN classification had better prediction ability for 5-year DSS with a lower AIC (1929

Table 3. Comparison of the performance of the AJCC TNM and T-New N-M staging system

	Figure	Subgroups	Linear trend χ^2	AIC	Harrell's c-statistics
AJCC TNM stage	3A	I, II, III, IVA, IVB	61	1937	0.692
T-New N-M stage	3B	I, II, III, IVA, IVB	105	1905	0.730

AIC, Akaike information criterion.

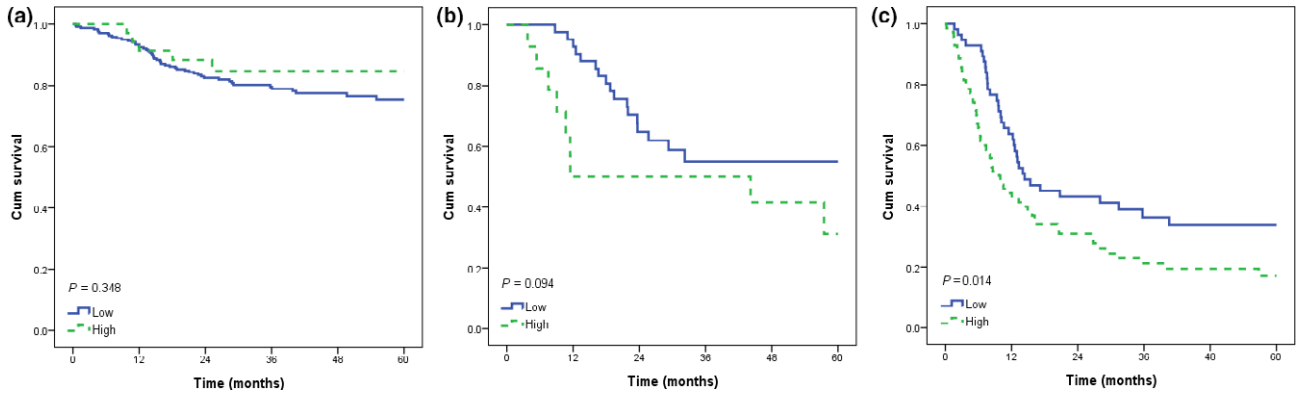

Fig. 2. 5-year disease-specific survival curves according to LODDS and pN category: (a) pN0, (b) pN1 and (c) pN2 (log rank test).

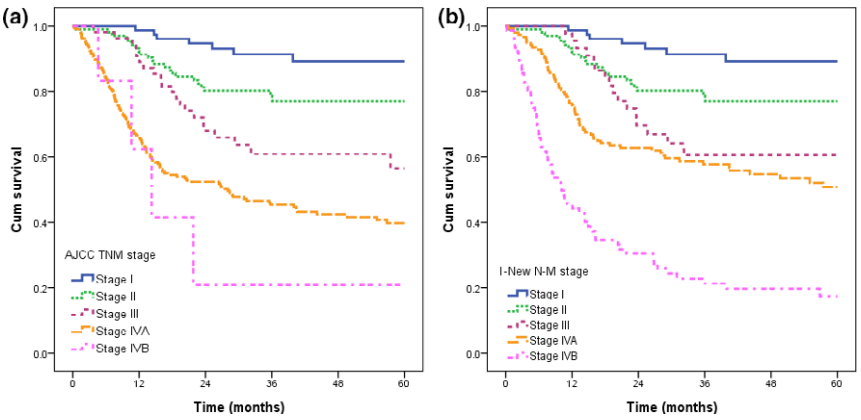

Fig. 3. Impact of AJCC TNM (a), T-New N-M (b) staging on 5-year disease-specific survival in patients with oral squamous cell carcinoma.

Table 4. Multivariate analysis of overall survival and model discrimination

	Model 1: AJCC TNM stage		Model 2: T-New N-M stage	
	HR	95% CI	HR	95% CI
Gender (female)	1.51	0.86–2.67	1.61	0.92–2.83
Age (>40 years)	1.11	0.66–1.84	1.05	0.63–1.74
pT				
T1	1		1	
T2	1.40	0.79–2.46	1.39	0.80–2.44
T3	2.16	1.07–4.35	2.17	1.09–4.32
T4	2.24	1.23–4.05	2.46	1.37–4.41
Site of primary tumour				
Other	1		1	
Tongue	1.01	0.73–1.37	0.90	0.64–1.27
Margin				
Negative	1		1	
Positive	0.69	0.41–1.15	0.74	0.44–1.23
Differentiation				
Well/moderately	1		1	
Poorly	1.28	0.80–2.05	1.24	0.78–1.98
Adjuvant therapy				
Nil	1		1	
Chemotherapy or radiotherapy	0.79	0.54–1.16	0.77	0.53–1.13
Tumour thickness (>5 mm)	1.45	0.81–2.60	1.53	0.86–2.72
Perineural invasion	1.50	1.07–2.11	1.56	1.11–2.19
Lymphovascular invasion	1.38	0.88–2.17	1.36	0.87–2.12
Alcohol	1.22	0.81–1.85	1.20	0.79–1.81
Smoking	0.92	0.42–2.01	0.83	0.38–1.81
Areca quid	1.25	0.63–2.46	1.39	0.71–2.68
pN				
N0	1			
N1	2.16	1.31–3.56		
N2	4.58	3.08–6.83		
New N classification				
N0			1	
N1			1.79	1.00–3.18
N2			3.15	2.03–4.90
N3			6.77	4.38–10.46
Discrimination of model				
AIC	1897		1883	
Prediction accuracy of model				
Harrell's c-statistic	0.764		0.768	

LODDS, log odds of positive nodes; AIC, Akaike information criterion; HR, hazard ratio; CI, confidence interval.

versus 1995), a higher linear trend chi-square (110 *versus* 44) and a higher Harrell's c-statistics (0.708 *versus* 0.655). We proposed the reason is that LODDS category did not consider the distribution or size of metastatic lymph nodes, which are recognised as important prognostic factors.[20,21] Therefore, different to our previous preliminary report, we decided to incorporate the LODDS into the AJCC pN category to establish a new N classification. It had the strengths of pN classification and LODDS weighted on the number of pathologic lymph nodes versus total retrieved lymph nodes.

Comparison with other studies

The presence of regional lymph node metastasis is widely accepted as a major prognostic factor, and recent studies have focused on the total number of lymph nodes and the ratio of positive to negative lymph nodes.[16,22] The LNR and

LODDS are two new classifications that are considered better than the traditional number-based classification system (pN0-pN3). In our previous study, we found an association between poor prognosis and high LNR for head and neck cancer.[23] Although the LNR classification performs well for head and neck cancer, its prognostic value has some limitations, because LNR0 is defined the same as pN0. Some previous studies found that LODDS was superior to the pN and LNR systems. For example, Qiu *et al.*[11] compared LODDS and LNR with pN (AJCC 7th edition) and concluded that LODDS performed better in prediction of gastric cancer prognosis. La *et al.*[9] reported similar results for pancreatic cancer. Another study of 440 colon cancer patients reported that the overall survival rates correlated well with the different LODDS groups (LODDS0: 81%; LODDS1: 74.2%; LODDS2: 50%; $P = 0.020$).[19] The results of these previous studies motivated us to combine the LODDS system with the current AJCC pN classification instead of the LNR category to improve classification.

Staging systems are designed to compare similarly staged patients who are given different treatments to determine overall prognosis for individual patients.[21] The current AJCC pN classification guidelines for OSCC are based on pathological evaluation of lymph node size, number of lymph nodes, and presence of contralateral or bilateral regional disease. However, cancer staging based on the TNM system is considered imperfect for prognostic purposes. When there is stage migration, pN staging underestimates the true extent of lymph node disease as more pathologic lymph nodes are removed after neck dissection. Thus, patients with the same pN classification, but a different number of examined nodes, will be given different prognoses. For example, a pN1 patient with higher LODDS should not be treated the same as a pN1 patient with lower LODDS because the former patient has a higher risk of occult metastases and worse prognosis. Similarly, those patients with different pN stage and same level of LODDS should not be treated the same intense adjuvant therapy. For this reason, we reserve the current pN classification by addition of the LODDS category, due to the shortcomings of ratio-based system weighted on the number of pathologic lymph nodes without the lymph node size and location (ipsilateral *versus* contralateral). Ebrahimi *et al.*[24] also demonstrated that the prognoses of patients with N2b and N2c OSCC cancer appear to be similar after adequate adjustment for the burden of lymph node metastases, irrespective of laterality. These findings confirm our study hypothesis. The new N classification described here has improved prognostic performance based on the number of metastatic lymph nodes and is reliable and feasible for use in clinical practice.

Weaknesses of the study

This study has several limitations. First, the number of patients in some subgroups (pN1 with LODDS1; pN2 with LODDS 1 and LODDS 2) was small, so estimation of survival rates was unreliable. These three groups were not included in our new N classification. Second, application of the new N classification requires neck dissection, so we did not include OSCC patients with cT1-2 disease who underwent resection of the primary tumour without neck dissection. Third, none of the patients in our study had N3 disease. In our previous study, only 0.3% of patients had N3 disease.[12] Future researchers should consider recruitment of patients with stage N3 cancer. However, several researchers recommend against surgical intervention for patients with N3 OSCC due to poor survival and high comorbidity.[25]

Conclusion

This is the first study to use and test the prognostic utility of a merger of the LODDS and pN classifications to create a new N classification for patients with OSCC. This new N classification significantly improved risk reclassification for 5-year DSS and could be used to identify high-risk OSCC patients for more intensive adjuvant therapy.

Keypoints

- This study aimed to validate the prognostic values of the log odds of positive lymph nodes (LODDS) for patients with oral squamous cell carcinoma.
- The LODDS, lymph node ratio, and AJCC pN classifications had similar diagnostic performance in prediction of 5-year disease-specific survival.
- A new N classification which includes LODDS and pN had better discriminability and monotonicity of gradients than the AJCC pN classification.

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Conflict of interest

The authors have no conflict of interests.

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Supporting Information

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